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CLINICAL GENETICS

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CLINICAL GENETICS

Edited by

ARNOLD SORSBY

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PREFACE

RECOGNITION of the fact that some diseases are hereditary is as old as medicine itself. The observations that have accumulated in the pre-mendelian age are indeed impressive, as is shown by the earlier volumes of the *Treasury of Human Inheritance*; but these observations tended to be regarded as collectors' items, for they were drawn chiefly from rather uncommon affections and thus lacked contact with the main body of medicine. So widespread was this attitude that the pioneers in mendelian genetics, as applied to man, believed they were dealing with special cases when they showed that the inheritance of some human affections conformed to mendelian laws. In spite of many such findings, it was assumed that most hereditary affections, and certainly the inheritance of normal features, were determined in some other manner.

The general application of mendelian genetics to man in health and disease has emerged only during the past two or three decades. In consequence the theoretical basis of human genetics has broadened so quickly in recent years that the original situation—a mass of data without theoretical illumination—has become reversed.

Nowhere in clinical studies, is theory—itself rapidly changing—so much in advance of empirical observations. Rapid progress is thus possible and is in fact being made, so that clinical genetics is no longer the study of curiosities, but has become essential in elucidating the common problems of health and disease.

The present volume assumes that the reader is acquainted with the elements of genetics. In any case excellent expositions both of general and human genetics are available, and it is to supplement rather than to replace these that the first part of the book has been planned. The second and main part is more strictly clinical.

A book of this type is at the present essentially a contribution to clinical pathology. Other aspects are, however, not lacking: the diagnostic implications of clinical genetics are obvious and far reaching, as are the therapeutic possibilities—splenectomy in acholuric jaundice, blood transfusions in Rh encephalopathy, and the treatment of diabetes are portents of things to come.

ARNOLD SORSBY.

August, 1953.

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CLINICAL VARIETIES OF GENETIC DISEASE

ARNOLD SORSBY

GENERAL CONSIDERATIONS

Genetic disease as a dynamic process

OWING to the historical accident that a hereditary factor was most clearly recognized in congenital anomalies, the older clinicians tended to equate genetic disease with congenital defects. As the congenital defects generally showed little change over years there also grew up a belief that hereditary anomalies were largely rigid, unchangeable entities. Both these views were erroneous. In the first place many hereditary affections are not congenital, but begin after birth, and are relentlessly progressive. This is seen in retinitis pigmentosa with its onset in early adult life and in Huntington's chorea which generally sets in in middle age; myotonia atrophica, Friedreich's ataxia, and xerodermia pigmentosum are furhter examples of affections with postnatal onset and progressive course. Secondly, the congenital anomaly present at birth does not arise as a finished entity but is merely the end stage of an evolutionary process that has run to its conclusion in antenatal life, and even then some congenital anomalies show progressive postnatal changes as is seen in the increasing crippling in osteogenesis imperfecta.

The widespread belief that genetically determined diseases are unalterable finished entities has therefore no basis in fact. The study of environmental affections called for the isolation of the noxious agent, the recognition of its causal relationship to the end process, and an understanding of the evolutionary course. Likewise the study of genetically determined disease calls for more than the recognition of the causal relationship between the pathogenic gene and the end stage. The whole of a dynamic process, sometimes largely prenatal and sometimes largely postnatal, needs to be laid bare.

Interaction between genetic and environmental factors

These and other considerations make meaningless any sharp antithesis between genetically determined disease and affections induced by environmental agents. Only in extreme cases can hereditary and environmental factors be clearly disentangled in the effect they produce, and there is in fact much overlap. At the one extreme there are clinical conditions, such as, say, albinism, which are always genetic in origin; at the other extreme there are such lesions as a stab wound which are always environmental in character, but frequently both environmental and genetic factors may be equally significant. Even the effects of such a well-defined environmental factor as trauma may be influenced by the genetic

constitution of the patient. A blow which would give little pathological disturbance in one individual may lead to fracture of the femur in a patient with fragilitas ossium of genetic origin. Exposure to tuberculous infection will precipitate clinical tuberculosis in members of some families as readily as it does in strains of rabbits bred for special susceptibility to tuberculosis, whilst similar exposure will not harm other individuals, or animals from strains bred for special insusceptibility to tuberculosis.

Doubtful specificity of clinical appearances

Furthermore, the appearances of an affection definitely of genetic or definitely of environmental origin may be clinically indistinguishable. Optic atrophy, whether derived genetically or caused by injury to the optic nerve, will look very much alike and will give the same blindness. Mental deficiency may be genetic in origin or caused by many different environmental factors; disseminated sclerosis cannot always be readily distinguished as of genetic or of environmental origin. Pedigrees such as shown in Fig. 1, which depicts all the three members of a sibship

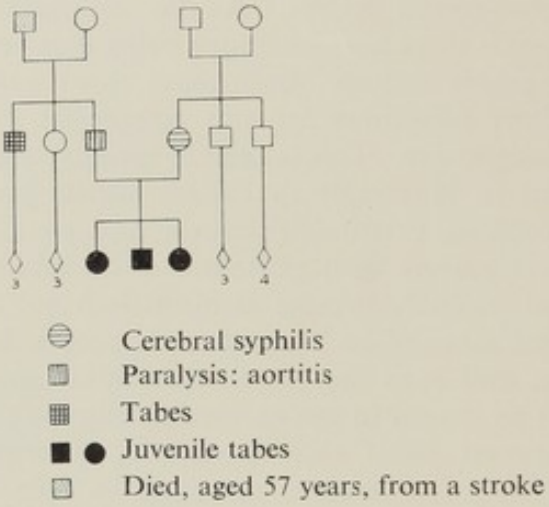
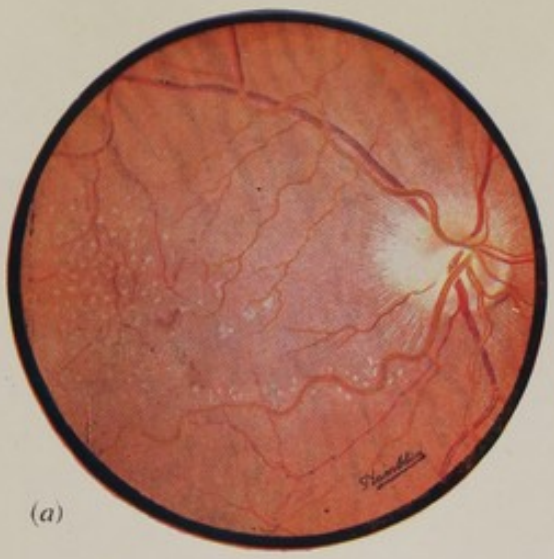


FIG. 1.—Occurrence of syphilis of central nervous system in a family. Pedigree. (*After F. Curtius and H. Schlotter* (1934). *Dtsch. Z. Nervenheilk.*, **134**, 44.) This pedigree illustrates the difficulty in incriminating an environmental or a genetic factor in a particular situation.

as suffering from juvenile tabes, and both their parents also affected with syphilis of the central nervous system, suggest a genetically determined susceptibility of the central nervous system to the pathogen of syphilis, or alternatively that these individuals harboured a spirochaete with a special affinity for the central nervous system. Both suppositions are speculative, but they emphasize the difficulty in ascribing a fully developed clinical condition to a definitely environmental or definitely genetic origin.

The same difficulty may be met in the course of an affection that has not yet run to its end stage. Plate I shows successive stages of a generalized fundus dystrophy that is dominant in character and sets in at about the age of 40 years. The earliest stage is indistinguishable from the fundus reactions seen in vascular or metabolic disturbances; it could be taken for an illustration of "neuroretinitis". At later stages appearances generally interpreted as the result of



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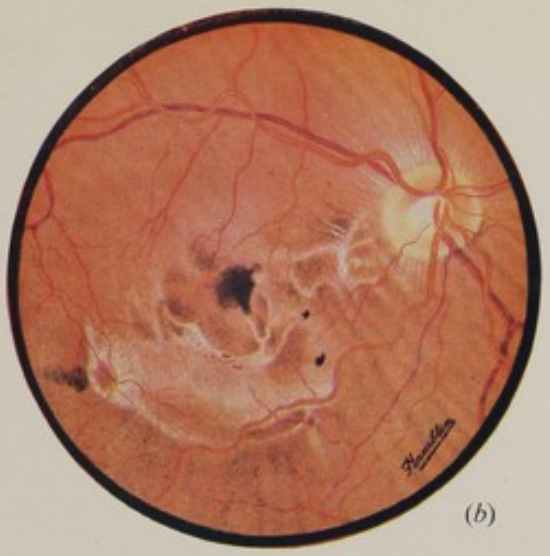

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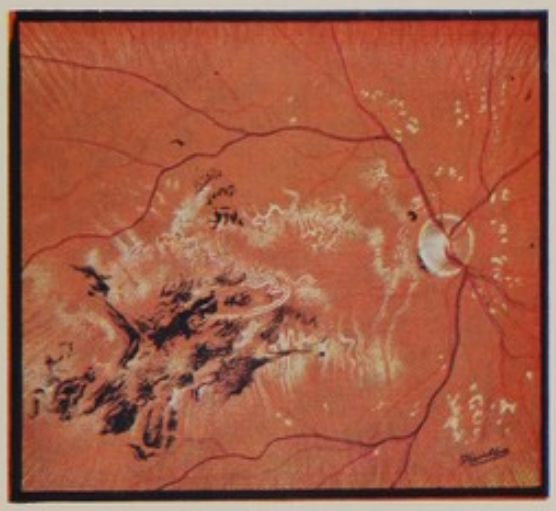

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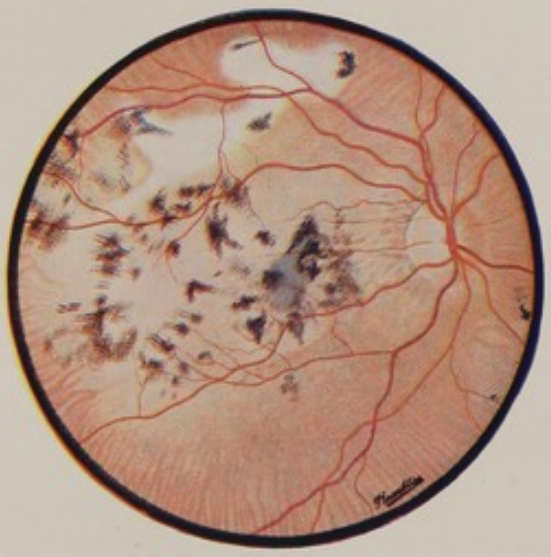

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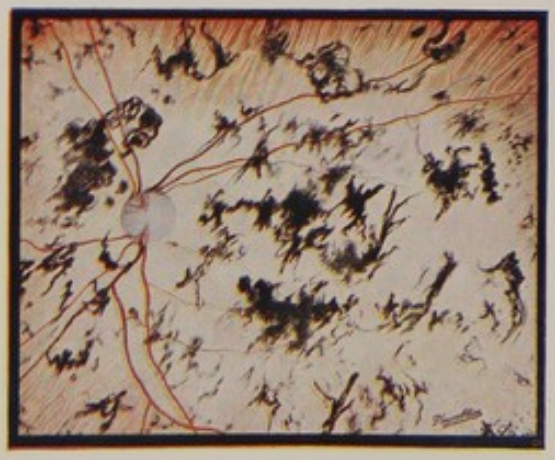

(*e*)

PLATE I

Generalized dominant fundus dystrophy. Range of ophthalmoscopic appearances as seen in one family. (*After A. Sorsby and M. E. Joll Mason (1949). Brit. J. Ophthal.*, **33**, 67.) (*a*) Earliest stage showing neuro-retinal oedema, haemorrhages and exudates in a patient aged 41 years. (*b*) The same eye 22 months later, showing scar formation. (*c*) Appearances in a cousin of the patient at the age of 68 years; patterned exudates, pigmentary reaction, and early choroidal sclerosis are all evident. (*d*) Appearances in an uncle at the age of 57 years. There is considerable atrophy. (*e*) Appearances in an aunt at the age of 77 years. There is extensive atrophy and considerable choroidal sclerosis, and some pigmentary disturbance. There is also a coincidental glaucomatous optic atrophy. These illustrations show that lesions generally ascribed to environmental factors occur in a clearly genetic affection.

[*To face p. 2*

inflammatory or infective reactions are evident, particularly emphasized by the pigmentary changes, and patches of atrophy. The end stage is again indistinguishable from an inflammatory reaction and is somewhat reminiscent of an unusual form of retinitis pigmentosa—a genetically determined affection.

The difficulties in assessing the causal factors in an incompletely developed affection become still more real in such genetic affections as may be expressed only partially, so that no clear picture emerges. Fragility of blood corpuscles may be all that is seen in one individual whilst another member of the family may show acholuric jaundice with enlarged spleen and liver, as shown in the pedigree in Fig. 2. This is discussed more fully in the next chapter, Figs. 3 and 4 of which give yet further examples.

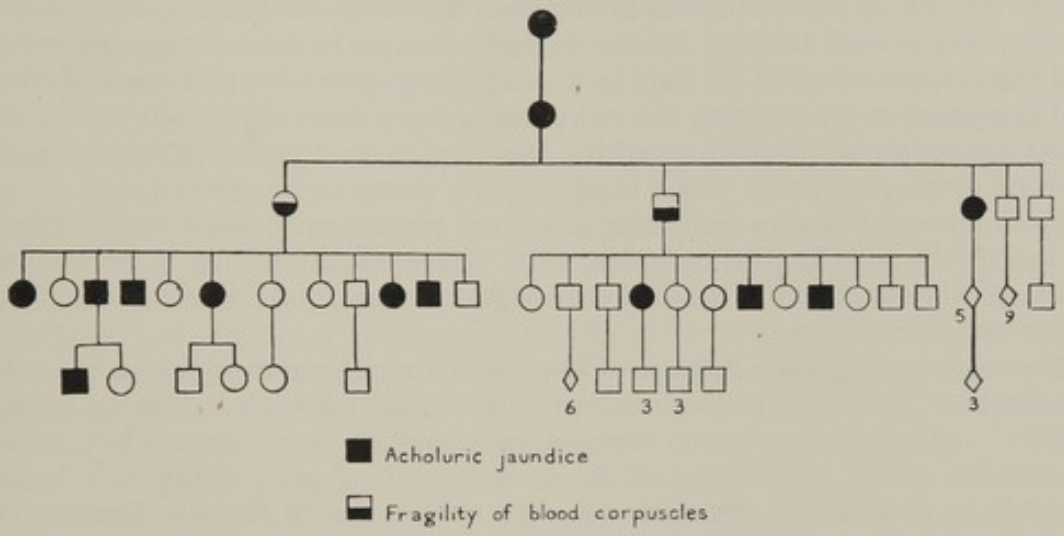

FIG. 2.—Acholuric jaundice. Dominant inheritance. (*After J. M. H. Campbell and E. C. Warner* (1926). *Quart. J. Med.*, **19**, 333.) Not all individuals are affected clinically. Some show only laboratory evidence of abnormal fragility of blood corpuscles, but their children can nevertheless be fully affected.

A TENTATIVE CLASSIFICATION

Any classification of the clinical varieties of genetic disease is therefore bound to be exceedingly tentative, for the manifestations of genetic disease impinge almost everywhere on those that are traditionally regarded as manifestations of disease of environmental origin. With these reservations the following classification has some value.

Congenital anomalies

Environmental factors.—There are clearly established environmental causes of congenital anomalies. The conception of intra-uterine infection favoured by the older clinicians is valid, but not in the extreme form which was previously held. Congenital syphilis, the classical example of intra-uterine infection, is one of the exceptions to the general rule that maternal infections are kept back by the placental barrier from reaching the embryo. The stage of development at which intra-uterine infection with syphilis occurs, and the severity of the infection, determine whether there results a miscarriage, a stillbirth, or a child born with

all the stigmata of congenital syphilis, or a child apparently normal at birth with the stigmata of congenital syphilis coming on only later in life. Likewise, German measles contracted by the mother in the first two months of pregnancy may lead to widespread congenital anomalies including microphthalmia, mental deficiency, deaf-mutism and congenital heart disease. Toxoplasmosis is yet another environmental factor that produces widespread congenital defects.

Apart from infection, prematurity—or rather the ill-understood causes of it—may result in serious congenital defect. The wide variety of congenital defects seen in the premature infant, kept alive by the fine methods developed in recent years, may arise from semi-lethal genes or semi-lethal environmental causes.

Experimentally, many abnormalities have been produced ranging from non-viable monstrosities to minimal anomalies. The non-mammalian embryo lends itself readily to such studies. Relatively slight changes in the temperature, oxygen, and salt concentration of the fluid in which the embryo grows give marked effects, and the younger the embryo, the more marked are these effects. It would seem that once the tissue is fully formed the effects of environmental factors are slight; it is the developing tissue which is particularly prone to be affected.

Environmental factors disturbing a normal process may therefore be infective as in syphilis, rubella and toxoplasmosis, " developmental " as in prematurity, or chemical as probably in some of the congenital anomalies for which no infective agent can be established.

The causation of genetic defects.—The clinical similarity of many of the congenital anomalies of genetic origin with those of environmental origin raises the question whether ultimately a common mechanism underlies both types. Only a fuller knowledge of the physiology of the embryo and of gene action will make it possible to answer such speculations. The wide range of clinical affections consequent on abnormalities in the metabolism of phenylalanine, shown in Fig. 64 on page 175, suggests that while the end result may be complex the fundamental processes are relatively simple.

Clinical considerations.—For the present all that can be done is to distinguish in extreme cases those anomalies that are clearly of environmental or of genetic origin. Many of the congenital anomalies do not definitely fall into one or other group. A genetic anomaly may be suspected if two or more children in a sibship show fundamentally similar lesions, and if in addition the family history supports the diagnosis. Frequently, however, the family history is negative or incomplete. On clinical appearances a lesion in an isolated case is more likely to be genetic rather than environmental in origin if there is a striking symmetry in bilateral organs and if inflammatory reactions are lacking. Symmetry is, however, not conclusive; in a family with anophthalmos there may be individuals with microphthalmia on one side and anything ranging from normalcy to anophthalmos on the other.

Abiotrophies

Abiotrophic lesions have not been studied to any extent in animal genetics. Abiotrophy is, however, an undoubted clinical phenomenon, as shown by the classical example of retinitis pigmentosa. Here the children are born apparently normal and retain normal vision until the onset of the genetically determined disturbance of the fundus. Abiotrophies affecting children and young adults

have been recognized for many years especially in neurology, ophthalmology and the metabolic diseases. It is only lately that there has been any clear appreciation of the fact that genetically determined anomalies may not become manifest until well in middle life, or even possibly in old age. The conception of abiotrophy implies not only hereditary transmission of a disease process, which is sometimes latent for many years, but also carries the implication that the hereditary disturbance becomes manifest in a tissue that had developed normally and had functioned normally for some years. Evidence that the tissue was in fact normal is unlikely to be available from human observations. An excised eye showing retinitis pigmentosa gives no information as to the state of the retina before the affection developed.

An increasing number of abiotrophic processes are being isolated, and many are proving to be of late—" pre-senile "—onset. Clinically, four features are generally ascribed to the abiotrophies:

Familial stamp.—Within the same family there is said to be a striking similarity in onset, clinical course, and appearances of the particular affection, such as say retinitis pigmentosa or Friedreich's ataxia. This is true to a large extent, but is no absolute rule. Affected members of a family share not only the same pathogenic gene, but to a large extent a similar total genetic constitution, and to a certain extent also a similar environment. These are all factors that tend to produce uniformity and similarity in clinical manifestations within a particular group, and help to explain variations as between different family groups. Individual variations within a group, however, do occur not infrequently, as different members do not, of course, have an identical total genetic constitution or environment. In assessing dissimilarity as between different members of a group, it must be borne in mind that the abiotrophies are generally progressive and strictly comparable stages are not frequently seen within a sibship.

Symmetry of the lesion in bilateral organs.—Symmetry as to site, general appearance and effects is frequently present in abiotrophic lesions. The bilateral onset of retinitis pigmentosa or macular dystrophy, and the parallel course in the two eyes are indeed characteristic aspects of these two and of other typical abiotrophies. Departures from this strict symmetry are, however, not uncommon, particularly as to onset and the early stages in some other abiotrophies. Sometimes, as in the dominant chorioretinal dystrophy setting in at about the age of 40 years, there may be an interval of several years between the onset of the affection in the two eyes, and even at a later stage the two eyes are not necessarily identical in appearance.

A characteristic reaction.—This has been especially stressed in the ocular abiotrophies. The pigment reaction in retinitis pigmentosa, the mottling in one form of macular dystrophy and the hard granular aspect of dominant corneal dystrophy are generally unmistakable. They are, however, unmistakably of the particular affection and not of abiotrophic lesions generally. To regard as abiotrophic only those appearances which satisfy the somewhat well defined lesions in the better recognized abiotrophies is to ignore the fact that such undoubted abiotrophies as Leber's disease, or the dominant chorioretinal affection with onset at about the age of 40 years, show features that are ophthalmoscopically indistinguishable from inflammatory or oedematous reactions. It is

true that frankly inflammatory reactions, such as vascularization of the cornea and vitreous opacities, are not commonly seen in the ocular dystrophies, but any suggestion that the abiotrophies have specific and characteristic reactions is an over-simplification and a diagnostic pitfall.

Anticipation.—Myotonia dystrophica in particular is frequently given as an example of anticipation—or the belief that in dominant abiotrophies the affection appears at successively earlier ages in the younger generations. There is little support for this view in well established and easily recognized abiotrophies, and it is likely that the concept of anticipation has emerged in the study of slowly evolving affections and that early cases are discovered incidentally as a result of a systematic study of affected families. It is true that occasionally an individual may be affected at an earlier age than his ancestors, but the opposite has also been observed.

Phakomatoses

The anomalies known as phakomatoses show features seen in both the congenital anomalies and the abiotrophies, the classical examples of which are neurofibromatosis, tuberose sclerosis, and the haemangiomatosis group. In the phakomatoses the lesion, as in the hereditary congenital anomalies and in the abiotrophies, is genetically determined. In contrast to the congenital anomalies there is no congenital defect, and in contrast to the abiotrophies the individual is not altogether normal at birth. Minor blemishes such as *café au lait* spots and moles are present on the skin, and these or similar hidden lesions burst into activity with growth or later in life. It is thus that neurofibromatosis develops as a widespread affection, or the signs of tuberose sclerosis become obvious. Sometimes phakomatoses, or rather a particular phakoma, may become malignant—a good example of the old theory of Cohnheim, which postulated development of cancer from congenital cell-nests. As yet only the more extreme forms of the phakomatoses have been recognized, and they are generally dominant. They are of interest not only as a link between the congenital anomalies and abiotrophies, but also as a link with the hereditary tumours.

Neoplasms

An outstanding example of hereditary tumours is presented by " glioma " of the retina. There is nothing to suggest that these retinoblastomas are malignant phakomas for there are no associated general conditions as in phakomatoses. Direct transmission of retinoblastoma over two generations has been observed repeatedly, and there is at least one authenticated example of transmission over three generations. Less definite evidence with other tumours is common experience.

Metabolic and endocrine disorders

Metabolic disorders roughly fall into the following categories:

Abnormal excretion products.—This group is the best known, and was clinically recognized long before the others. Alkaptonuria, cystinuria, porphyrinuria and steatorrhoea are classical examples. Here the abnormal metabolic products can be recovered from the urine or faeces early in infancy, or possibly at birth. In affections like diabetes mellitus and gout the onset is generally in adult life.

Abnormal metabolism producing somatic effects, but no abnormal excretion products.—Albinism is the classical example; urine, faeces and blood chemistry reveal no abnormality, but an abnormal intracellular metabolism has been demonstrated.

Abnormal blood and tissue chemistry.—The classical instances in this group are acholuric jaundice with its early or late onset, and the lipoid metabolic errors, some of which appear to be congenital, whilst others develop later in life. Considerable changes in blood chemistry and in the chemical constitution of different organs are present.

Unrecognized metabolic anomalies.—It is not unlikely that with further refinements in biochemical and biological techniques, many genetic anomalies will ultimately prove to have a metabolic basis, and that the structural defects by which they are now recognized will be seen as secondary features.

These different affections appear to be essentially genetic disorders. The significance of heredity in other metabolic disorders such as gout and lithiasis is still uncertain. As for the endocrine disorders, the outstanding example of significance of a genetic tendency is shown by hyperthyroidism.

Functional anomalies

The psychoneuroses and the hypertensive vascular diseases are presumably functional in origin and the significance of the heredity factor in these affections is still obscure. Two functional anomalies of the eye, colour-blindness and night-blindness, are generally genetic in character, though both anomalies may be seen as symptoms in ocular disease of environmental origin, illustrating once more the difficulty in assessing a sign or a symptom as exclusively of genetic or of environmental origin.

Syndromes

Syndromes—a clinical conception—emphasize the lack of precise knowledge on the nature of hereditary anomalies. It was a landmark in general medicine when the hypertrophied heart and the contracted kidney could be visualized as different aspects of the same underlying vascular disturbance. In the absence of the necessary knowledge by which the changes in the two organs could be correlated, Bright's disease might well have been regarded as a syndrome in modern terminology. In the present-day use, the term " syndrome " does not always carry a genetic implication, though there is an increasing tendency for the term to be limited in this sense. All the components of a syndrome need not necessarily appear at the same time. In the syndrome of macular coloboma and apical dystrophy of hands and feet both components are clearly congenital in nature. The syndrome of angioid streaks, pseudo-xanthoma elasticum and vascular hypertension, consists of components that become manifest in postnatal life. In the Laurence-Moon-Biedl syndrome some of the components, such as polydactyly, are clearly congenital, whilst others, such as the retinal lesion and obesity, might perhaps be regarded as abiotrophic. Some syndromes are, therefore, a combination of congenital anomalies, and others are essentially abiotrophic, whilst yet others are a mixture of both. The phakomatoses illustrate this further still, in so far as malignant changes may occur late in life on the basis of minimal congenital

anomalies. These considerations emphasize the tenuous nature of any attempt to sort out different varieties of genetic disease as fundamentally different entities. Until a clearer understanding of the mechanism of the gene is obtained, the clinical groupings employed currently serve a useful purpose in classification and description.

SCHEMATIC PRESENTATION

In general terms it may be said that there is strong presumptive evidence that some pathological processes are largely genetically determined, whilst in others disease is largely a matter of the interaction of genetic and environmental factors with variable stress on one or the other. Relatively few affections are entirely environmental in origin. Schematically this is represented in the following Table.

TABLE

SCHEMATIC REPRESENTATION OF THE SIGNIFICANCE OF HEREDITARY INFLUENCES IN PATHOLOGICAL DISTURBANCES

Affections mainly genetically determined	Affections resulting from the interaction of genetic and environmental factors	Affections mainly of environmental origin
Some congenital defects	Some congenital defects	
	Some infections	Some infections
Abiotrophies		
Phakomatoses		
Metabolic disorders		
Some endocrine disorders	Some endocrine disorders	
Some neoplasms		Some neoplasms
Some functional anomalies		Some functional anomalies
Some "senile degenerative" affections	Some "senile degenerative" affections	Traumatic lesions

CHAPTER 2

PENETRANCE AND EXPRESSION

LAURENCE H. SNYDER and PAUL R. DAVID

SPECIFICITY, PENETRANCE AND EXPRESSIVITY

CLINICIANS recognize that the same aetiological agent (the spirochaete of syphilis, for example) may produce any or several of a variety of effects. There are many familiar instances, also, of infections which are frankly pathological in some persons, and asymptomatic in others. Furthermore, it is a commonplace that any infectious disease may vary greatly in its severity from one case to another. Analogous phenomena are exhibited in the action of genetic factors. Variation in the kind of effect produced by the same gene or gene complex in different individuals has been designated as variability in *specificity* ; *penetrance* is a statistical concept and refers to the frequency with which a characteristic expression of a gene or genotype is manifested among those who possess the gene or genes in question or, sometimes, to the frequency with which any discernible effect at all is exhibited ; *expressivity* is the degree or severity of expression in a particular individual.

The italicized words were first used in these senses by Timoféeff-Ressovsky (1934) in his studies on *Drosophila funebris*. The term *specificity*, in Timoféeff's sense, has not been widely used by other investigators, but *penetrance* has achieved some currency in the literature of human genetics, and *expressivity* is occasionally used by authors in this field. More commonly, however, such phrases as " irregular expression " or " variable manifestation " are used, and it is usually clear from the context whether the variability referred to relates to type of manifestation (specificity), frequency of manifestation (penetrance), severity of manifestation (expressivity), or to any combination of these.

PENETRANCE

It is worth remarking at the onset that the terms under discussion, when used without qualification, may be subject to some ambiguity. Thus, if we use the expression " incomplete penetrance " to imply the occasional absence of *any* abnormal effect of a given gene or genotype, this must necessarily be understood in a provisional sense, because we can never be certain that we have exhausted all possibilities of detecting the presence of the gene.

Hereditary acholuric jaundice, for example, in most pedigrees appears to depend on the presence of an autosomal gene which is regularly manifested in heterozygotes by jaundice and splenomegaly and the occurrence of acute haemolytic crises which sometimes prove fatal. In a number of the pedigrees, however, the disease occasionally skips a generation, that is, it would appear that the gene has been transmitted from a grandparent who suffered from the disease, through a parent who himself shows none of the clinical signs, to one or more of his grandchildren in whom the disease reappears. Laboratory examination of the clinically

undiseased transmitters, however, has invariably revealed that they possess one or another of the haematological abnormalities, particularly hyperfragility of the erythrocytes, which characteristically are associated with the frank disease (Race, 1942). Consequently, so far as currently available data go, we may regard the gene as fully penetrant in heterozygotes (if we are considering any and all effects of its presence which are detectable) but as variable in expressivity ; alternatively we might refer to the gene as completely penetrant with respect to certain of its haematological effects, but incompletely penetrant in respect to its expression as frank disease.

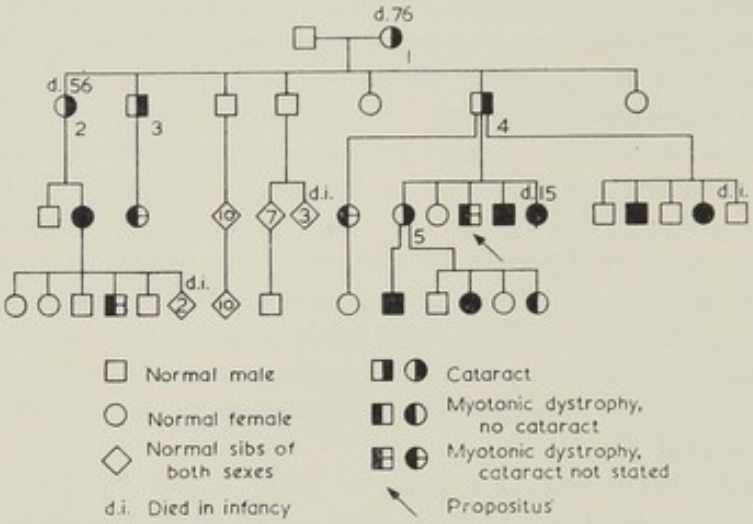

FIG. 3.—Pedigree of myotonic dystrophy. (*After Thomasen, E.* (1948). " Myotonia." *Opera ex Domo Biologiae hereditariae humanae Univ. Hafniensis*, **17**.)

The extent to which an evaluation of penetrance, unless qualified, depends on the acuity of examination may be further illustrated by reference to Fig. 3 which shows a fairly representative pedigree of myotonic dystrophy (Thomasen, 1948). Cataract is frequently found, and when it is not obvious, slit-lamp examination usually (though not always) reveals lenticular opacities of a rather characteristic type. Of the 47 patients examined by Thomasen with the slit-lamp, 6 had manifest cataract, and the characteristic slit-lamp opacities were seen in 35 more. In the pedigree shown here, there are 5 individuals without signs of myotonic dystrophy among whose progeny the disease nevertheless appears ; 3 of the 5 (1, 2 and 3 on the chart) exhibited manifest cataract, while in numbers 4 and 5 (aged 62 and 46 years respectively) cataractous changes in the lens were discovered only on slit-lamp examination.

From the numerous pedigrees of myotonic dystrophy recorded by Thomasen and by others, it is difficult to escape the conclusion that an autosomal gene is involved which is manifested as myotonia and dystrophy (with or without cataract) in about 60 per cent of the heterozygotes in whom it is present, and as cataract, without signs of neuromuscular disorder, in 20–40 per cent more.

" *Irregular dominance* "

Genes with effects which are sometimes, but not invariably, manifested in heterozygotes are often referred to as *irregularly dominant*, which is another way

of saying that they show incomplete penetrance in the heterozygous state. In human material, it is usually not known whether or not an irregularly dominant gene is completely penetrant when homozygous. In experimental animals, genes which are irregularly manifested in heterozygotes are often completely penetrant in homozygotes, but sometimes not. (Genes of this category are also sometimes called *conditional* dominants ; but as used by Levit (1936) and others, this term designates genes which in heterozygotes produce detectable effects, whether regularly or not, but whose homozygous expression is as yet unknown ; perhaps *provisional* dominant would have been a happier phrase. *Conditioned* dominance is used in experimental genetics to describe cases in which the expression of a gene in heterozygotes is modified by genetic modifiers.)

EXPRESSION

A consideration of phenomena relating to the variable expression of genetic factors is of especial relevance to medical genetics. Although there is a large number of conditions in man known to depend on the presence of single genes whose effects appear to be invariably pathological (either in heterozygous or homozygous state), these conditions are almost without exception either excessively rare or, at most, rather uncommon ; even in the aggregate, they account for only a minor portion of human disability. On current theories of evolution genetics, we should expect this to be the case, and conversely, we should expect that such genetic factors as are significant in the aetiology of the less rare diseases would commonly be characterized by irregular manifestation (for a valuable discussion of this point, *see* Roberts, 1940). In fact, evidence is rapidly accumulating that many diseases of wide distribution, both infectious and organic, are contingent upon the presence of genetic factors whose pathological effects are not manifested under all circumstances. The identification of these factors in particular diseases may be expected to assist in the discovery of the circumstances under which they are expressed, in the disentangling of predisposing, precipitating, and perpetuating causes, and in the elucidation of mechanisms of pathogenesis.

Modifying environmental factors

In experimental animals it has been found that the expression of many genes can be influenced by a variety of factors, both genetic (modifying genes, so called) and environmental. A majority of the investigations dealing with environmental factors affecting gene expression have made use of insects, especially in cases in which experimental treatment during developmental stages is involved, since such treatment is technically rather easier with them than in homoiotherm animals. There are, nevertheless, a number of instructive illustrations in mammals (and in birds) of the dependence of all aspects of gene expression (penetrance, expressivity, specificity) on conditions of the prenatal or postnatal environment.

Intra-uterine environment; maternal age

Alterations of the intra-uterine environment associated with age changes in the mother have been shown to have conspicuous effects on the manifestation of a variety of genotypes in mammals. The expressivity of some, but not all, genetic factors for white spotting in the guinea-pig, as measured by the extent of

unpigmented areas, increases moderately with increasing age of the mother. The penetrance of genetic factors predisposing to polydactyly, in the same animal, undergoes marked reduction with increasing maternal age ; in some genotypes, the incidence of the abnormality is five times as high among the progeny of mothers aged 3–6 months as it is in litters produced when they are a year older. The penetrance of hereditary hare-lip in the mouse also decreases with increasing maternal age. In man, no effect of maternal age on the incidence of hare-lip or cleft palate is discernible. On the other hand, in a series of 582 cases of severe congenital malformations of varied types, in some of which genetic factors are with little question aetiologically important, Murphy (1947) found convincing evidence for the significance of maternal age—severe malformations, in the aggregate, appear to be three or four times as common among births to mothers in their forties as they are two decades earlier ; specific types of malformation would doubtless reveal considerably greater differentials.

Mongoloid idiocy, for which there is some reason to suspect genetic predisposition as an aetiological factor, occurs among children born to mothers in their late forties with forty or fifty times the frequency found among children of mothers in their twenties (Penrose, 1949). In congenital pyloric stenosis, which may depend upon the presence of a single autosomal gene with about 20 per cent penetrance in homozygous condition (Cockayne and Penrose, 1943) the effects of maternal age may be in the opposite direction. The apparent excess of cases among first-born children has frequently been commented on and the reality of the excess has been established by Ford, Ross and Brown (1941). These observations are usually interpreted as indicating that conditions specifically associated with primogeniture are responsible for the relatively high incidence among first-born children ; but the data strongly suggest that there is a fairly consistent decline in frequency with increasing birth rank, so that the intra-uterine conditions favouring manifestation should perhaps be sought among those which change with maternal age (or with successive pregnancies) rather than in conditions peculiar to primogeniture.

Variations in temperature during developmental stages have been found to have conspicuous effects on the manifestation of several score of genes in *Drosophila*. It is unfortunate that there appear to have been no phenogenetic studies in mammals in which experimental alteration of maternal body temperature during pregnancy was attempted ; it has been shown experimentally, however, that the localized development of pigment (after birth) in the pelage of Himalayan (C^h/C^h) rabbits and in Siamese cats is temperature dependent. In poultry, Sturkie (1943) has studied the effects of temperature reduction in varying degree and at different times during incubation on the manifestation of a gene for polydactyly. Among control stocks, the gene was fully penetrant in homozygous condition, and about 94 per cent penetrant in heterozygotes ; with the most effective treatments, penetrance was roughly halved in the homozygotes, and in heterozygotes was reduced to only 4 per cent.

Nutrition

Effects of nutrition on gene expression have long been known. Yellow fat is formed in rabbits of genotype Y/Y, when xanthophyll is present in the diet ; feeding a diet free of xanthophyll suppresses this manifestation of the Y gene,

although *Y*/*Y* (and *Y*/*y*) rabbits can still be distinguished from those not possessing the *Y*-allele by the fact that there is no xanthophyllase in their livers. In poultry, the manifestation of a dominant gene for yellow shanks is similarly contingent upon the presence of carotinoid pigments in the food. A striking illustration of the effects of a dietary supplement on the expression of a gene-contingent pathological trait in a mammal is seen in the results of administering massive doses of vitamin A to mice homozygous for the *rhino* (hypotrichosis cystica) gene (Fraser, 1949). Untreated mice of this genotype, after shedding the first pelage, remain hairless throughout life ; there is marked hyperkeratosis of the hair follicles, and a progressive development of cysts in the follicles and in the sebaceous glands. Vitamin A treatment fails to restore the hair coat, and apparently it will not cause a regression of cysts that have already formed; but it does inhibit cyst development, so that old mice which have been treated from youth with the vitamin preserve a relatively normal skin. It is of interest to note that the rhino condition in mice has points of resemblance to human hyperkeratosis follicularis (Darier's disease), which appears in some families to be contingent on the presence of a single dominant gene, and which has been reported sometimes to respond favourably to vitamin A therapy. Conceivably, the *hyperkeratosis* gene may act by increasing the vitamin A demands of the affected epithelial tissues. (That individual differences in nutritional requirements can be genetically determined has been shown in experimental animals in numerous instances : in poultry, for example, with respect to riboflavine demands, by Lamoreux and Hutt (1948) ; and in rats, with respect to choline requirements, by Engel (1943).)

Infection

Genetic differences in respect to susceptibility to infection of course have obvious manifestations only when there is exposure to the appropriate infecting organism. Differences of this kind have been amply demonstrated in experimental animals (for review, *see* Gowen, 1948) and there is little doubt of their existence in man, for example in the case of tuberculosis (Kallmann and Reisner, 1943) or of diphtheria (Rosling, 1929). Analogously, genetic predisposition to allergic disease (Wiener, Zieve and Fries, 1936) requires contact with an appropriate allergen for full manifestation of the genes involved.

Hormone levels

Hormone levels in many cases conspicuously influence the expression of specific genotypes. In so far as the nature or quantity of the hormone concerned is itself determined by genes other than those responsible for the effect which the hormone modifies, such cases might formally be classed as illustrative of the effects of genetic modifiers (*see below*) ; but since hormone levels are rather generally subject to environmental modification, these cases also illustrate the effects of environmental agencies on gene expression. The most thoroughly studied example is pituitary dwarfism in the mouse. Mice homozygous for the *dw* gene fail to grow appreciably after the second or third week of life ; they remain sexually infantile, and are completely sterile. Histological examination reveals pathology of the anterior pituitary and abnormalities in other endocrine organs which are strikingly similar to those found in hypophysectomized rats. An almost complete clinical cure of these mice can be produced by the daily implantation

of fresh rat pituitaries over a period of several weeks. The treated animals resume growth, reaching a practically normal adult size; they mature sexually, and in at least one case a treated male has proven fertile; all of the endocrine abnormalities disappear except that of the anterior pituitary, which remains unaffected by the treatment (Francis, 1944, includes full literature review). The expression of the *yellow* gene in the mouse is also apparently subject to hormonal modification, although the nature of the effective hormonal factor has not been identified. Mice heterozygous for this gene (homozygotes are inviable), besides being yellow, have a subnormal basal metabolic rate and a tendency toward excessive obesity, often weighing, when adult, twice as much as their non-yellow litter mates. No histologic abnormalities of either thyroid or pituitary have been detected ; nevertheless, if a young yellow mouse is joined in parabiotic union with a normal mouse and cross-circulation becomes established, neither the yellow nor the normal member of the pair becomes obese ; pigmentation is unaffected (Weitze, 1940). A somewhat comparable effect of parabiosis with a genetically normal animal has been observed in cases of mice homozygous for the *jittery* gene (De Ome, 1945). Ordinarily these animals develop signs of muscular incoordination, of rapidly progressive severity, within about two weeks after birth. Slightly later they begin to exhibit convulsions, referred to as " tetany " by De Ome, although Grüneberg (1947) finds the description more suggestive of epileptic seizures. Growth ceases shortly after the onset of the seizures, which recur with progressively increasing frequency until terminal prostration ensues, followed shortly by death at a mean age of 31 days. A variety of treatments suggested by the symptomatology and pathology had no discernible effect. In jittery mice parabiosed with normal litter mates shortly after the appearance of first symptoms, however, growth continued at a normal rate, the convulsive seizures were entirely suppressed, and length of life was significantly prolonged, although only to an average age of 51·5 days ; in the meanwhile, the signs of muscular incoordination persisted.

Diabetes in man.—Accumulating evidence that diabetes mellitus in man generally develops on the basis of genetic predisposition (Harris, 1949, 1950) makes the affection a good illustration of the possibility of modifying genotype expression by hormone treatment ; in this instance the aetiological implication of other environmental influences is also very probable, as is suggested by the heterogeneity of incidence in different social classes, and by the frequently wide disparity of age of onset in identical twins. The familial occurrence of the rare abnormality, diabetes insipidus, is almost certainly attributable to the segration of a conditionally dominant gene with not quite complete penetrance (which, however, probably accounts for only a minority of non-familial cases), and posterior pituitary preparations are often effective in controlling the manifestation of the gene.

Phenocopies

Experimental observations

The examples of the effects of environmental factors on gene expression have involved particular genes or gene complexes which, when present in animals reared in environments within the normal range, result in phenotypic aberrations. Aberrations simulating the effects of known mutant genes, but produced by the

action of unusual or artificial environmental disturbances acting effectively (as a rule) on any of a wide variety of genotypes, are known as phenocopies. They represent effects of environmental variables on the expression of genetic factors ; in this case, the genotypes whose expression is modified may be " normal " genotypes, that is, those which are generally characteristic of the species. Since the initial experiments of Goldschmidt, phenocopies of nearly every known mutant type in *Drosophila* have been produced by temperature shocks, x-radiation, or other treatments during larval development. The type of phenocopy produced depends upon the stage of development treated, the nature of the treatment, its intensity and duration, and the genetic constitution of the treated animals (Goldschmidt, 1938).

In mice, phenocopies of several mutant-gene effects (pseudencephaly, flexed tail, hydrocephalus and others) have been produced in the offspring of females subjected to x-radiation at different stages of pregnancy by Kaven (1938) and by Russell (1950). Other workers (for references *see* Russell, 1950) have obtained comparable results with rats, using x-radiation, injections of nitrogen mustard and of trypan blue. Nutritional impairments during pregnancy have also been shown to result in the production of young with various abnormalities which resemble defects known to occur on a genetic basis in one mammal or another. O'Dell and Hogan (1950) found more than 20 per cent hydrocephalics among the young of female rats whose diet had been treated with a folic acid inhibitor; females of the same stock, on a diet without the inhibitor but otherwise identical, yielded only about one per cent hydrocephalic offspring. The extensive studies of Warkany and his collaborators (reviewed in Warkany, 1947) are especially noteworthy; they have experimented with a number of differently deficient maternal diets, and have found that each results in a characteristic type of abnormality in a large proportion of the progeny. In poultry, several investigators have produced phenocopies, chiefly of micromelic and rumpless mutants, by deficiencies in maternal nutrition or by injection of various chemicals into the yolk sacs of the developing embryos themselves. Of particular interest among experiments using the latter technique are those in which injection of one substance (insulin, for example, or sulphanilamide) had teratogenic effects which were suppressed if another chemical (nicotinamide) was injected into the same eggs (Landauer, 1948; Ackermann and Taylor, 1948; Zwilling and DeBell, 1950). Just as there is some reason to suspect that the incidence of congenital malformations in man might be somewhat reduced by greater attention to the adequacy of maternal diet (*see* Murphy, 1947), it is conceivable that investigations of this kind may ultimately point the way to more radical methods of normalizing the expression of genetic factors which ordinarily lead to pathological development.

Clinical observations

There is little doubt of the occurrence of phenocopies in man. Pathological conditions for which genetic factors appear in some cases to have major aetiological significance may in other cases be induced by specific environmental conditions, or may result from developmental accidents, largely without regard to genotype. Numerous pedigrees are on record, for example, which make it fairly evident that congenital cataract, of one type or another, may result from the presence of any one of several genes which are fully penetrant, or very nearly so, in heterozygous condition (Harman, 1912 ; Lutman and Neel, 1945) ; there is also evidence for the existence of regularly recessive transmission in some cases. Extensive data indicate that a large proportion of cases of deaf-mutism are contingent on the presence of a gene (perhaps again, any one of several genes) which is regularly

manifested in homozygotes (Lindenov, 1945 ; Hopkins and Guilder, 1949). Yet, as appears from the observations of Gregg (1941), and of others since, either or both of these abnormalities may be found in children who do not possess any of the genes referred to, as a consequence of rubella infection of their mothers in the first trimester of pregnancy. Similarly, while it is probable that familial microcephaly is often referable to an autosomal gene with complete or approximately complete penetrance in homozygous condition (Penrose, 1949), Murphy's observations suggest that pelvic irradiation during early pregnancy can also produce this malformation in the offspring. The data of Bartels (1941) on thyroid disease indicate the likelihood that simple goitre, in non-endemic areas, is commonly dependent on the presence of a recessive autosomal gene which exhibits very low penetrance (about 1 per cent) in male homozygotes, but is manifested as simple goitre in about one-third of women who are homozygous for it, and as Graves' disease in roughly another one-third, while the remainder are apparently unaffected. Clinically indistinguishable goitre, as is well known, may result from iodine-deficient diet, and in regions of high endemicity, as Eugster's (1936) twin studies show, individuals succumb to the disease apparently irrespective of genotype, although genetic factors may influence its severity and other characteristics. Pernicious anaemia, there is reason to suspect, may develop only on the basis of a specific genotype in the majority of cases, but most of its characteristic features can be induced, apparently in persons of any genotype, through diet lacking in Castle's " extrinsic factor ", or as a secondary effect of sprue, for example.

The total genic constitution

The preceding discussion should give some idea of the varied and far-reaching ways in which environmental factors may influence genic expression. It is important not to overlook the fact, however, that even in a fixed environment, the expression of almost any gene (to some extent, quite likely, of every gene) is influenced by the nature of genes present at other loci.

Evidence of the foot and eye anomaly in the mouse (*Little and Bagg*)

A classic illustration of the extent to which the effects of a single gene can vary under the influence of other genetic factors in the organism is provided by the foot and head abnormalities in the house mouse, originally described by Little and Bagg. They discovered that any or several of a variety of morphological aberrations including varying degrees of agenesis or atrophy of the eyes and associated structures, malformations of the feet (club foot, syndactyly, hypodactyly, polydactyly), and defective development in other areas, could result from the presence in homozygous condition of a single recessive gene. In some animals homozygous for the gene (*my*/*my*) eye defects alone are present; in others, the eye defects are accompanied by anomalies of the forelimbs, or of the hind limbs, or of both. Rather rarely, defects of the forelimbs are found without discernible abnormality of the eyes.

In addition to the variability in the type and location of defect in the abnormal mice, there is great variability in the severity with which any given organ or region is affected in different mice. The effects manifested in the eye and its associated structures, for example, range from a minimal defect of the lids alone (such that they merely fail to cover the eye completely) through complete absence of the lids to the extreme cases in which the lids are absent and in addition the eyeball itself is markedly atrophic and the optic tract reduced or lacking.

Finally, in the original Little and Bagg stocks, matings in which each parent exhibited

one or more of the anomalies yielded progeny of which about only 80 per cent showed any of the defects in question, while about 20 per cent were without visible abnormality. In all cases in which the phenotypically normal progeny were genetically tested, they proved to be homozygous for the gene responsible for the defects in their parents. We might say, therefore, that the penetrance of the gene in homozygous condition was approximately 80 per cent in this material, if we consider obvious manifestations of all kinds. On the other hand, eye defects (without abnormalities of the limbs) were much commoner in the homozygotes than limb abnormalities; that is, we could say that the penetrance of the gene in respect to the development of eye defects was higher than in respect to the effects on the limbs.

In later studies of the Little and Bagg anomalies, it was found possible to obtain, by selective breeding, inbred strains of *my/my* mice which differed conspicuously in the distribution and frequency of the obvious defects. In one selected line, for example, nearly 90 per cent of the animals had abnormalities of both the anterior limbs and the eyes; in another, the eyes were affected in about 90 per cent of the individuals, the limbs in fewer than one per cent; in a third strain the incidences of both eye and limb abnormalities were reduced to below one per cent. Thus, it is evident that an appreciable part of the variability in the manifestation of the *my/my* genotype must be attributed to the action of modifying genes, that is, of genes other than the one on which the development of the anomalies is primarily contingent.

Innumerable other illustrations of the effects of genetic modifiers on the specificity, expressivity, and penetrance of a particular gene could be cited, among which the studies of Timoféeff-Ressovsky, (1934) on the expression of the *vti/vti* genotype in *Drosophila* are perhaps the most detailed. But the present illustration in mice is particularly instructive because embryological investigations (*see* especially Bonnevie, 1934) have at least partly revealed the mode of action of the manifestation modifiers, as well as of the main gene involved.

During the embryogeny of normal mice, a quantity of cerebrospinal fluid is expelled from the fourth ventricle through a temporary opening (the foramen anterius) in the roof of the myelencephalon; it accumulates briefly under the epidermis in the concavity of the neck region, where it is soon absorbed. In *my/my* mice there is an excessive accumulation of this fluid (whether because of accelerated production or defective absorption is not known). The excessive fluid becomes displaced, perhaps through pressures imposed by the elasticity of the overlying epidermis, and tends to follow the course of concavities in the body surface, spreading along the dorsal surface of the head and body toward the eyes and nose on the one hand, and toward the extremities or tail on the other. The moving fluid appears to do no harm, but wherever it finally settles it forms a small bleb or blister, the pressure of which causes haemorrhagic lesions and local disturbances of development. Hence, if fluid comes to rest in the groove over the snout and around the eyes, abnormalities of the nose and eyes result. Blebs on the dorsal surface of the foot produce syndactyly with dorsal flexion; on the ventral surface, syndactyly with ventral flexion. Distal blebs on the extremities are responsible for hypodactyly; polydactyly is apparently due to minute peripheral blebs on the feet, and so on.

It is obvious that the localization of the blebs must depend to some extent on what might be called the surface modelling of the embryo at the time of bleb formation, and it appears from Bonnevie's findings that the genes which modify the expression of *my/my* in the various strains may do this through their effects on the surface modelling. Thus the occurrence of forefoot and shoulder abnormalities is associated with the presence of a large saddle-like bleb covering the shoulder region. The settling of fluid here would clearly be favoured by the presence of a concavity in this area. It was in fact found that in strains characterized by a high incidence of shoulder and forelimb abnormalities there was a large preponderance of embryos with concave profiles in the shoulder region at

the period during which the blebs become localized (reflecting actually precocious development of the shoulder concavity), while the converse was true in strains in which shoulder and forelimb anomalies were less common.

It is worth noting parenthetically that Ullrich (1949) has characterized a human syndrome involving unilateral defects of the pectoralis muscle and atrophy of the overlying skin and its appendages, together with which are frequently found major defects in the cranial nerve region, deformities of the hand, abnormalities of the ocular adnexa, and other peculiarities. From the association of defects observed in various cases, Ullrich concludes that the mechanism of pathogenesis is essentially the same as that described for the assortment of anomalies in the *my/my* mice, that is, that the defects result from the localization of blebs containing fluid of myelencephalic origin. This of course does not imply that genetic factors are necessarily of aetiological significance for the human analogues of the Little and Bagg mouse anomalies, as Ullrich is careful to point out. Indeed, it cannot be too frequently nor too strongly emphasized for students of medical genetics, that the very same disturbances in developmental processes which are initiated by genetic factors in the case of pathological conditions in which heredity is of primary aetiological significance can also be produced in other instances by environmental interference or by non-genetic accidents during embryogeny.

Evidence of otocephalus in the guinea-pig (Wright, 1934)

The foot and eye anomalies in mice which we have discussed above represent a variable syndrome of defects resulting from the presence of a single major gene in homozygous condition, variously manifested in different strains under the influence of genetic modifiers which are probably multifactorial. Somewhat the converse of this situation is seen in the series of otocephalic monsters in guinea-pigs studied by Wright (1934). The otocephalic condition in these animals ranges in severity from varying degrees of reduction of the mandible with ventral approach, and, ultimately, fusion of the ears, through complete absence of the lower jaw (associated with reduction of the upper jaw and with cyclopia), to types which are almost completely headless. In spite of the diversity in superficial appearance of the various types, Wright presents convincing arguments for regarding the whole series of malformations as constituting a single nosologic entity (Wright and Wagner, 1934). Except in the high-incidence strain which Wright studied, otocephalic monsters of various grades occur sporadically in guinea-pigs with an incidence of about 0·05 per cent. In the high-incidence strain, comprising more than 6,000 individuals, all descended from a single mating made in 1906, the over-all frequency of the monsters was 4·3 per cent. Within this strain, however, three major groups of substrains, derived through exclusively brother–sister matings for from 13 to 19 generations, became significantly differentiated from one another in respect to the incidence of otocephaly; the frequencies of otocephalics in these subdivisions of the high-incidence strain were about 1·5 per cent, 5 per cent, and 28 per cent respectively. Analysis of the history and breeding data of the substrains indicates (1) that the members of the groups of substrains characterized by the 5 per cent and 28 per cent frequencies all possessed in common an identical complex of genes in homozygous condition which differentiated them from stocks in which otocephaly was non-existent or rare, while (2) the difference between these two groups was contingent upon a single semi-dominant modifying-gene which increases the likelihood of otocephalic development from 5 per cent to about 20 per cent when heterozygous and to a considerably higher value when homozygous; the modifier probably does not increase the risk of otocephaly except when the gene complex referred to under (1) is present.

Clinical implications

It would be easy to cite from laboratory materials many other examples of

pathological conditions contingent upon the presence of a single gene or gene complex whose expression may be altered by a modifying gene or by polygenic modifiers. In respect to its relevance for problems of pathological heredity in man, the phenomenon is of more than academic interest. Thus, we may encounter a disease or syndrome which appears to depend on single-gene determination, but which varies conspicuously from case to case in severity or form. It is then desirable to know whether the different forms of the disease are all referable to the same " main " gene, the expression of which varies from one case to another under the action of different genetic modifiers, or whether different main genes with similar but not identical effects are involved. The potentially practical importance of the distinction rests upon the fact that different major genes often produce similar phenotypes through diverse developmental pathways. The mechanisms of development of dominant and recessive rumplessness in poultry, for example, have been shown to be quite different, and the same is true in mice for dominant and recessive hairlessness, and for several superficially similar but genetically different types of taillessness.

We would reasonably expect that the same preventive or therapeutic treatment might to some degree be effective for all variant forms of a pathological condition if they were all expressions of the same gene acting, in different cases, under the influence of different modifiers. We need not expect this if the variant cases are contingent upon different genes. There are, in fact, numerous instances in experimental animals of the differential responses of different genotypes which have similar phenotypic expressions.

There is, for example, in *Drosophila*, an autosomal recessive gene, *abnormal abdomen*, which produces defects of varying degree in the chitinization of abdominal skeletal structures in a portion of flies homozygous for it. Homozygotes which develop in a fresh, moist culture medium are predominantly of normal phenotype, and the 20 per cent or so in which the abnormality can be detected exhibit it in very mild degree; as the culture medium becomes old and dry, both penetrance and expressivity increase, until 100 per cent of the developing homozygotes exhibit the defect, all in severe degree. An entirely different gene, a sex-linked dominant, produces the same type of abdominal defects, but in this case penetrance and expressivity are *decreased* by the drying out of the culture medium. Other well known genetic factors in *Drosophila* resulting in phenotypes designated as *Bar* and *Infrabar*, respectively, reduce the size of the eyes. Each is fully penetrant, that is, all flies of either genotype exhibit an appreciable reduction in eye size. Expressivity is rather variable, however, and in each case it is conspicuously affected by the temperature at which the flies develop. For *Bar* flies, the higher the temperature during development, the greater is the reduction in size of eye, while the reverse is true for flies of *Infrabar* genotype. Also in *Drosophila*, an almost identical effect on eye colour is produced by any of several genes (vermilion, scarlet, cardinal, and so on) in homozygous condition. These genes are known to be at different loci, and it is also known that the vermilion gene differs from the others in respect to the process by which the defective eye pigmentation is produced; as a corollary of this fact, it has been found that injection of kynurenin into the larvae of vermilion flies results in the development of normal eye colour, whereas the same treatment is ineffective for scarlet or cardinal flies. It is conceivable that genetic heterogeneity associated with different patterns of pathogenesis may account for the fact that in human chronic thrombocytopenic purpura, splenectomy is spectacularly effective for some cases and without effect for others.

In laboratory animals, it is obviously rather easy to determine whether variant forms of an hereditary abnormality are attributable to modifiers affecting the expressivity of a single gene, or to the existence of more than one main gene. In human material the problem is also simple if the patterns of hereditary transmission are clearly different. Thus, marked differences in age of onset and in rate of progress are seen in cases of progressive muscular dystrophy, depending on whether they are found in pedigrees which indicate dominant, autosomal recessive or sex-linked recessive transmission ; the same is true for retinitis pigmentosa, peroneal atrophy, and a number of other diseases. When differences in clinical type, age of onset, or severity are not associated with obvious differences in pattern of heredity, the problem of determining whether modifiers of a single principal gene or different main genes are responsible is likely to be more difficult. In general, if the variability in expression is conspicuously less among affected sibs than it is among affected members of different sibships, we have strong evidence that different main genes are involved.

In amaurotic idiocy, for example, the familial incidence and the frequency of parental consanguinity are both consistent with dependence on a fully penetrant, single recessive gene. The onset of some cases is during the first year of life ; in others, it ranges from age 4 to 11 years. But when several cases occur in a sibship, it is invariably found either that they all have had their onset before age 1 year, or that the onset had been after age 3 years in all cases. In this instance, there could be little doubt of the existence of different principal genes for the infantile and juvenile forms of the disease, even if no clinical differentiation were possible. Not all situations in which different major genes exhibit similar pathological expression can be expected to permit as clear-cut a differentiation as this, of course. Nevertheless, when different principal genes rather than modifiers of a single main gene are responsible for an appreciable part of the variability in some quantitative characteristic of a disease that appears to constitute a clinical entity, their existence may be demonstrable by quantitative methods.

As Haldane (1941) has pointed out, the segregation of modifiers can result in a correlation between sibs in respect to age of onset, or other quantitative features of the disease of as much as 0·5, but cannot yield a coefficient of correlation significantly above this value. Hence, if the correlation between sibs is found to be significantly in excess of 0·5, there is strong presumptive evidence for the implication of different major genes in different families. The same principle holds, in the case of dominant genes, for parent–child correlations. On this basis Haldane tentatively infers that dominantly transmitted peroneal atrophy is genetically heterogeneous, that is, that there are at least two different major genes behaving as dominants, either of which can produce peroneal atrophy; whether they are mutually allelic, or occupy different loci, cannot be stated. Haldane finds similar evidence of genetic heterogeneity in recessive peroneal atrophy, dominant glaucoma, and for both dominant and recessive types of Friedreich's ataxia, spastic ataxia, and spastic paraplegia. Data which yield correlations between sibs, for age of onset, in the neighbourhood of 0·5 or below (Huntington's chorea, optic atrophy) are less readily interpreted. Such low correlations would be obtained if the same major gene is responsible for all cases of the disease under consideration. But even if several different major genes are operative, the relatively high correlations they would be expected to produce in the absence of disturbing factors may be obscured by the effects of intrafamilial environmental variability. Consequently, while high correlations in age of onset

and so on speak strongly for an hypothesis that more than one principal gene is involved, moderate or negligible correlations do not necessarily exclude this hypothesis.

Genetic and non-genetic factors

The detection of genotypic heterogeneity through simultaneous attention to clinical variability and familial distribution is well illustrated by Fogh-Andersen (1943), in his study of hare-lip and cleft palate. As is well known, either of these anomalies may occur separately, or, about as frequently, both may be found in the same individual. Formerly, it was usual to regard isolated hare-lip and isolated cleft palate, respectively, as partial manifestations of a developmental arrest which, when more severely effective, produced both defects together ; and most genetic studies have proceeded on the assumption of a common genetic basis for hare-lip, cleft palate, and for the combination of the two. Fogh-Andersen's analysis shows, however, that among sibs and other relatives of persons with either hare-lip or hare-lip and cleft palate, both of these phenotypes occur with frequencies significantly in excess of their incidence in the general population ; on the other hand, isolated cleft palate is found among these relatives no more frequently than in the population at large. Conversely, there is an excessive incidence of isolated cleft palate among relatives of individuals with isolated cleft palate ; but in this group, neither hare-lip alone nor hare-lip in combination with cleft palate occurs more often than would be expected on the basis of their respective population frequencies. It appears, therefore, that hare-lip alone and hare-lip with cleft palate in many or most cases may be referable to the same main gene, but that isolated cleft palate is genetically distinct. The distinction is further reflected in the fact that familial incidence (that is, frequency of the defect among sibs of affected persons) is higher for hare-lip, with or without cleft palate, than for isolated cleft palate. It is quite possible that not even all cases of hare-lip with or without cleft palate are contingent upon the same principal gene. Indeed, it is plausible to assume that some may be phenocopies, produced through developmental accident without regard to genotype. Nevertheless, data on familial distribution, population frequency, and twin concordance are all reasonably consistent with an hypothesis that a single main gene is a predisposing cause in a preponderant majority of the cases ; and that both penetrance (which may be in the neighbourhood of 10 per cent) and expressivity are at least in part influenced by non-genetic factors. It is clear, too, that penetrance is conspicuously influenced by the sex of the developing foetus, and it is of interest to note that the effects of sex on penetrance in the case of hare-lip with or without cleft palate and of isolated cleft palate, respectively, are in opposite directions : hare-lip, and hare-lip with cleft palate, are manifested about twice as frequently in males as in females, while the converse is true for isolated cleft palate, an observation which affords additional basis for their differentiation. In neither case do we have any evidence to indicate whether the effect of sex on penetrance is intermediated through hormones or is in some other way a consequence of the different sex-chromosome : autosome ratio in the two sexes.

PENETRANCE AND EXPRESSION IN RELATION TO DIAGNOSIS

Establishment (or disproof) of the significant implication of genetic factors in the aetiology of a disease, identification of hereditary mechanisms (patterns of

transmission), and differentiation among genetically different categories when they exist, are of course only first steps toward the application of genetics to medical science. That even these first steps may have some immediate utility has been pointed out by numerous authors (Snyder, 1946, 1947 ; Sorsby, 1950 ; Neel, 1951). In many instances they make it possible to predict the risk that a disease or abnormality existing in one member (or more) of a family will develop in another member or in a prospective child (genetic prognosis) ; diagnosis of a disease in its incipient stages may be facilitated, and on occasion its further development may be forestalled ; and applications in the field of preventive medicine can already be envisaged (Burks, 1943). The contributions to medicine which further studies in human genetics can make extend, however, considerably beyond those just indicated, and in this connexion consideration of the phenomena of incomplete penetrance and variable expression are particularly pertinent.

Consideration of penetrance and expression lead to the conclusion that the presence of genetic factors which are incompletely penetrant with respect to frankly pathological expression may nevertheless be detectable through careful

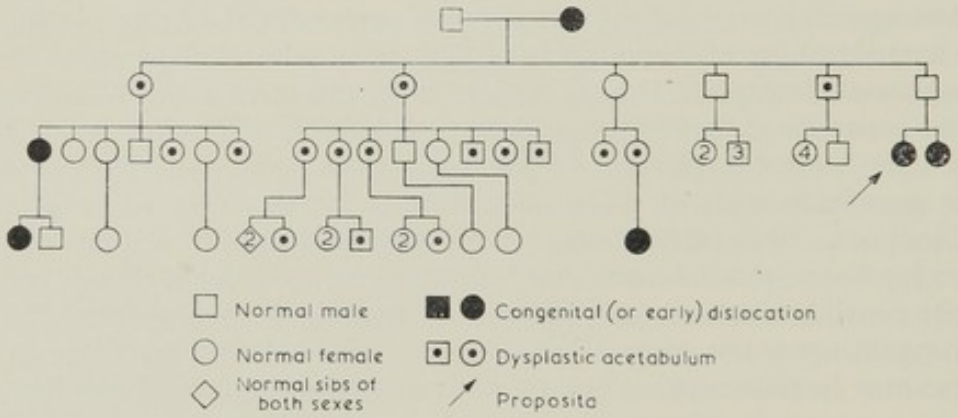

FIG. 4.—Part of a pedigree of congenital dislocation of the hip. All individuals shown were radiologically examined. The original pedigree includes spouses of all persons shown here as having progeny; in each instance, the spouse was normal. (*After Faber, A. (1937). Z. Orthop.*, **66**, 140.)

clinical and laboratory examination in most or all of the superficially normal persons who possess them. The point may be additionally illustrated by reference to Fig. 4 which shows part of a rather typical pedigree of congenital dislocation of the hip. In this pedigree, as in a majority of other unselected pedigrees of the same condition, the distribution of the clinically affected individuals (solid black symbols) affords ground for little more than a suspicion of a genetic basis for the disability, but radiological examinations of the cognates of affected individuals (Faber, 1937, 1938) have revealed the widespread occurrence of a dysplasia of the acetabulum (symbols with black dots) reflected anatomically in its being shallower or flatter than in the normal hip. The distribution of the dysplasia strongly suggests that it is contingent on the presence of a single autosomal gene which is manifested as congenital or early dislocation of the hip in only a fraction (possibly 10 per cent) of the heterozygotes who carry it ; in another fraction, according to

Faber, the anatomical abnormality associated with the dysplasia may lead to disability later in life. The dysplasia itself, however, as the pedigree suggests, is manifested in a very much larger proportion of those who inherit the gene, and conceivably it may exist in all of them to a degree not always apparent on radiological examination.

Whether the interpretation of these observations on congenital hip is correct or not, it is obvious that the discovery of subclinical effects, with high manifestation frequency, for genes which exhibit low penetrance in respect to frankly pathological expression, will in general greatly facilitate genetic analysis. Moreover, they are likely to be of great importance in early diagnosis. We have already indicated that any genetic factors which are of aetiological significance for relatively common diseases are likely to exhibit sharply reduced penetrance with respect to the manifestation of severely pathological effects. On the other hand, as Roberts (1940) points out, if a gene has multiple effects, which indeed seems to be the rule rather than the exception, its less conspicuous manifestations tend to be more regularly expressed. The more regularly expressed effects may represent abortive or precursory stages in the development of the less frequently manifested frank disease (as appears to be the case in the hip dysplasia mentioned above), or constitutional signs of predisposition to the disease, or both. In any event, it seems reasonable to expect that their discovery should ultimately shed light, in many instances, on early phases in the processes of pathogenesis, the nature of which may well have become obscured through subsequent events in patients in whom the disease is fully developed.

It is only in rather recent years that investigations oriented by recognition of the principles just indicated have been undertaken ; they have usually been on a small scale, and many of them have failed to make full use of the co-operation of clinician and geneticist that appears to be desirable for the most effective planning of such research as well as for the interpretation of results. Consequently, it is hardly surprising that we cannot point out examples of spectacular solutions of medical problems that have been accomplished through this type of approach. Nevertheless, results have been obtained in a number of studies, discussed more fully elsewhere in this volume, which we think are highly suggestive of its potential fruitfulness.

In several instances, the discovery of what may be regarded as precursory abnormalities in the cognates of diseased individuals has perhaps done no more than afford support to ideas of pathogenesis that had previously been arrived at without benefit of genetically oriented methodology. This would be true, for example, of the finding of abnormally elevated serum uric acid levels in relatives of patients with gout, or of the significantly high frequency of precocious hypochlorhydria and achlorhydria among cognates of patients with pernicious anaemia ; or of the prevalence of abnormal glucose-tolerance curves in the relatives of diabetics (for references, *see* Neel, 1947 ; also Smyth, Cotterman and Freyberg, 1948 ; Stecher, Hersh and Solomon, 1949). Nevertheless, each of these observations suggests the possibility, through further studies along the same lines, of identifying still earlier stages in the development of the diseases in question, and (in the case of diabetes) of securing evidence pertinent to the hypothesis that forms of the disease which appear to be clinically differentiable (*see* Lawrence,

1951 ; Lister, Nash and Ledingham, 1951) may in fact differ in respect to the primary steps of their pathogenesis.

On the other hand, the possible relationship between hypercholesterolaemia and coronary (or other) atherosclerosis has been a rather controversial question. Boas, Parets and Adlersberg (1948) found that about half of the sibs of 50 cases of coronary artery disease beginning before the age of 50 years (unselected, except for the exclusion of patients known to be members of xanthomatous families) had abnormally high levels of serum cholesterol (*see* Stecher and Hersh, 1949). In another study (Adlersberg, Parets and Boas, 1949) the propositi, most of whom came to the investigators' attention because of cardiac complaints, were patients who exhibited one or more of the signs of xanthomatosis. Of 89 tested parents, sibs and children of these cases, 55 were hypercholesterolaemic, and among the 39 male relatives above 35 years of age who showed elevated serum cholesterol, there were 8 cases of coronary artery disease. These data, especially in respect to the occurrence of coronary disease among the hypercholesterolaemics, where the number sampled was too small to permit us to accept the rate as significantly high, must be considered as suggestive rather than conclusive, but as far as they go they tend to confirm the suspicion of an intimate relationship between cholesterol metabolism and coronary artery disease, and they point toward new ways of exploring the nature of this relationship.

Electroencephalographic abnormalities in clinically normal relatives of epileptics and, more recently, of victims of Huntington's chorea (Löwenbach, 1939 ; Lennox, Gibbs and Gibbs, 1940 ; Patterson, Bagchi and Test, 1948) are also of interest. In the case of epilepsy, it has been generally recognized that we are probably dealing with an aetiologically heterogeneous group of conditions. The electroencephalographic studies of epileptics and of their non-epileptic relatives have indicated a possible means of resolving some of the heterogeneity. They also suggest the possibility of identifying genetic predisposition to epilepsy, under some circumstances, in non-epileptic relatives of epileptic patients. Whether or not these studies lead to the discovery of hitherto unsuspected factors in the environment which can precipitate the disease in some persons, it seems almost certain that they must eventually contribute to clarifying the physiological mechanisms which underlie the development of epileptic symptoms.

GENETICS AND CONSTITUTIONAL MEDICINE

It should be apparent from the preceding discussion that consideration of phenomena of variable gene expression and penetrance in relation to medical genetics suggests a viewpoint and a methodology which bear some resemblance to those of so-called constitutional pathology. In fact, the point of departure is essentially the same, namely, the presumption that there is such a thing as organic predisposition to disease, and that there are individual differences, in part genetically determined, in the degree of predisposition to specific ailments. But the investigative approach suggested by an appreciation of genetic principles is somewhat broader than that which has characterized such constitutional studies as have restricted their field of inquiry to the diseased patient. It would be guided by the thesis that if there are constitutional peculiarities, anatomical or functional, which reflect

predisposition toward the development of a given pathological state, the most favourable opportunity for discovering them will be provided by systematic examination of the undiseased immediate relatives of affected individuals. The principle involved is thus an extension of constitutional study to the family group. Constitutional investigations in the narrower sense, that is, those restricted to the diseased individuals themselves, may be helpful to the extent of revealing presumptive constitutional correlates of the disease. But they afford no means of determining whether such correlates are constitutional in the genetic sense, or reflect the operation of extrinsic factors ; moreover, they do not permit discrimination between aberrations which are antecedent to the disease and those which are consequent upon it. Obviously, attempts at formal genetic analysis which employ as their data only diagnosed cases of frank disease, and therefore ignore possible constitutional or acquired correlates, can shed no light on these questions either. But the search for subclinical and possibly pre-pathological signs of abnormality in the families of diseased persons, accompanied by an analysis of the familial and demographic distribution of these signs which makes use of the techniques of the geneticist and the epidemiologist, offers fair promise, we think, of contributing usefully to our knowledge of many diseases whose aetiological backgrounds are currently obscure. It is a matter of some importance to note that the utility of this type of attack is equally great whether, in a given instance, genetic factors are of major or minor aetiological significance.

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CHAPTER 3

THE DETECTION OF THE GENETIC CARRIERS OF INHERITED DISEASE

JAMES V. NEEL

EXCEPT for the minority of cases where an hereditary condition is determined by a dominant gene with complete penetrance prior to adolescence, the parents of an individual with a genetically determined trait may, during all or part of their reproductive lives, superficially appear quite normal. This is true where there is recessive heredity or irregular dominance, where the onset or recognition of the trait is late in life, and, as a rule, where multifactor inheritance is involved. The term " genetic carrier " has been applied to an apparently normal person who serves as the transmitter of an inherited disorder.

Frequency of the carrier state

Where a dominant disease has a late onset, as in the case of Huntington's chorea, the number of carriers simply equals the number of persons who will later develop the condition. Where a disease is due to an irregularly dominant gene, the number of apparently normal carriers may be less, equal to, or greater than the number of affected individuals, depending upon the penetrance of the gene in question. But in the case of an uncommon, recessively determined disease, the heterozygous carrier is always far more frequent than the homozygote who exhibits the disease. Thus, albinism has a frequency of the order of 0·0001 in Europeans. The frequency of the gene responsible for albinism (p), disregarding isolate and consanguinity effects, would then be $\sqrt{\cdot 0001}$, or ·01, and the frequency of the carrier, [2p(1–p)], would be approximately 0·02, or 200 times that of the homozygote. The rarer a gene, the higher is the ratio of heterozygote to homozygote. When one considers the large number of diseases which are certainly or probably due to recessive genes, the probability emerges that each of us is a carrier of not one but several genes which in the homozygous condition would have highly undesirable effects.

Importance of the recognition of carriers

The recognition of " carriers " with respect to any given disease may lead to fundamental contributions from the standpoint of understanding the mechanism of gene action, since it provides material for the study of " minimal " gene effects, as contrasted to the more marked effects seen in the full-blown disease. Carrier recognition is thus of importance in developing a picture of the physiological genetics of man. There are, moreover, certain practical implications. There are situations, too well known to require enumeration here, where it is of value to know whether a given individual is heterozygous for a certain recessive gene, or whether, in the case of a dominant gene whose effects do not appear until after adolescence, an individual may be expected to develop a certain disease at some

later date. However, a word of caution seems indicated regarding attempts to apply our present knowledge of carrier states. The information currently available is far too meagre to permit well intended but premature attempts to utilize it except in a few special cases.

In recent years there has been an increasing realization that completely recessive genes are less common than was originally thought to be the case. For instance, Stern and Novitski (1948) studied a series of 33 sex-linked "recessive lethals" of *Drosophila melanogaster* with respect to their effect in heterozygous females, and found an average lowering of viability of 10 per cent. Recognition of the ultimate basis for this impaired viability may be expected to proceed slowly in the fruit fly, where the organism is so small and so much of the necessary background data is lacking. In man, on the other hand, the detailed anatomical, biochemical, and physiological information available and the size of the organism tremendously facilitate the detection of small departures from the norm that might pass unnoticed in a primrose or a fruit fly. The apparently greater incidence of " dominant inheritance " in man than in laboratory material, so clearly pointed out by Levit (1936), is undoubtedly due in whole or part simply to our greater familiarity with minor departures from the norm in man. Muller (1950) has recently calculated on theoretical grounds that in the genetic constitution of the average man there are at least eight " recessive " genes with some detrimental effect when heterozygous, and possibly double or triple that figure.

Tabulation of available data

The table presents a partial summary of the available information concerning carrier states. The 33 diseases for which some sort of data are available have been entered in alphabetical order.

In each instance the most probable mode of inheritance has been indicated, but it should be emphasized that in some instances the data regarding the mode of heredity are quite deficient, and the assignment to a particular category made somewhat arbitrarily.

There is a very wide disparity in the diseases entered in the table both as regards the extent of the observations concerning the existence of a carrier state and the validity and usefulness of those observations. A number of additional diseases for which a carrier state has been suggested have been omitted because of contradictory or very dubious evidence. An attempt has been made to indicate the reliability and general applicability of the observations by a grading system of 1 through 4, where 1 indicates the most reliable. An arbitrary upper limit of three pertinent references for each disease has been adopted. This obviously necessitates considerable selection in the case of such widely studied diseases as epilepsy and pernicious anaemia. The present author has elsewhere presented a more extended bibliography, as well as a critical review, of a number of the diseases included in the table (Neel, 1947, 1949).

Some of the carrier relationships summarized in the table are probably special for a particular family or group of families. Thus, Yamazaki (1927) has described a family in which mild and extreme myopia may be related to one another as heterozygote to homozygote. But while this may well be true for the particular family under study, it is unlikely that this can be applied as a general relationship. The anatomical bases of myopia are too diverse and complicated to permit any such simple interpretation.

TABLE

CLINICAL DATA ON CARRIER STATES FOR SOME AFFECTIONS

Disease	Mode of inheritance	Characteristics of carrier state may be	Genetic relationship of carrier to manifest disease	Reliability*	Reference
1. Afibrinogenaemia	a.r.	Fibrinogenopenia	As heterozygote to homozygote	2	Risak (1935) Macfarlane (1938) Schönholzer (1939)
2. Allergic state (early, severe)	a.r.	Development of mild allergies sometime after puberty	As heterozygote to homozygote, but only about 1 in 5 heterozygotes ever develop symptoms	4	Wiener, Zieve and Fries (1936)
3. Anhidrotic ectodermal dysplasia (sex-linked type)	s.l.r.	Very mildly affected females	Carrier females heterozygous for a gene for which affected males are hemizygous	3	Roberts (1929) Levit (1936)
4. Anophthalmia	a.r.	Small eyeballs	As heterozygote to homozygote	4	Sorsby (1934)
5. Ataxia, hereditary	d.l.	Minimal signs of pyramidal tract involvement	Heterozygous for same genes, but phenotypic effects by which gene usually recognized are not yet apparent	3	Schut and Böök, unpublished
6. Choroideraemia	s.l.r.	Presence in females of same family of atypical and minor choroidoretinal changes	Carrier females heterozygous for a gene for which the affected males are hemizygous	2	Goedblad (1942) McCulloch and McCulloch (1948)
7. Colour blindness	s.l.r.	Females with minor impairment of colour vision	Carrier females are heterozygous for a gene for which affected males are hemizygous	3	Wieland (1933) Schmidt (1934) Pickford (1949)

(1) a.r.—autosomal " recessive " (incomplete recessive, semi-dominant, and so on); (2) s.l.r.—sex-linked " recessive ";
(3) d.v.—autosomal dominant or dominants of variable expression; (4) d.l.—autosomal dominant of late onset;
(5) s.l.r.l.—sex-linked recessive of late onset; and (5) Un.—mode of heredity not clear.

* Graded as described in text.

TABLE—(*cont.*)

CLINICAL DATA ON CARRIER STATES FOR SOME AFFECTIONS—(*cont.*)

Disease	Mode of inheritance	Characteristics of carrier state may be	Genetic relationship of carrier to manifest disease	Reliability*	Reference
8. Congenital dislocation of hip	d.v.	Defective acetabular development	Heterozygous for same gene, which in carriers is so mildly expressed that dislocation of hip does not result	3	Faber (1938)
9. Diabetes mellitus	Un.	Impaired glucose metabolism as shown by abnormal glucose tolerance curve	Not clear	3	Pincus and White (1934) Steiner (1936) Lemser (1938)
10. Dystrophia myotonica	d.v.	Cataract	Heterozygous for same gene	4	Thomasen (1948)
11. Epilepsy	d.v.?	Abnormal electroencephalogram	Heterozygous for same gene	3	Lennox, Gibbs and Gibbs (1940, 1942) Lennox (1946)
12. Friedreich's ataxia	a.r.	Pes cavus and absent tendon reflexes	As heterozygote to homozygote; findings in heterozygote inconstant	4	Davidenkov (1940) Spillane (1940)
13. Gout	d.v.	Hyperuricaemia	Heterozygous for same gene, which produces gout in small fraction of the carriers	1	Smyth, Cotterman, and Freyberg (1948) Stecher, Hersh and Solomon (1949)

(1) a.r.—autosomal " recessive " (incomplete recessive, semi-dominant, and so on); (2) s,l.r.—sex-linked " recessive "; (3) d.v.—autosomal dominant or dominants of variable expression; (4) d.l.—autosomal dominant of late onset; (5) s.l.r.l.—sex-linked recessive of late onset; and (5) Un.—mode of heredity not clear.

* Graded as described in text.

TABLE—(*cont.*)

CLINICAL DATA ON CARRIER STATES FOR SOME AFFECTIONS—(*cont.*)

Disease	Mode of inheritance	Characteristics of carrier state may be	Genetic relationship of carrier to manifest disease	Reliability*	Reference
14. Haemophilia	s.l.r.	Females with minor prolongation of coagulation time	Carrier females are heterozygous for a gene for which affected males are hemizygous	3	Günder (1938) Andreassen (1943) Fonio (1949)
15. Hereditary haemolytic jaundice	d.v.	Asymptomatic spherocytosis and increased erythrocyte fragility to hypotonic saline solutions	Heterozygous for same gene, with "subclinical" haematological effects in the carriers	1	Campbell and Warner (1926) Race (1942) Young, Izzo and Platzer (1951)
16. Huntington's chorea	d.l.	Electroencephalographic abnormalities	Heterozygous for same gene, which has not yet reached the level of clinical expression in the younger carriers	2	Patterson, Bagchi, and Test (1948)
17. Hypertension (essential)	d.v.?	Positive reaction to cold pressor test	Not clear; carriers may have same genetic constitution but do not show the disease because of youth or absence of specific eliciting factors	3	Hines (1937)
18. Keratosis follicularis spinulosa	s.l.r.	Mild keratosis follicularis	Carrier females are heterozygous for a gene for which males are hemizygous; only a single extensive pedigree of this disease known	1	Siemens (1925)
19. Laurence-Moon-Biedl syndrome	a.r.	Obesity, skeletal abnormalities, atypical retinal changes	As heterozygote to homozygote, but carrier state changes of a very non-specific nature	4	Sorsby, Avery and Cockayne (1939)

(1) a.r.—autosomal "recessive" (incomplete recessive, semi-dominant, and so on); (2) s.l.r.—sex-linked "recessive"; (3) d.v.—autosomal dominant or dominants of variable expression; (4) d.l.—autosomal dominant of late onset; (5) s.l.r.l.—sex-linked recessive of late onset; and (5) Un.—mode of heredity not clear.

* Graded as described in text.

TABLE—(*cont.*)

CLINICAL DATA ON CARRIER STATES FOR SOME AFFECTIONS—(*cont.*)

Disease	Mode of inheritance	Characteristics of carrier state may be	Genetic relationship of carrier to manifest disease	Reliability*	Reference
20. Morquio's disease	a.r.	Small stature and short mid-phalanges of hands and feet	As heterozygote to homozygote; relationship observed in only a single family	4	Grebe (1943)
21. Myopia (extreme)	a.r.	Mild myopia	As heterozygote to homozygote	4	Yamazaki (1927)
22. Ovalocytosis with haemolytic syndrome	d.v.	Asymptomatic ovalocytosis	Heterozygous for same gene	1	Lambrecht (1938) Mason (1938) Cooley (1942)
23. Pernicious anaemia	d.v.	Achlorhydria; mild pernicious anaemia-like blood changes	Heterozygous for same gene or genes	3	Hurst (1925) Conner (1930) Baggi and Romei (1949)
24. Peroneal atrophy (sex-linked type)	s.l.r.l.	Mild and non-progressive peroneal atrophy	Carrier females are heterozygous for a gene for which males are hemizygous—not all s.l. pedigrees exhibit this relationship	3	Raffan (1907) Bell (1935)
25. Pick's disease	d.l.	Abnormal response to Rorschach test some years before onset of clinical disease	Heterozygous for same gene	4	Sanders (1939)
26. Retinitis pigmentosa of sex-linked type	s.l.r.	Presence in females of same family of a "tapetal" reflex in the fundus	Carrier females heterozygous for a gene for which the affected males are hemizygous; not all pedigrees manifest this relationship	3	Falls and Cotterman (1948) Sorsby (1951)

(1) a.r.—autosomal "recessive" (incomplete recessive, semi-dominant, and so on); (2) s.l.r.—sex-linked "recessive"; (3) d.v.—autosomal dominant or dominants of variable expression; (4) d.l.—autosomal dominant of late onset; (5) s.l.r.l.—sex-linked recessive of late onset; and (5) Un.—mode of heredity not clear.

* Graded as described in text.

TABLE—(*cont.*)

CLINICAL DATA ON CARRIER STATES FOR SOME AFFECTIONS—(*cont.*)

Disease	Mode of inheritance	Characteristics of carrier state may be	Genetic relationship of carrier to manifest disease	Reliability*	Reference
27. Schizophrenia	a.r.	Schizoid personality	As heterozygote to homozygote	4	Rudin (1916) Hoffmann (1921) Strohmayer (1925)
28. Sex-linked hypochromic anaemia	s.l.r.	Females with increased numbers of pale, oval erythrocytes and/or splenomegaly	Carrier females are heterozygous for a gene for which males are hemizygous	1	Rundles and Falls (1946)
29. Sickle-cell anaemia	a.r.	Sickle-cell trait	As heterozygote to homozygote	1	Neel (1949)
30. Spina bifida	d.v.?	Spina bifida occulta	Both heterozygous for same gene	4	Schamburow and Stilbans (1932)
31. Thalassaemia major	a.r.	Thalassaemia minor	As heterozygote to homozygote	1	Gatto (1942) Dameshek (1943) Valentine and Neel (1944)
32. Xanthomatosis (extreme form)	a.r.	Hypercholesterolaemia	As heterozygote to homozygote	1	Fliegelman, Wilkinson and Hand (1949) Adlersberg, Parets and Boas (1949)
33. Xeroderma pigmentosa	s.l.r. (incomplete)	Excessive freckling	As heterozygote to homozygote	4	Siemens and Kohn (1925) Cockayne (1933)

(1) a.r.—autosomal " recessive " (incomplete recessive, semi-dominant, and so on); (2) s.l.r.—sex-linked " recessive ";
(3) d.v.—autosomal dominant or dominants of variable expression; (4) d.l.—autosomal dominant of late onset;
(5) s.l.r.l.—sex-linked recessive of late onset; and (5) Un.—mode of heredity not clear.

* Graded as described in text.

In addition to the diseases included in the Table, it should be pointed out that there are a number of " dominant " genes in man which are so uncommon that individuals certainly or probably homozygous for the gene in question are very rare indeed. However, such homozygous individuals when they do occur may show a marked accentuation of the effects of the " dominant " gene, which must then be regarded as an " incomplete dominant ", with the heterozygotes " carriers " for a much more serious genetic disability. Included in this category may be brachyphalangy (Mohr and Wriedt, 1919), hereditary sebaceous cysts (Munro, 1937), hereditary haemorrhagic telangiectasia (Snyder and Doan, 1944), and the Ehlers-Danlos syndrome (Johnson and Falls, 1949).

Recognition of carriers through linkage systems

As an alternative to the clinical approach to the detection of genetic carriers, it has been suggested that where the gene responsible for a pathological condition is linked to one producing a harmless trait (for example, a serological characteristic), one could use the latter gene to " tag " the former. While theoretically this is a feasible method for the detection of carriers, in actual practice many serious difficulties arise (Neel, 1949). The linkage between the marker and the marked gene should be close (within 5 units), and the marker gene to be of maximum usefulness should approximate a 50 per cent frequency and be distinguishable in the homozygous and heterozygous conditions. However, since a given phenotype may be inherited in several different ways, it will be difficult, unless an extensive pedigree is available, to determine the appropriateness of utilizing a particular marker gene. These facts combine to suggest that a very extensive knowledge of human genetics will be necessary before the linkage approach can be of significant practical value.

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CHAPTER 4

TWIN STUDIES

J. A. H. WATERHOUSE

TWINS make a dual demand on the attention of the clinical geneticist. In the first place there is their intrinsic interest as comparative rarities—as ill-understood genetic and physiological abnormalities in a species normally monotocous. Here the problem has been to devise adequate tests to assess the truth of many rather uncritical assertions. In the second place is that Galton, in 1857, was one of the first to recognize, the value of the " History of Twins, as a Criterion of the relative powers of Nature and Nurture ". The nature-nurture question, which, though he did not initiate, Galton assiduously pursued and sponsored for the rest of his life, was too often presented as a struggle of heredity *versus* environment rather than as a co-operative effort, and led to much bitter controversy and special pleading. Nevertheless, in the form in which it is generally used today the method of twin control can yield valuable information about the presence of a hereditary influence, though quantitatively inconclusive.

The literature abounds with references to twins and twinning from all aspects and of all qualities. Comprehensive reviews may be found in Dahlberg (1926), Newman (1942), Gates (1946) and Gedda (1951). Modern work, not only on twins but particularly in the sphere of human genetics, has rendered much of the earlier work obsolete, or of historical interest only, and necessitated a reorientation of outlook.

ORIGIN OF TWINS

Monovular and binovular twins

It is generally held that twins arise either from (1) the early division of the fertilized zygote into two separate, or partially separate, embryos, or (2) the fertilization of two ova released at about the same time. By reason of its mode of origin the former type of twin-pair—monozygous (MZ), monovular, or identical—must be of the same sex and possess exactly the same hereditary material in duplicate, whereas the latter type—dizygous (DZ), binovular, or fraternal—will be no more alike in sex or heredity than any pair of children of the same parents. And the existence of these two kinds of twins provides a natural basis for a controlled experiment to test the relative influences of heredity and environment. Dizygous twins, especially those of the same sex, are brought up in very much the same environment—an environment very much more similar than that of same-sex sibs of unequal ages—but differ in their heredity: whereas monozygous twins, separated very soon after birth and reared apart, provide the complementary material, genetically identical but differing in their environment. Such a situation might represent the ideal for a controlled biological experiment but is very seldom realizable in practice, and in any case overlooks the period of intra-uterine life when the environments presumptively are very closely similar. Newman, Freeman

and Holzinger (1937) include a study of 19 pairs of identical twins separated in infancy, and this number represents the useful yield of a careful search for such pairs over a number of years. Consequently, most studies are constrained to utilize the theoretically less efficient method of comparison between sets of like-sex pairs reared together, one set consisting of monozygous pairs and the other of dizygous.

Other modes of origin of twins have also been suggested. Of these, that which has found most favour in the literature involves fertilization by different sperms of both the ovum and the second polar body, formed from the second meiotic division. Such an occurrence would lead to a pair of twins who were more alike genetically than sibs, though not identical, for, apart from the chromosomal material exchanged in the first meiotic division of the ovum, they would possess a common maternal inheritance while differing in their paternal contribution. Such a pair could of course be of opposite sex, and in fact it is usually to account for the appearance of unlike-sex pairs showing many features in common that this suggestion has been made. While the possibility of the existence of this type of twinning cannot be ruled out, it is almost certainly of rare occurrence.

There is an urgent temptation, peculiar to the human geneticist, to explain an otherwise apparently anomalous finding by recourse to a genetic mechanism known to exist in some experimental animal, but not yet demonstrated in man. Sometimes a good *prima facie* case can be made out for analogical extension of a genetical mechanism to man, but somewhat superficial similarity is not sufficient justification, especially in isolated cases, or where it is a rare occurrence in animal genetics. If such statements are recognized as hypotheses in support of which the sceptical biologist would require more rather than less confirmatory evidence to overcome their prior improbability, no harm is done except to tend to conceal the existence of a problem. Many hypotheses of this kind are as difficult to disprove as to prove, and to this category must be allotted many of the theories both of the origin and of the genetics of twinning postulated in the literature.

Conjoined twins.—Double monsters, *pygopagi*, conjoined or " Siamese " twins, are monozygous twins as is evident from their possession, by definition, of at least some tissue in common—a state of affairs which could not endure for long unless they were genetically identical because of the very high specificity of graft tissue. Degrees of doubling from a small duplication to almost completely separate individuals have been reported, but surgical separation is seldom successfully accomplished. Such twins may be united at any part of the head or trunk, but at the same position on each individual.

Placenta and chorion as criteria

The type and condition of the membranes found in the afterbirth, once considered as immediately diagnostic of the type of twinning, has occasioned some controversy. A single chorionic membrane is now generally accepted as evidence of monozygous twinning, although the possibility of the fusion of the two chorionic membranes surrounding like-sex dizygous twins is admitted by some writers as a rarity. About one-quarter of dichorial like-sex twins are monozygous; the presence of one or two placentae seems to depend in the case of dizygous twins upon the proximity of implantation in the uterus, and in the case of monozygous twins upon the stage at which separation occurs. Monochorial twins are sometimes also mono-amniotic, but about 90 per cent are diamniotic,

according to Steiner; all the other types will of course be diamniotic. It is by no means easy always to determine the condition of the membranes, and there are only few reliable figures available. The frequencies given above, and the figures in the ensuing Table, adapted from Steiner (1935), may well be subject to variation with environmental agencies. Maternal age is almost certainly a factor affecting these figures so that they represent an aggregate corresponding to the European pattern of fertility by age.

TABLE

Placenta	Chorion	Amnion	MZ	All like sex	Like sex DZ	Unlike sex DZ	All DZ	All Twins
1	1	1	3	3	—	—	—	3
1	1	2	29	29	—	—	—	29
1	2	2	8	39	31	49	80	88
2	2	2	16	61	45	55	100	116
Total	–	–	56	132	76	104	180	236

Circulatory anastomoses

There appears to be no evidence in human twinning of the " freemartin effect " observed in cattle, where the female of unlike-sex twins is infertile. In cattle this has been shown to be due to anastomoses between the placental circulations of the two embryos, and though such anastomoses have been recorded in human twin placentae no such drastic effect of interchange of sex hormones has been observed. The subject of circulatory anastomoses between the embryos in twin pregnancies, and in particular the dynamic asymmetry of the resulting mutual circulation, was studied in detail by Schatz in the latter half of the nineteenth century. Several later writers have also suggested that inequalities in the mutual circulation often found in monochorial pairs may well play a large part in the causation of the observed differences between monozygous twins at birth. It is true that there has been no comparable repetition of the detailed work of Schatz since his time, and that the effects of such circulatory derangements in producing modifications of the phenotype attributable to the prenatal environment might be to underestimate the effects of heredity, thus reducing the value of monochorial monozygous twins in twin-control experiments (*see*, for example, Price, 1950). But although the extent of the influence of such factors is uncertain, it is unlikely in most cases seriously to affect the results of adequately controlled experiments. It remains as a reservation to be borne in mind, particularly in studies involving low values of the penetrance and expressivity of a gene, where a division of the monozygous pairs into monochorial and dichorial, and analysis of the results in these terms, might be advantageous.

REVERSED ASYMMETRY

The noticeably higher frequency among twins of various manifestations of " mirror-imaging " and visceral transposition, from superficial pattern reversals

with or without left-handedness to partial or complete *situs inversus viscerum*, has long excited speculation on its relationship to twinning. *Situs inversus viscerum* is not only very rare (a recent estimate of its frequency is 1 in 10,000), but it is not readily noted unless specially sought. With the advent of mass radiography, if the picture includes enough of the viscera, more information about the distribution and extent of *situs inversus* should become available, comparable for instance to that of Torgersen (1950). Cockayne (1938) has shown visceral inversion to be inherited as a simple recessive condition, independent of left-handedness, and not closely related to twinning—a view with which Torgersen concurs. It seems at least not improbable that superficial mirror-image effects between the members of a twin-pair, such as those of hair whorls and fingerprints, might result from the disturbance of normal development caused by the fission of an embryo to form a monozygous pair, and that the later such fission occurs the more difficult it becomes for the embryos to recover from the amount of asymmetry development already determined. Of all monozygous pairs, conjoined twins exhibit most reversal of asymmetry. As such pairs result from incomplete fission of the embryo at a relatively late stage of development, and are monochorial, it suggests that monochorial but separate monozygous twins might show more frequent inversion than dichorial pairs. Thus while a certain degree of asymmetry reversal may serve as an indication of the monozygous origin of a twin-pair, it can also in rare instances result from a purely genetic effect, possibly of variable expression, acting in one twin only of a dizygous pair.

FREQUENCIES OF TWINNING

Presented with the numbers or proportions of the three sex-groups in a sample of twins, it is comparatively easy, if the sample has been taken at random, to determine the ratio of monozygous to dizygous pairs. Weinberg (1901) pointed out that if dizygous pairs are in effect no more than sibs who happen to be occupying the uterus at the same time, then the sex-groups will be distributed just as they would be for pairs of single-birth sibs. If M denote a male and F a female, there should then be $\frac{1}{4}$ MM : $\frac{1}{2}$ MF : $\frac{1}{4}$ FF pairs, if the numbers of the sexes at birth are equal. Thus the numbers of like-sex and unlike-sex pairs will be equal, and this is also very nearly true if the sex ratio diverges slightly from $\frac{1}{2}$. All monozygous pairs must, of course, be like-sex pairs, so that to obtain the number of monozygous pairs in the sample the number of MF pairs is deducted from the number of like-sex pairs (MM + FF). This may be expressed symbolically as follows.

		MM	MF	FF	Total
Number of twin-pairs in sample	=	A	B	C	N
Number of monozygous pairs	=	$A + C - B = N - 2B$			
Number of dizygous pairs	=	2B			

If the sex ratio is estimated from the sample and taken into account in computing the relative numbers of monozygous and dizygous pairs, the formulae above become

Proportion of males	=	$(2A + B) / 2N$
Number of monozygous pairs	=	$(4AC - B^2) / (2A + B)(B + 2C)$
Number of dizygous pairs	=	$2NB / (2A + B)(B + 2C)$

If these formulae are applied to the gross birth statistics of most European countries it is found that monozygous twins form approximately one quarter of all twin-pairs. The total rate of twin maternities to all maternities averages about 1 per cent, but varies quite widely from one country to another. When statistics of twin maternities are tabulated by the age of the mother and are compared with the numbers of all maternities by maternal age, it is found that the proportion of maternities resulting in twins increases with the age of the mother. To this fact is attributable almost the whole extent of the variation in gross twinning rates between countries which are composed mainly of white European populations, and possibly that between other countries also, sometimes ascribed to such ambiguous differentials as race and latitude.

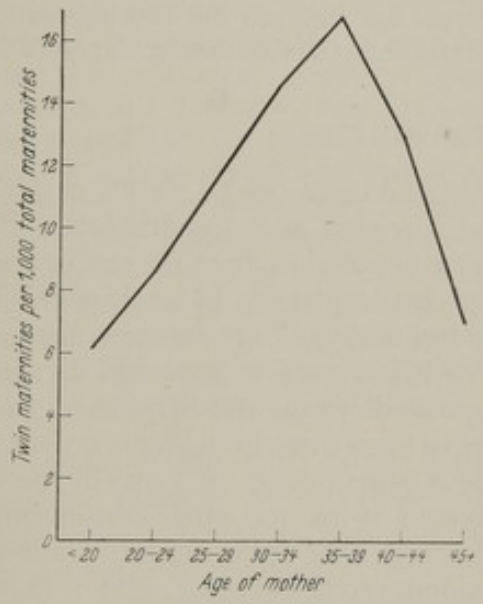

FIG. 5.—Rate of twinning for England and Wales over 10½ years. Note variation with maternal age.

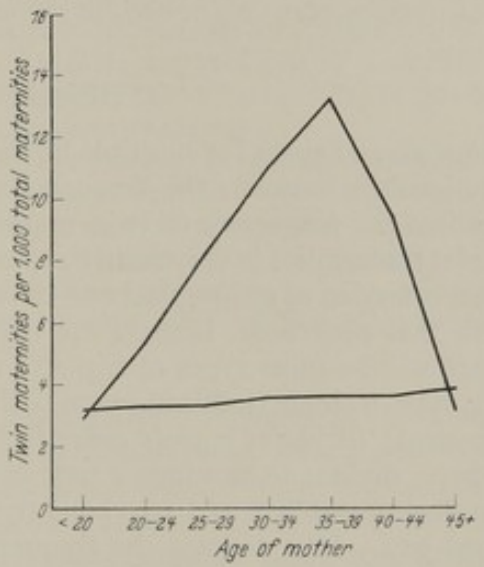

FIG. 6.—Results as in Fig. 5 expressed as proportions of total maternities by age, after application of Weinberg's method.

Fig. 5 shows how the rate of twinning varies with maternal age for England and Wales over a 10½-year period. If Weinberg's method is applied to distinguish the relative numbers of monozygous and dizygous twin maternities for each maternal age-group, and if the results are expressed as proportions of the total maternities by age, Fig. 6 is obtained. Thus monozygous twinning is virtually independent of maternal age, only rising from 3·2 to 3·8 per 1,000, while the dizygous rate rises sharply to a maximum of 13 per 1,000 in the maternal age-group 35–39 years, and falls again after this age. There is some evidence (Waterhouse, 1950) that the dizygous rate at ages under 20 years is well below the monozygous rate, and it is possible that any twins born to mothers of 15 years old or younger are exclusively monozygous. If this is so, the low rate of dizygous twinning found in some Eastern countries (Japan, for example) may be explicable on the basis of a relationship sensibly the same as that depicted in Fig. 6, taken in conjunction with the early age of marriage customary in such countries, and Fig. 6 may perhaps represent a physiological relationship between polyovulation and maternal age. Parity has also an effect, as several authors have observed, but one which is difficult to

distinguish from that of maternal age. Taken together they suggest that the internal environment of the mother may exert a powerful influence on the expression of any genetic mechanism concerned in the production of dizygous twins.

Kuczynski (1935), among others, has pointed out some of the shortcomings of official statistics, particularly in countries new to them, or where the population is scattered over a wide area. When almost the only method of analysis is statistical and must be based on very large numbers, as it is here, it is important to recognize the assumptions implicit in the method. They include both a certain degree of homogeneity and an absence of bias in the collection of the data: unless the basic data are impeccable in these respects the conclusions drawn may be erroneous. Consequently it is possible that the different rates of twinning between the white and coloured populations reported by Enders and Stern (1948) in America may be partly due to the heterogeneity of the population over so vast an area, or to the relatively small size of the coloured population, or may even be ascribable to wide differences in parity by maternal age between the two populations. Such questions can only be decided by very much extended and more detailed investigation.

OTHER MULTIPLE BIRTHS

From gross figures for multiple births Hellin (1895) discovered a simple empirical relationship between the frequencies of twins, triplet and quadruplets. If p denotes the frequency of twin maternities in a population, then the frequency of triplet maternities is very nearly p^2, and that of quadruplet p^3; by analogy this has been extended to quintuplets and the expected frequency, p^4, appears in accordance with that observed. If there are two types of twins, monozygous and dizygous, there will be three types of triplets: monozygous, dizygous and trizygous. In the first type, a single fertilized ovum twice divides to form three individuals genetically identical; dizygous triplets differ from dizygous twins only in that one of the two zygotes divides to produce a pair of monozygous twins, the other continuing to develop normally; and trizygous triplets of course arise from the fertilization of three ova. If u denotes the frequency of monozygous twinning, and v that of dizygous, then

$$p = u + v$$

and

$$p^2 = u^2 + 2uv + v^2$$

Here the first term (u^2) represents the frequency of monozygous triplet maternities, the second term that of dizygous, and the third term that of trizygous. The relative frequencies, however, may well be distorted at birth by differential mortality *in utero* according either to sex or to mode of origin. Obviously this method of analysis can be carried further: Hellin's law can be applied separately to each maternal age-group—a more rational procedure than its application to gross rates if it is interpreted as the chance of a second occurrence of an event known to be linked with age. Jenkins and Gwin (1940), and Waterhouse (1950), have each adopted this method in a more detailed examination by the technique of regression equations.

HEREDITY OF TWINNING

Several varieties of pedigree material contribute to show that there is an hereditary factor in twinning, but the determination of the type of genetic mechanism involved is made much more difficult by its very low penetrance.

In the first place, some very long pedigrees have been published showing an incidence of twinning higher than normal. But a single pedigree extensive enough to provide the numbers of twins required for adequate statistical analysis must include at the same time so much admixture of other stock that it cannot be regarded in any relevant sense as homogeneous, unless it contains a large and known amount of inbreeding. Secondly, there are in the literature numerous isolated pedigrees with a remarkable concentration of twins among close relatives. No figures of incidence in any way comparable with those from the first type of pedigree are calculable from such incomplete data, and it is difficult to class them otherwise than as suggestive but essentially anecdotal.

A third method, comparable to the first but in another dimension, obtains the incidence of twins among sibships of index pairs determined in some unbiased manner. In 1902 Weinberg found, on data from Stuttgart, that the incidence of twins among the sibs of monozygous twin-pairs was no greater than that in the general population, but that the incidence was more than twice as great among the sibs of dizygous pairs. And in 1909 he came to the same conclusion from a larger sample. Dahlberg, on less numerous data, claimed also an increased number of monozygous pairs among the subsequent children of mothers of a dizygous pair. He was led to postulate the existence of a doubling tendency, an hereditary disposition of the egg (or possibly of the sperm also) to double formation, responsible for both monozygous and dizygous twinning.

The fourth type of pedigree analysis involves the systematic collection of family material. These data may then be analysed either by determining the incidence of twinning among various classes of relatives of the propositi, a method exemplified by Greulich (1934), or by internal comparisons of one form of relationship with another, typified by Waterhouse (1950). Each of these methods depends upon the grouping of a sufficient number of individual pedigrees, all ascertained in the same way, and free from serious bias, to be of significance statistically.

By means of this latter form of pedigree analysis the frequency of twinning among the relatives of dizygous twins has been found to be raised above its normal value, whereas in the families of monozygous twins the incidence does not differ from that in the general population. It would appear reasonable to suppose the production of dizygous twins to be sex-limited, exhibition being confined to the female, and the part of the male being that of an intermediate host for the factors responsible. And indeed most studies agree in finding the incidence generally to be higher in the female line, except for some results which appear to show a direct effect attributable to the father. Unless, as has been proposed, polyovulation is of much more frequent occurrence than there is evidence to suppose, and the genetic constitution of an embryo—to which of course the father contributes—determines its survival to birth alive, it is difficult to envisage how this could be accomplished.

Animal investigations have revealed the existence of polyovular follicles in the ovaries of some females, in some cases as a rarity and in others as a rule, and similar findings have been reported from examination of some human ovaries. Dizygous twinning might thus be the result of the inheritance of ovaries containing at least some binovular follicles, or it may result from a defect of timing such that two or more ova are released nearly simultaneously, either from different follicles in one and the same ovary, or separately from each ovary. In any event, the condition must admit of considerable variation in exhibition with age and parity. And if the hypothesis referred to above, that polyovulation is more frequent than is generally assumed, be admitted, then it may be that maternal age and parity

affect the penetrance of the genes determining the intra-uterine survival of dizygous embryos. Several other conditions partly genetic in origin, such for example as mongolian idiocy, are known in which the expression depends upon one or both of these factors.

DIAGNOSIS OF ZYGOSITY

Criteria

For investigations involving the relative numbers of monozygous and dizygous twins in a large sample drawn at random, Weinberg's differential method effects the distinction easily and accurately. But it does not of course specify which individual pairs within the sample belong to each class, nor is it strictly applicable without modification to later age-groups. For selective mortality will disturb the sex ratio, as it must indeed be disturbed even if there is no difference between the mortality rates of monozygous and dizygous individuals, by differential mortality rates between the sexes, and the method is invalidated. As the twin method is frequently employed in heredity-environmental studies it is necessary to know which pairs are monozygous and which dizygous. Inevitably the diagnosis can only be based on the manifestation of a comparatively few genes from the whole genetic complex, which is equivalent to founding a judgment of genetic identity upon the statistical unlikelihood of the simultaneous occurrence in both members of a dizygous pair of a number of characteristics known to be determined genetically, but independently of one another. Though it is exceedingly unlikely that any pair of individuals even possessing the same parents would possess precisely identical complements of genes unless of monozygous origin, two individuals alike with respect to all of a small number of tests would not be hard to find.

Evidently the desiderata for tests of zygosity are for each test that it shall depend upon a characteristic determined genetically and subject to the least environmental variation in its expression—a character, in fact, of full penetrance—and for all tests that, taken together, they are sufficient in number and discriminatory power to leave a residue undecided which is negligible for the size of the sample in question. In practice such high-penetrance genetic substitutions are not always readily available nor sufficient in number or power to leave a negligible residue, so that other characteristics of lower penetrance, or subject to greater environmental variation, must be included in the armoury of diagnostic criteria. A difference between the members of a pair with respect to any one of the qualitative criteria is usually enough to discredit the assumption of monozygosity, but for graded or quantitative tests a standard of rejection must first be established. It is difficult to establish such standards without incurring the risk of a circular argument, and in consequence qualitative tests are in general to be preferred to quantitative ; another reason for the preference, where a quantitative test may break down because of the intrusion of an environmental influence of unexpected magnitude, will be referred to later.

Sex: blood groups

The first and most obvious criterion to apply, that of sex, belongs of course to the first category, and so also do the blood groups. In fact if the present rate of discovery of fresh groups and new subgroups continues, blood group tests will

very soon suffice for nearly all ordinary samples, if the necessary antisera are conveniently available. Blood groups constitute the purest known examples of the ideal diagnostic criteria, for they are simply determined genetically and as completely free of environmental influence in their manifestation as the genes themselves. Other characters subject to only small environmental variation are the "taste-sense" (wherein a simple recessive gene substitution confers the inability to taste phenyl thiourea and certain substances related to it) and the " secretor " property (a simple dominant gene being responsible for the property of secreting blood group antigens in body fluids; this property appears to be closely related to the Lewis blood group system). Although the various blood group systems differ widely in their ease of determination, some of them requiring considerable skill and experience to perform successfully, it is interesting to compare their discriminatory power on the assumption that all the necessary antisera at present known are available. This power is dependent on the " local " frequencies of the genes involved, as indeed the power of any test of this kind is, and the figures quoted here are based on the gene frequencies given for England by Race and Sanger (1950). The MNS system, if anti-*s* is used, is the most effective, leaving an undiscriminated residual of about 44 per cent, and the Rhesus is next with about 46 per cent; the Landsteiner groups leave a residual of about two-thirds undiscriminated, while none of the rest (including both the taste and secretor properties) leaves less than about 75 per cent. If all are used in combination (that is: ABO; MNS; P; Rh; Lutheran; Kell; Duffy; Kidd; Taster; Secretor) there remains a residual of about 4 per cent undiscriminated. The most effective single system could not leave a residual of less than one-quarter of the population, supposing the most advantageous distribution possible—a multiple allelomorphic series with an indefinitely large number of alleles each of vanishingly small frequency, and possessing no dominance relationships.

Fingerprints and other physical factors

The use of fingerprints in the diagnosis of zygosity requires some method of assessing their degree of similarity, for they are never precisely identical, as their value in criminal investigation might testify. Stocks (1930) has developed a technique for this purpose, and considers pairs possessing seven or more corresponding patterns to be monozygous. Of the eyes, their colour and more precisely the iris structure and pigment pattern should correspond in monozygous twins; of the hair, its colour, form, and texture should correspond. Dahlberg has put forward the structure and pattern of ears as a criterion; other suggested criteria are the order of development of the carpals, and indeed the order of ossification of all bones is considered to be more concordant in monozygous pairs; the structure of capillaries; the presence or absence of hair on the dorsum of the first and second phalanges of the fingers; electrocardiographic, and electroencephalographic traces. Very many other criteria have been employed or proposed for the diagnosis of zygosity, some of them—and not only the more recondite—upon inadequate evidence of their mode of inheritance and susceptibility to environmental influence.

Anthropometric measurement

A general physical resemblance, particularly in the features, though unreliable is, as Dahlberg remarks, quite good as a guide. This is also true of such quantitative

criteria as height and weight, and other anthropometric measurements: identical twins tend to be very much alike in these respects but not always so.

Maternal age

The mother's age at the birth of the twins is sometimes useful as a guide, for in the region 35–39 the chances are about 3 : 1 in favour of a dizygous pair (*see* Fig. 6). As a check on the accuracy of the diagnostic methods, the proportions of dizygous twins of similar and dissimilar blood groups, for instance, should be in fair agreement with the expectation for pairs of sibs, and the results for the whole sample should conform to the average local incidence.

Skin graft

The most effective test of zygosity is that of a skin graft. Though somewhat drastic perhaps as a method of diagnosis for use in most twin control investigations, it has been used as a conclusive test of identity in some forensic cases.

RESEMBLANCES AND DIFFERENCES BETWEEN MONOZYGOUS TWINS

There are many cases in the literature of close resemblances between the members of a twin-pair, not only in general physical similarity, but in respect of the occurrence of similar events: for example, each member has the same disease at the same time, with similar outcome. Such cases are well summarized by Siemens (1924) and by Gates (1946) and need not concern us here. Those of greater interest and importance concern the differences observed between monozygous twins, of which, if the diagnosis of zygosity is accurate, the only cause must lie in some environmental agency. Two cases showing opposite effects of the pituitary gland may be cited: in the first, of unknown origin, the effect was to retard growth and to produce symptoms of diabetes insipidus in one twin; in the second, the effect of a cranial injury received at about the age of 12 was to cause pituitary hyperfunction resulting in a very marked difference in height and weight and pronounced acromegaly. Two other instances of wide divergence between monozygous pairs in height and weight were attributable to disease in infancy, one to severe rickets in one twin of a pair when only a few months old, the other to severe paralytic poliomyelitis affecting one twin only. In all these instances, except possibly that first cited, the cause of the large size differences was evidently environmental in origin (in the first case, a pituitary fossa smaller than usual for the age of the boy was revealed, though no cause was found), but although the diagnosis of monozygosity was established on a basis of mainly qualitative criteria, any criterion dependent upon differences in gross size would have rejected the diagnosis with a high probability.

THE TWIN METHOD IN HEREDITY-ENVIRONMENT STUDIES

Several methods of exploiting the occurrence of the two forms of twinning have been used in attempting to assess the parts played by heredity and environment in the causation of various conditions.

Uniovular twins reared apart

Newman, Freeman and Holzinger (1937) succeeded in collecting over a period of some years 19 pairs of monozygous twins who had been reared apart from one another from a very early age. These they compared, for a number of characteristics, with three other groups: one of 50 pairs of identical twins reared together, one of 50 pairs of like-sex fraternal twins reared together, and one of 52 pairs of like-sex sibs compared where necessary at the same ages. Mean differences and correlation coefficients showed the monozygous pairs, whether reared together or apart, to resemble each other very closely, and showed a very close parallel between the figures for dizygous twin-pairs and for sib-pairs.

Quite apart from the considerable difficulty of collecting a large number of monozygous twins reared apart, there are some objections to the method on theoretical grounds. It is of the essence of every controlled experiment that the experimental and control groups should be as alike as possible in every relevant particular except that under test, and this is not strictly true of monozygous twins reared apart. The method of co-twin control provides an alternative to the foregoing method by using as a control the monozygous co-twin of each individual included in the experimental group. This method is of rather limited application in the field of heredity-environment studies, and has in fact been most used with young children (*see* Gesell and Thompson, 1929); it is most suited to assessing the effect of environmental differences on a constant genetic background, though the genetic differences between different twin-pairs may bias any but a null result.

Concordance for a character

Probably the most widely used method employing twins to assess the extent of hereditary influence is due to Siemens. The method consists in a comparison of the relative proportions of pairs concordant for the condition under investigation among monozygous and dizygous groups of twins. The dizygous group is usually chosen to comprise only like-sex pairs in order to eliminate any bias due to sex, but occasionally unlike-sex pairs are retained to form a third group for comparison with the first two. The concordant group embraces all those twin-pairs both members of which exhibit the effect in question, the discordant those of which only one member exhibits the effect. The method usually applied is to seek for the co-twin of an affected *propositus*, so that pairs concordant in that neither member is affected are excluded.

Some very extensive studies employing this method have been made, particularly into susceptibility to tuberculosis by von Verschuer and his school, and by Kallmann and Reisner (1943). Many other conditions, pathological and psychological, and processes of development and behaviour, have been investigated in this way: the Maxim Gorki Medico-Biological Institute had embarked on a programme of very intensive research largely planned on such lines, and reported some of the results in its *Proceedings* (vol. 3, 1934), before the scheme was given up. There has been no other integrated scheme of comparable magnitude, but from published studies, in the field of pathology for instance, there appears a grading of conditions from infectious diseases possessing little or no hereditary component to those known also on other grounds to be chiefly of genetic causation. But such a graduation should be regarded with the utmost caution for, though the

extremes may receive confirmation from ancillary sources, the inevitable heterogeneity of the environmental circumstances in such a composite collection, quite apart from differences in penetrance and expressivity, renders comparison very difficult.

The method is principally of value in showing qualitative effects and is unreliable or even misleading in attempting to assess results in a quantitative manner. It provides a rapid and easy first test for the presence of a genetic factor and is best regarded as the forerunner of a more detailed investigation.

In broad terms the same conclusions apply to any use of twins in clinical genetics. In certain circumstances twins provide a natural opportunity of performing a controlled experiment where it might be otherwise impossible. But an experimentalist wishing to utilize the method has only a limited range of control within his own volition: for the rest he must discover the extent of the control provided by nature.

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CHAPTER 5

SEX LIMITATION

E. B. FORD

THEORETICAL CONSIDERATIONS

THE GENES interact with one another and with the environment to produce the qualities for which they are responsible. Provided a gene is situated in the same genetic background and environment, it will always produce the same results. The variation consequent upon placing it in different genetic settings is not here our direct concern, though it will have to be kept in mind. On the other hand, environmental variation, with one aspect of which this chapter deals, is a wide term; it comprises all the diverse circumstances in which the genes may act, apart from changes in the gene-complex itself.

Highly evolved organisms are more independent of their environment than are primitive forms, and in this respect the mammals are particularly well " buffered ". They are indeed so protected from external variations in temperature or humidity that the effects of such changes can rarely be studied in them. It is otherwise with their physiology. Here, too, we find the body " buffered " with great exactitude in certain respects, but not in others. It is often highly sensitive in its response to the activity of the ductless glands, but to an extent which certainly differs on a genetic basis from one individual to another. Now of all the physiological and anatomical distinctions which subdivide individuals of a given race, those due to sex are the most profound. They provide not only different organs for the genes to control but sharply contrasted alternative backgrounds for their action.

Terminology

It is to be expected therefore that the expression of some of the genes should be dependent upon the sex of the individual in which they operate. When a gene produces certain of its effects more often, or differently, in one sex than in the other, not because it is sex-linked (situated in the X- or Y-chromosomes) but because of the physiology or the anatomy of the setting in which it has to act, such qualities are said to be *sex limited.* This is the sense in which that expression is used here, though I am inclined to favour the expression " sex controlled " as applied to such characters, since it is less easily confused with sex linkage.

Some writers (for example, Stern, 1949) have used sex limitation and sex control in different senses: taking sex-limited qualities to be entirely restricted to one sex, in contrast with those that are sex-controlled in which the restriction is partial, or the manifestation is of a different kind in the male and female. This terminology leads to confusion and is to be avoided. It has even caused Stern to combine as " sex-limited " features like milk-yield, which can normally be judged only in one sex, with total sex-linkage in the Y-chromosome. In fact, *sex-linkage* (in any of its three forms) must be rigorously distinguished as a separate phenomenon, due to the location of a gene in a sex chromosome.

Apart from this, it must be recognized that all gradations may exist between those conditions which are normally confined to one sex and those slightly affected in frequency or type of expression by the sex in which they occur.

Partial sex limitation

Sex limitations therefore may be partial in the sense that the *penetrance* or the *expressivity* of a gene may vary with sex. There are two reasons for this: the obvious one, that genes modifying the organs appropriate to one sex have little or no opportunity of working in the other, or that certain genes act only, or more frequently, in the environment provided by one of the two sexes, though they may not affect the sexual organs or the qualities directly associated with sex.

Thus in sex-linkage a character appears in one sex more frequently than in the other for purely mechanical reasons. The genes responsible for sex-limited conditions, on the other hand, may be situated anywhere in a sex chromosome, whether in the pairing or non-pairing segments, or in an autosome; usually the latter, since the number of autosomal loci is so much the greater. There is no tendency, so far as we know, for the male or the female, the heterogametic or the homogametic sex, to be the one to which sex limitation is more usually confined. Here we note a further contrast with sex-linkage: for recessive sex-linked characters must appear in man more frequently in males than in females, whereas with the sex-linked dominants the reverse is true.

Determination by multifactorial action

The great majority of the characters of the human body are genetically determined by multifactorial action. That is to say, they have not been brought under the major control of a single pair of genes which act as a switch in determining one or another of the phases they assume. The development of the primary, secondary, and accessory sexual organs is certainly in normal circumstances multifactorial (the switch-mechanism here being chromosomal). These multifactorial qualities, controlling, for instance, the development of the functional breast or of the penis, must necessarily be sex-limited. Yet the genes concerned, being in general autosomal, are transmitted equally by males and females; in consequence, each sex possesses the entire genetic equipment necessary for the complete and successful development of the other.

It is obvious that sex slightly affects the action of many of the multifactorial systems, whether these be polygenic or due to the interaction of a number of major genes. A good example is provided by human height in which, though women are on the average the shorter, the two parents contribute equally to the genetic control of height in both their sons and their daughters.

SOME CLINICAL ILLUSTRATIONS

Baldness

The effect of sex upon the expression of single genes has been studied extensively in many animals and it is unfortunate that we know so little of this subject in man. One of the examples most fully investigated is that of hereditary early baldness. This is controlled by one gene the effect of which is generally described as dominant and sex-limited to the male. That is, however, but an approximation.

CHAPTER 7

EVALUATION OF LINKAGE

ALASTAIR G. MACGREGOR

THE TERM linkage is applied to any two pairs of genes which are situated upon the same pair of chromosomes. The word is applicable whether or not the genes are on the same, or opposite, chromosomes of the pair. If the two genes for the characters in question are upon the same chromosome of the pair, with their normal allelomorphs at the corresponding sites on the other chromosome of the pair, then the genes are said to be linked in coupling. If, on the other hand, they are on opposite chromosomes, and each chromosome of the pair carries one abnormal gene, and one normal allelomorph, then the genes are said to be linked in repulsion. Fig. 11 shows that when genes are linked in coupling they tend when transmitted to remain together, whereas, if they are linked in repulsion they invariably separate.

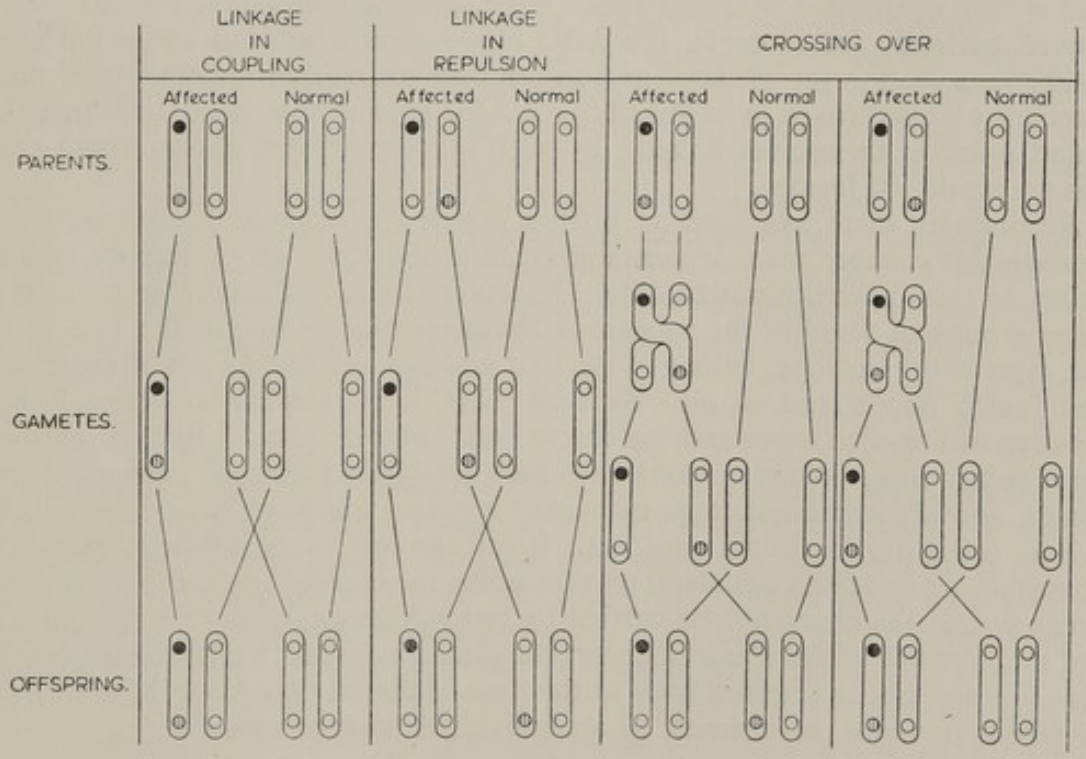

FIG. 11.—Diagram illustrating mode of transmission of linked genes in the absence, or presence, of crossing over.

The effects of crossing over

" Crossing over " may disturb this simple arrangement (Fig. 11). It is obvious that the further apart are a pair of genes the more likely it is that the chromosome

divides between them. Therefore the linkage between two pairs is closest when the least number of crossings over occur when gametes are formed. If the genes are so far apart that crossing over occurs in over half the cases, then it is apparent that it will not be possible to state that the genes are in fact linked, as their behaviour in transmission will be the same as though they are being carried on different pairs of chromosomes. If the " cross-over value ", which represents the percentage of times that crossing over occurs between two gene pairs, is low, only 5 or 10 per cent, then linkage between the characters is probable, and the probability of its existing diminishes with a rise in the cross-over value for the pair of genes in question.

MARKER GENES

It is possible in some cases that gene pairs may be shown independently to be definitely linked to a third characteristic, and this is good evidence that they are in fact carried on the same chromosome pair. The occasion seldom occurs in human genetics to study two or more abnormal traits simultaneously in the same group of people, and the opportunity should therefore always be taken to record any such simultaneous occurrence of abnormal characteristics when they do occur. What can, however, be done more often is to record, with any abnormal trait, the presence or absence of one or several of various well defined, normal, and widely distributed characteristics. If in such circumstances, linkage can be proved between, for example, the ABO blood groups and an abnormal characteristic x in one set of data, and in another set of data an abnormal characteristic y is also proved to be linked to the ABO groups, then it can be shown that x and y are in themselves linked. By such studies detailed chromosome maps can eventually be formed.

Accordingly there has been an intense search for suitable characters, and a considerable number are now available (such as the blood group factors, and the ability to taste phenylthiocarbamide). Kloepfer (1946) has been able to examine large groups of families for numerous characteristics including the size of the ear, type of the ear lobe, colour of the hair and eye, relative length of the second and fourth finger, and so on. By such work it is possible to define linkage between certain characters and thereby to find " marker genes " for each chromosome pair in man. When markers have been established for each pair of chromosomes, another important stage in human genetics will have been achieved, but this as yet is only a distant prospect. If linkage can be established between an abnormal gene and any or several marker genes, the clinical application is obvious, because then the characteristic carried by the marker gene may be used to trace out the presence of the abnormal characteristic in a family, a characteristic which may not necessarily manifest itself at the time of the investigation, but knowledge of whose presence, or absence, in an individual may be of value.

SEX LINKAGE

A particular trait is said to be sex linked when it is carried on the X or Y chromosomes (*see* Chapter 10, page 108). In these chromosomes crossing over of genes is, of course, limited to the homologous parts. The three different types of sex-linked

inheritance depend, of course, upon whether the gene is carried on the homologous portion of the chromosome, or on the non-homologous portion of the X or of the Y chromosome. By convention, when " sex-linked " inheritance is indicated, the type of inheritance referred to is that in which the character is carried upon the non-homologous portion of the X chromosome.

There are a few characters known to have been transmitted on the non-homologous part of the Y chromosome (holandric inheritance). A pedigree of such a character is quite typical, there being father-to-son transmission throughout.

Characters transmitted on the non-homologous portion of the X chromosome are, with only a few exceptions, recessive in their transmission. The few dominant totally sex-linked characters carried on the X chromosome are twice as common in women as in men, as females have twice the chance of carrying an affected X chromosome. Transmission from an affected female is exactly like that of autosomal transmission, half the offspring being affected, and the affected sex ratio is equal. Only the daughters of an affected man can show such a characteristic, as the son of an affected man inherits his X chromosome from his unaffected mother.

Recessive sex-linked transmission gives a highly characteristic pedigree, and is typically illustrated by pedigrees of colour-blindness and haemophilia, discussed elsewhere. The striking feature of such a character is the way in which affected males have normal sons and daughters, but the latter, all of whom must be heterozygous for the character, transmit the ailment to half their sons, and to half their daughters who themselves act as carriers. A sex-linked recessive trait can therefore be carried through several generations down a female line of descent. The final striking feature about such inheritance is the extreme rarity of affected females, for their production is dependent upon the marriage of an affected male to a heterozygous female carrier, or, even more rarely, to an affected female. The chances of this occurring are most remote. Only very recently has the first fully authenticated female haemophiliac been discovered and described (Israels, Lempert and Gilbertson, 1951).

Partial sex linkage

It is extremely difficult to detect the third type of sex linkage, partial sex linkage, which refers to genes which are carried on the homologous pairing portions of the pair of sex chromosomes. Crossing over can occur among these genes but normally the transmission of such characters will appear to be autosomal in nature, and it is only when bulked pedigrees of the character are studied that it can be seen that there is a tendency for the traits to be transmitted in a particular fashion. In the absence of crossing over partially sex-linked dominant genes will tend to remain on the same chromosome of the pair, and there is the probability that there will be a greater proportion of affected grandchildren of the same sex as their father's affected parent than is likely to occur if the gene is born on an autosomal chromosome pair. Similarly, with regard to a recessive partially sex-linked gene, one of which may possibly be achromatopsia (Fig. 12), pooled pedigrees of such characters show a distribution of affected persons different from the normal 1 : 3 ratio expected for autosomal transmission of a recessive character.

RECOGNITION OF LINKAGE

Linkage between inherited characters can be recognized and determined by several techniques, some simple but others fairly complex.

Pedigree analysis

In certain circumstances it is possible to exclude the possibility of linkage from a study of a single, or of very few, pedigrees; it may become apparent that in a particular line of descent the two conditions are absent, together, or appearing separately, too frequently to give the low cross-over value necessary before linkage can be adduced. This can be seen in a typical example illustrated in Fig. 12 where is charted the transmission in part of a large family of two common inherited dominant conditions, otosclerotic deafness and essential hypertension, and a very rare recessive character, achromatopsia, or congenital total colour-blindness.

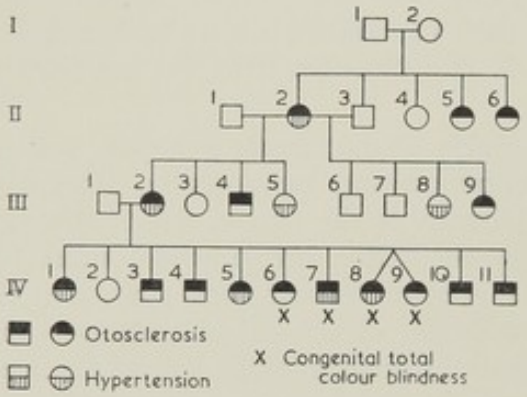

FIG. 12.—Pedigree illustrating transmission of dominant otosclerosis and essential hypertension, and of recessive achromatopsia (congenital total colour-blindness). (*From Macgregor, A. G., and Harrison, R.* (1950). *Ann. Eugen.*, **15**, 219.)

If it is desired to test the possibility of linkage between otosclerosis and hypertension, then in the individual II 2, where both conditions are present, they may be, if linked, either on the same chromosome (coupling) or on the opposite chromosome (repulsion) of the pair. If linked in coupling on II 2, then, in the absence of crossing over in her offspring, the conditions should appear either together, or be totally absent, but never separately. Therefore four of her offspring, III 4, 5, 8 and 9, in whom the conditions appear singly, must be crossovers, and similarly six of the offspring of her daughter, III 2, must be crossovers (IV 3, 4, 6, 9, 10, 11), giving a proportion of 10 crossovers in the 19 children of the two generations.

If, on the other hand, the conditions were originally linked in repulsion in II 2, then, in the first generation, III 2, 3, 6 and 7 must be crossovers, for the condition should only, in the absence of crossing over, appear singly and not together or be absent altogether. Appearing once again together in III 2, who must now be a crossover with the genes linked in coupling, there are again the six crossovers in her offspring.

In any event, therefore, linkage between those two conditions is highly improbable.

With regard to the recessive character, achromatopsia, both III 1 and III 2 must be heterozygous for this defect for it to appear in their children. If the dominant gene for essential hypertension were linked to the recessive gene for

achromatopsia in III 2, then a similar analysis as that carried out for otosclerosis and hypertension shows that this linkage is most improbable.

It is always more probable that any two gene pairs are on different rather than on the same chromosome pair, that is, they are transmitted independently, but in this pedigree it can be seen that there is the possibility that otosclerosis and achromatopsia are linked and that the linkage is in coupling, the two conditions appearing together in all the four individuals who are totally colour-blind. If they were linked in repulsion in III 2, then there would be 4 crossovers in the 11 offspring, but if in coupling then the distribution found here could be accounted for. The 10 deaf members of the family have all received the chromosome from their mother which bears the recessive gene for achromatopsia and the dominant gene for otosclerosis, but only the 4 colour-blind children have also received the chromosome bearing the recessive gene from their father, the others receiving the other chromosome of the pair carrying the normal allelomorph of the abnormal gene.

The possibility of such a linkage being actually present can, of course, be demonstrated only by pooling several pedigrees in which both conditions exist together or by being able to demonstrate linkage between both of these conditions with another marker gene for a particular chromosome pair.

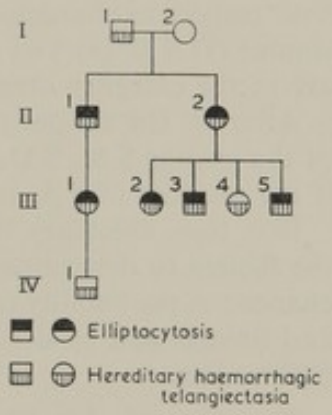

FIG. 13.—Pedigree illustrating the simultaneous occurrence of two rare dominant characteristics, elliptocytosis and hereditary haemorrhagic telangiectasia. (*From Penfold, J. B., and Lipscombe, J. M.* (1943.) *Quart. J. Med.*, N.S. **12.** 157.)

The potential value of isolated records such as this can also be appreciated from a study of the pedigree published in 1943 by Penfold and Lipscombe of two rare traits occurring simultaneously, elliptocytosis and hereditary haemorrhagic telangiectasia. A simplified portion of their pedigree is reproduced in Fig. 13 and it can be seen by analysis similar to the above that whatever the source of the elliptocytosis in generation I, be it from the father or from the mother, the subsequent transmission of the defects is such that the high incidence of crossovers makes this linkage most improbable.

These cases illustrate the use to which small pedigrees may be put in the establishment or refutation of the possibility of linkage between any two conditions. But this is not a technique applicable to the study of large numbers of individuals. Complicated mathematical analysis of the data obtained from the examination of parents and children, or of grandparents, parents, and children, with respect to two characters enables conclusions to be drawn about linkage.

Sib-pair method

Penrose, in 1935, first showed that it is possible to deduce linkage between characters on the autosomes by examining numbers of pairs of siblings all of one generation without knowledge of their parental characteristics, and this technique has the very great advantage that by it large numbers of family groups, such as school children, can be examined.

The principle of the technique is that if linkage exists between two conditions, then examination of large numbers of pairs of siblings with respect to these conditions reveals that there is a greater number of cases in which the sibs are similar in both characters, or dissimilar in both, than there are cases in which the sibs are similar in respect to one character and dissimilar in respect to the other.

This principle can be simply illustrated as follows.

If there are n children in a family, then the number of " sib-pairs " that can be studied is $\frac{n(n-1).}{2}$ Thus a family of 4 children represents 6 sib-pairs. If 2 characters, P and Q, are studied in these children, then each sib-pair will fall into one or other of four categories: (1) the pair is similar with respect to both characters. This group we shall describe as " similar-similar " (S.S.). (2) Both children are alike with respect to character P, but they differ with respect to character Q. This group is similar-dissimilar (S.D.). (3) The children are unlike with respect to character P, but alike with respect to Q. This group is dissimilar-similar (D.S.). (4) The children are dissimilar in respect of both P and Q. They are in the category dissimilar-dissimilar (D.D).

After all the sib-pairs have been allocated to one or other category, the totals of the groups S.S., S.D., D.S., and D.D. are noted, and linkage can be suspected if the product of S.S. and D.D. exceeds that of S.D. and D.S.

It is then necessary to apply the standard statistical χ^2 test of significance to the figures to determine the probability that the two conditions are associated by chance. A probability of under 0·05 is usually taken as possibly indicating linkage, and linkage can be definitely established if the χ^2 test indicates a probability of 0·01 or less.

The value of χ^2 is determined by the formula

$$\chi^2 = \frac{n(\text{S.S.} \times \text{D.D.} - \text{S.D.} \times \text{D.S.})^2}{(\text{S.S.} + \text{S.D.})\,(\text{D.S.} + \text{D.D.})\,(\text{S.S.} + \text{D.S.})\,(\text{S.D.} + \text{D.D.})}$$

A typical example of the demonstration by this technique of linkage between two characteristics is shown in the Table, adapted from Taillard (1951). In this case, sib-pairs, totalling 171 pairs, from 20 families have been studied with regard to the incidence of two characteristics of the ear: (1) the manner by which the ear is attached to the skull, whether it is flat or whether projecting from the head, and (2) the fashion of attachment of the lobe of the ear: whether it is completely free or whether it is attached to the skin of the cheek at the angle of the jaw. The Table shows the incidence of similar and dissimilar pairs in each family with the totals in each category, and χ^2 has been calculated according to the above formula. Its value of 9·55 indicates a probability of 0·001 (derived from standard statistical Tables) which means that there is only 1 chance in 1,000 that the association of these two characteristics so frequently could be due to chance.

TABLE

FREQUENCY AMONG 171 SIB-PAIRS IN 20 FAMILIES, OF PAIRS WHO ARE SIMILAR AND DISSIMILAR FOR TWO INHERITED CHARACTERISTICS OF THE HUMAN EAR (TAILLARD, 1951)

Fam. No.	SS	SD	DS	DD	Number of pairs
1	3			3	6
2	1	1	2	2	6
3	3		3		6
4	3			3	6
5	3			3	6
6	3		3		6
7	3		3		6
8	3		3		6
9	2		4		6
10	1	2	2	1	6
11	2		4		6
12	4	6	3	2	15
13	6			4	10
14	1	1	4	4	10
15		2	3	5	10
16	6		4		10
17	6	4	1	4	15
18	6	4			10
19	10				10
20	4		6	5	15
	70 a	20 b	45 c	36 d	171

Calculation of χ^2

		Mode of attachment of the ear		
		S	D	Total
Lobe of the ear	S	a (70)	b (20)	90 (a + b)
	D	c (45)	d (36)	81 (c + d)
	Total	115 (a + c)	56 (b + d)	171 (n)

$$\chi^2 = \frac{n(ad - bc)^2}{(a + b)(c + d)(a + c)(b + d)} = \frac{171\,(70 \times 36 - 20 \times 45)^2}{90 \times 81 \times 56 \times 115} = 9{\cdot}55$$

Probability: 0·001.

By similar techniques to this linkage has been established between, among other characteristics, red hair and the ABO blood groups, and between congenital absence of certain teeth and hair colour. If information is also available regarding parental characteristics, or from members of several generations in a group of families, other statistical techniques have been evolved which greatly increase the accuracy of the deductions that can be made from the available data. The mathematical computations involved are rather more complex, and are outwith the scope of this article.

Clinical applications

The value of these techniques is that if a group of individuals is tested for some of these tracer characteristics such as the blood groups and hair or eye colour, *at the same time* as spontaneously occurring inherited defects, then it is probable that after several such pedigrees are pooled it may be possible to allocate the inherited defect to one or other of the known linkage groups.

The sex chromosomes act in themselves as markers, and sex-linked characters such as haemophilia and colour-blindness are themselves therefore linked. Consequently, a careful search through the somewhat rare haemophiliac families should reveal examples of the more common defect of colour-blindness occurring in the same families. This has in fact been done in Great Britain by Riddell, who has carefully investigated 14 haemophiliac families, and found colour-defective persons in 3 of the families. His work has brought the total of such families found to about 19 in all.

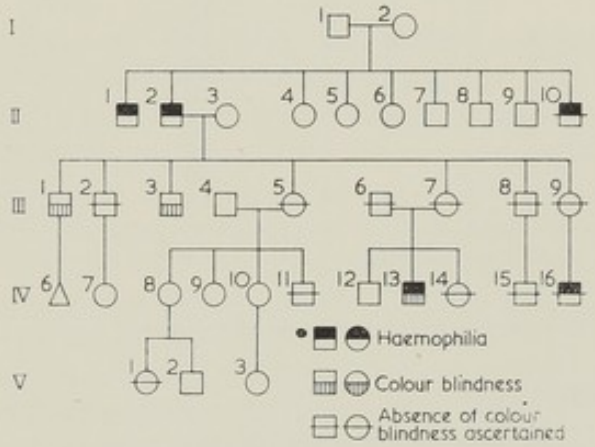

FIG. 14.—Pedigree illustrating the simultaneous occurrence in one family of two sex-linked characters, haemophilia and colour-blindness. (*From Riddell, W. J. B.* (1946.) *Ann. Eugen.*, **13**, 30.)

One of his pedigrees is shown in Fig. 14, where it can be seen that a haemophiliac male, II 2 married a woman obviously heterozygous for colour-blindness and among their offspring were 2 colour-blind sons and 2 daughters who transmitted haemophilia to their offspring, one of whom also was colour-blind. As the recessive genes for the two conditions in III 7 must have been on opposite X chromosomes, their appearance together on the X chromosome of IV 13 shows that crossing over must have occurred.

If the evidence for the linkage of haemophilia and colour-blindness is considered in all the reported families it is found that there is a cross-over value of about 4·5 per cent, meaning that the linkage between the two genes is fairly close, and that therefore their loci on the X chromosome must be near each other.

It is by the accumulation of data intelligently collected and interpreted in this fashion that increasing knowledge will be obtained which will enable us to make more detailed chromosome maps of some of the autosomes. This can already tentatively be suggested for the X and Y chromosomes and some of the genes carried on this particular chromosome pair can be approximately mapped.

Role of the clinician

The role of the clinician in the gathering of the evidence of linkage of inherited characteristics is essentially that of the collector, and detailed interpretation of

single and pooled pedigrees can be left to the statisticians and geneticists. The important aspect is that available information be recorded when it is first encountered and for this purpose there are several cardinal principles.

(1) Information should be sought of all members of an affected sibship in a family tree rather than isolated details from cousins.

(2) Parents should if possible be examined for the character detected in their offspring, and the grandparents as well, if they are available.

(3) When practicable, studies of the inheritance of abnormal characteristics should be combined in the same group of individuals with notes of the distribution throughout the family of some at least of the known " marker " characteristics. For this purpose blood grouping can be done and the co-operation of the National Blood Transfusion Centres should be sought for genetic studies. Supplies of solutions of phenylthiocarbamide can be obtained from the Galton Laboratory, Gower Street, London, W.C.1, in order to test for the dominant character of ability to taste the substance, and, if possible, note should be made in members of the family of some characters similar to those that have been described and used by Kloepfer (1946).

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CHAPTER 8

MUTATION

F. A. E. Crew

SPONTANEOUS MUTATION AND CHROMOSOME BREAKAGE AND RE-ARRANGEMENT

Normally, the process of chromosome reproduction is associated with self-copying on the part of the genes. Like begets like, and so similarity between parents and offspring in respect of their genes and therefore of their inherited characters is ensured. Exceptionally, however, a gene, before copying itself, undergoes a permanent change in its internal constitution—it mutates. Alternatively, the process of copying is not exact so that the new gene is, in respect of its internal constitution, unlike the one that brought it into being. A mutant gene of either of these kinds, when reproducing in its turn, brings into being a new gene like itself. It will, in its action upon the developing individual, affect the evolving characterization of the same tissue, organ or organ-system structurally or functionally as does the gene from which it sprang, but it will affect this evolving characterization to a different degree or in a different way and so give rise to a different end result. The mutant gene can be a hypomorph, doing its appointed job less efficiently than the original unmutated gene ; it can be a hypermorph, doing it even more efficiently ; it can be an antimorph, opposing the action of the unmutated allele or it can yield a new character, being a neomorph.

Gene mutation, the transformation of one allelic form of a particular gene into another form of the same gene, is not the only cause of novelty in characterization. The same effect can follow a faulty distribution of the chromosome material itself. A daughter nucleus can come to include within it more than the standard number of chromosomes, one or more or even the whole set of the chromosomes being present in triplicate, whilst in the other daughter nucleus there can be but one member of one or more or of every homologous pair. In many instances this abnormality in respect of chromosome number, of the number of loci, is reflected in specific changes in characterization and is commonly followed by abnormality in respect of the distribution of chromosome material in gametogenesis on the part of the individual concerned.

Quantitative abnormality of a similar kind frequently occurs when, following the breakage of chromosomes, sections of one or more become included in or absent from daughter nuclei. Following such breakages inversions and translocations can arise.

Age and sex in relation to mutation

In man a correlation would seem to exist between the frequency of the spontaneous mutation that yields chondrodystrophy and the age of the mother, older mothers having a significantly higher rate of mutant births. Birth rank is not

involved. It is not finally established as yet, however, whether the age of the father is also a factor that has to be taken into consideration. But in the case of haemophilia a separation for the two sexes has been made. Since haemophilia is the expression of an X-borne recessive gene, and since one such gene in the male yields the character, whereas for its expression in the female the gene must be present in duplicate, it follows that if the mutation rate were the same in both egg and sperm then the number of affected males in the population in relation to the number of " carrier " females would be as 3 : 1, for after fertilization one half of the ova carrying the mutant gene would develop into males and the other half into females, and all of the sperm carrying the mutant gene would yield females. If the mutation was restricted to ova, then equal numbers of afflicted males and carrier females would result. On the other hand, if mutation was restricted to the spermatozoa then carrier females would be expected. The available data concerning haemophilia strongly suggest that the mutation rate for haemophilia is much higher in male than in female gametes, possibly ten times higher.

The frequency of spontaneous mutation

Spontaneous gene mutation is an exceedingly rare event, being of the order, it has been estimated, of 1 in about 100,000 germ cells in man. But since in a given individual the total number of genes is so great (somewhere between 5,000 and 120,000 in man), mutation in the genotype as a whole is by no means uncommon. It can be accepted that any crop of germ cells contains, in addition to a few mutations of recent origin, ten or a hundred times as many mutant genes that arose in the individuals of the preceding generations and which have accumulated in the population. Every individual in a population like our own comes to differ from every other individual (save in the case of identical twins) in respect of the number, and especially in respect of the kind, of mutant genes within the genotype. That this remains largely unsuspected, prior to mating and reproduction, is due to the fact that most of these mutant genes, being present only in the simplex state, exert only a minute influence upon the individual's characterization.

Calculation of mutation rate

In the case of a dominant mutant gene with full penetrance and yielding an abnormal character that is never simulated by an acquisition, it is possible to estimate the mutation rate by taking a census of afflicted offspring born to parents who do not exhibit the abnormality. Thus in one genetic investigation of chondrodystrophy, 10 afflicted children were found among 94,075 born in a Copenhagen maternity hospital. Of these 10, two were found to have an afflicted parent. There were thus 8 cases which must have been the result of a gene mutation, or 1 in nearly every 12,000 births. Since each of these individuals received from its parents the two alleles, one from each, and since the mutant chondrodystrophy gene is a dominant, one mutant birth in 12,000 represents one mutant allele in every 24,000, or a rate of about 4×10^{-5}.

But this direct method of estimating the mutation rate cannot often be applied and another and indirect one has to be used. According to the genetical theory of evolution, generally accepted in Great Britain, all living organisms and all their characterizations have arisen through the preferential survival of those mutations that conferred some advantage upon the individuals possessing them. Between

the characterization of the species and of the individuals comprising it on the one hand and the conditions and circumstances of the external world on the other there has slowly come into being an equilibrium. If this be granted and if the conditions of the external world remain unchanged, then it follows that a change in the genotype of any considerable magnitude can mean the disturbance of this equilibrium. Since mutation is accidental and pursues no particular direction, it must in most instances be disadvantageous. It is the case that most gene mutations (99 per cent) are, in fact, demonstrably deleterious when judged by the yardstick of continuance and reproduction. The smaller their effects the less harmful they tend to be. The very rare ones, which turn out in experience to be advantageous and which therefore become incorporated into the genetical constitution of the species, usually represent quite small deviations in characterization from the pre-existing. Thus it is that evolution tends to proceed by slow accretions under the guidance of natural selection.

Gene equilibrium.—Since most mutant genes are harmful, interfering with the prospects of survival and reproduction on the part of the individual possessing them, it follows that their action can be revealed in the early mortality of individuals possessing them and in the size of the family in pedigrees in which such genes operate. Such elimination and such relatively small family size mean that such a mutant gene will not be transmitted to the same extent as are their "normal" alleles. If, for example, a dominant mutant allele leads to the death of its carriers before their families are completed, so that the size of family is on the average only half that of the population as a whole, then the frequency of this gene would decrease by 50 per cent in every generation and in the course of time would tend to disappear. If every case of epiloia or of chondrodystrophy was the offspring of a parent who was similarly affected then the incidence of these conditions in the population today should be far less than it was a few centuries ago. But this is not so. As far as can be ascertained, their incidence now is not lower than it was. Thus, if the records of the last few centuries are to be relied upon, elimination must have been paralleled by fresh mutations and considerable numbers of cases of such conditions as epiloia and chondrodystrophy must be the offspring of unafflicted parents.

It is commonly accepted that a population undisturbed by the action of mutagenic agencies of an artificial kind tends to reach an equilibrium between the numbers eliminated by early death or non-propagation and the number of fresh mutations arising in each generation, between loss and gain. It is this presumed equilibrium that allows calculation of mutation rates to be made also for recessive genes.

Some mutation rates

There are exceedingly few inherited human abnormalities among those that have been examined which have a frequency in the population exceeding 1 in 10,000, and the reason for this rarity is, of course, the rarity of mutation. In certain investigations colour-blindness has been found to have a frequency of about 7 per cent among males in the population of the United Kingdom. Premature baldness is even more common. But these need not be classified as pathological states even though they are deviations from the present standard of normality. Thalassaemia major, it has been estimated, occurs in about 1 in 2,500 individuals

of certain Mediterranean ethnic stocks in the United States of America. Sickle-cell anaemia in certain population isolates is even more common. The recessive forms of retinitis pigmentosa in Great Britain has a frequency of about 1 in 5,000, but possibly more than one gene produces this condition. It has been estimated that the mutation rate in haemophilia is 1 in 10,000 for the male and 1 in 100,000 for the female, that the rate for epiloia is 1 in 60,000–120,000 and for achondroplasia 1 in 20,000. It is established that in a wide range of animals and plants different genes within the genotype of the same species can vary widely in respect of their mutability. This presumably is also true for man.

The frequency of spontaneous mutation in *Drosophila* is regarded as being much too high to be completely accounted for by the amount of natural radiation that is received during the brief lifetime of the individual. A human life is far longer than that of a fly and the amount of natural radiation received by human genes is thus many hundred times as great. Yet for the most part the mutation rates that have so far been determined in fly and man are not too dissimilar. There are a number of human genes which have a much higher mutation rate than do any of the genes of *Drosophila*. But in spite of this, and in spite of the far longer period of exposure of human genes to radiation, it is generally agreed that in man, as in the fly, most mutations are caused by random energy fluctuations and internal mutagenic influences.

INDUCED MUTATION AND CHROMOSOME BREAKAGE AND RE-ARRANGEMENT

Gene mutation

A gene is known to be compounded of protein and nucleic acid. The spontaneous mutation of a gene would appear to be due to localized mishaps which occur during the course of thermal agitation, taking the form of random movements on the part of molecules and of their component parts. Since temperature affects the frequency of molecular and sub-molecular collisions, it is not surprising to find that the frequency of spontaneous gene mutation is increased several times when the germ cells (of selected experimental material) are exposed to a raised temperature. Nor is it surprising, in retrospect, that it should be found that a variety of chemical and physical agencies applied in particular ways and at particular times during gametogenesis affect the mutational frequency. High energy radiation, mustard gas, ethyl eurythane and formaldehyde, for example, being able to penetrate the cell and nuclear membranes, have been shown to have a pronounced action of this nature. Of these mutagenic agencies radiation is the only one to which human beings are likely to be exposed in the ordinary course of events and in quantity sufficient to yield any significant increase in the frequency of mutation.

Radiation

Exposure to such radiation, x-rays and radioactive substances generally, can result in the production of a wide range of gene mutations, but they are the very same as those that are the outcome of spontaneous mutation. When classified according to the effects they produce in certain forms of experimental material these artificially induced mutations are found to appear in substantially the same proportions as they do among spontaneous mutations.

The mutagenic action of radiation is held to be proportional to the total dose. It is not affected by the distribution in time of the dosage ; the effects are cumulative. There is good reason to conclude that there is no threshold dose, no dose so small as to have no effect. The intensity of radiation appears to be without effect upon the frequency of the mutation induced by a total dose. Thus in *Drosophila* the spontaneous mutation rate for certain sex-linked lethals is of the order of 0·15 per cent, and much higher than this for mutations in general. A dose of 50r induces a frequency of mutation in the immature germ cells equal to this spontaneous mutation rate for the whole generation time and becomes added to this. A dose of 50r, given in a fraction of a minute, appears to have the same effect as does the same dose spread over several weeks.

The mutation rate in general in *Drosophila* is about one mutation in every twenty newly produced germ cells. It has been found that 100r received by immature germ cells induced gene mutation with a frequency about equal to this, and that 200r doubled this rate.

Most kinds of radiation differ but little among themselves in respect of mutagenic effectiveness, but neutrons are exceptional in that their effectiveness is only about two-thirds that of x-rays.

Other mutagenic agents

Mutation is not an adaptive response to the action of a particular mutagenic agent ; there is no known relation between the kind of stimulus and the kind of mutant gene produced. There is some evidence, however, that the amount of mutation provoked by the action of a mutagenic agent is affected by a number of conditions. Chromosomes in the condensed state, as in the spermatozoon, would appear to be more susceptible to mutational changes caused by radiation, but not by chemical mutagens, than when they are in other states. Ovarian tissues appear to be somewhat less sensitive than testicular tissues. The concentration of oxygen in the immediate micro-environment of the chromosome, and the temperature of that environment (because temperature affects oxygen concentration) affect the frequency with which mutations are induced.

When once a mutation has occurred or has been artificially produced it is permanent so long as it does not itself undergo mutation. Individuals breeding long after exposure continue to produce gametes bearing the mutant gene(s). It commonly happens that following the exposure to the mutagenic agent there is a period of infecundity, but when this has ended the mutagenic effects are revealed.

Chromosome breakage

Mutagenic substances likewise cause chromosome breakage, which can be followed by maldistribution of the chromosomal material—inversion, translocation and deletion of whole chromosomes or of sections thereof. Breakage followed by abnormal reconstitution of the chromosome, as in inversion and translocation, results in a rearrangement of loci within the chromosome. Such rearrangement is sometimes followed by a change in the effect of the genes themselves upon development. A gene in a new position can have an effect upon characterization equal to that of a mutant gene. Such reconstituted chromosomes reproduce themselves

permanently in their novel form and can be responsible for much embryonic death.

The frequency of chromosome breakage following upon artificial radiation has been found to be somewhat higher than that of gene mutation. When it is followed by rearrangement its frequency is proportional to the total dose received. Neutrons are more effective in causing chromosome breakage than are x-rays.

SOMATIC AND GAMETIC MUTATIONS

Mutation occurs both in body cells and germ cells. Somatic mutations are, of course, not transmitted to succeeding generations. The irradiation of an individual may produce mutations of both kinds, the first affecting the individual's own body, the others not affecting the individual but being transmitted to its progeny. Aberrations in the distribution of chromosome material in both somatic and gametic cell are likewise produced by irradiation.

Somatic mutation

The effect of a somatic mutation is determined by the kind of cell in which it occurs, whether or not the cell is one which will undergo further multiplication. The effect of the mutation upon a cell that is to undergo no further division can vary from nothing discernible to the death of the cell, which will be a matter of no moment so far as the individual is concerned. If, on the other hand, a gene mutation has occurred in a somatic cell which can thereafter undergo division, this gene mutation will be transmitted faithfully to all its descendants, unless of course the mutation has been of such magnitude as to kill the cell itself. If the mutation is of a recessive kind no effect will be manifest ; but if it has been either a dominant or else a hemizygous sex-linked mutation these effects will be observable in the descendants of the cell. If these descendants remain together as a definite part of a tissue, organ or organ-system, then a sector of mutant cells will develop. On the other hand, if the daughter cells originating in a mutant cell of this kind become dispersed, as do the white blood corpuscles, then a proportion of the total number of the circulating cells will include the mutant genotype.

Since the majority of mutant alleles are recessive, it follows that most somatic mutations will remain unnoticed. But further mutation may occur which transforms the heterozygous into the homozygous recessive, when the abnormal characterization will become displayed. The same effect may be due to the unusual distribution of chromosome material, so that a daughter cell may come to possess two chromosomes each carrying the recessive allele.

Another method whereby the homozygous recessive form may appear is by chromosome breakage and faulty reunion in such a way that the daughter cell comes to possess two sections of a particular chromosome pair each carrying the recessive allele.

Chromosome fragmentation in the nuclei of somatic cells can lead to cellular death. Fragments without a kinetochore will become lost during mitosis so that the resulting cells will be deficient in respect of such segments. In many instances such loss will mean either the death or the abnormal functioning of the cells

concerned. The effect of such cellular loss upon the individual may be indeed small since the death of such abnormal cells is commonly compensated for by an increased reproduction of other cells which did not undergo such abnormal chromosome distribution.

At the present time but little is known concerning the quantitative aspects of somatic mutations induced by radiation. It would appear that different kinds of cells present a different grade of sensitivity, as do all of the same kind of cells in different stages of cell division. Radiation certainly yields a high incidence of chromosome breakage.

Gametic mutations

In gametic mutations the autosomal dominant with full penetrance becomes phenotypically manifest amongst the immediate children. Sex-linked alleles appear in an easily predictable fashion in an early generation. Recessive autosomal alleles will become visible only when two like gametes meet. This probability is affected by the breeding structure of the population, by the amount of inbreeding, by the formation of isolates and so forth.

Chromosomal aberrations can occur either in the immature or in the mature germ cell. Should they occur in the immature then their behaviour is the same as those present in the somatic cells and will lead to unbalanced relationships in respect of chromosome material in the cells derived from them. Such daughter cells with considerable abnormality in respect of chromosome material either die or are non-functional.

Fertilization involving a gamete with a less marked quantitative abnormality can result in the formation of an abnormal zygote. Investigations on the mouse and the rat have shown that many, if not all, zygotes with such chromosomal imbalance develop abnormally. According to the extent of the imbalance and also to the effect of the genes themselves upon the individual characterization development may come to an end at a very early stage, resulting in abortion or, at a later stage, in stillbirth.

Other grades of chromosome imbalance may produce a phenotypically normal individual but one which in its turn will produce abnormal offspring due to abnormalities in respect of the distribution of chromosome material during gametogenesis. Such individuals may therefore tend to be infecund.

It seems probable that in man the genetic effects of irradiation will be displayed more frequently among individuals which were conceived shortly after the irradiation of the mature sperm of their sires than amongst those which are the products of sperm produced much later, the reason for this being that the frequency of abnormally developing zygotes derived from sperm irradiated whilst mature is much higher than among such as originate in sperm which are descended from spermatocytes so irradiated.

MEDICAL AND SOCIAL ASPECTS OF MUTATION

If evolution has been the outcome of the interaction of the processes of mutation and of natural selection, it would seem reasonable, at first sight, to make deliberate use of the techniques of radiation to increase mutation frequency in order to pro-

The homozygotes are more seriously affected than the heterozygotes, while at least the majority of homozygous women also show some degree of baldness (Snyder and Yingling, 1935). The heterozygous expression is, however, not absolutely restricted to the male, for the condition is occasionally apparent in a heterozygous woman, though this is rare. Moreover, the age of onset and degree of the symptoms are variable, so that a heterozygous male occasionally escapes detection.

The situation therefore may be summarized by saying that half the sons of an affected male will develop early baldness, that his daughters will usually, though not quite always, be unaffected, and that the condition can be transmitted equally by either sex. Thus baldness may be brought into a family through a normal woman who shows no evidence of it, though her relations will do so.

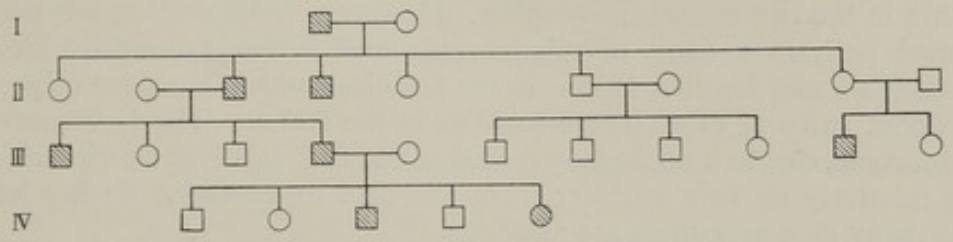

FIG. 7.—Inherited early baldness (omitting those who died before 35 years of age).

A fairly typical pedigree is illustrated in Fig. 7. The affected woman in the fourth generation is probably an instance of exceptional female manifestation in the heterozygote, already mentioned; but this is not certain, since the necessary details for her mother's family are lacking. If her mother were a heterozygote, then the affected woman in question would probably be a homozygote; though if that is the correct interpretation, it is rather surprising that only one of her three brothers is affected since, on the average, three-quarters of them are expected to be so.

Owing to the small size of human families, it is not usually possible to say whether or not a normal woman carries the gene for early baldness when her maternal grandfather was bald. This is a matter of some consequence, for it is applicable to all similar conditions of sex-limited inheritance. Consider the family of three sons and one daughter, all unaffected, in the third generation of the pedigree. The father (in generation II), though from a family in which the condition is hereditary, has retained his hair; therefore it is very unlikely that he has transmitted the gene. The mother comes from a family in which the necessary details have not been recorded. Let us suppose that it was an affected one, and that early baldness had appeared among her brothers. The chances that she carries the gene in question or its normal allelomorph are, of course, equal. But her three unaffected sons (in generation III) are quite insufficient to exclude the possibility that normal and affected males would appear in equality if the family were a very large one. We should in fact require a minimum of eight sons, all unaffected, to reach reasonable security on this point. That is to say, taken at its face value, we have no ground for concluding that the single daughter under

consideration in generation III is not a carrier because her three brothers are all normal, supposing her mother's family to be affected.

White forelock

The inheritance of dominant white forelock appears to be very similar to that of premature baldness. Indeed, as far as the evidence goes, its appearance in the female is even rarer, though the data available for forming such an opinion are less extensive (Cockayne, 1933).

Oligophrenia and the Laurence-Moon-Biedl syndrome

Several recessive conditions show evidence of partial sex-limitation, some appearing more frequently in the male and others in the female. In the majority of these, however, the information available to demonstrate the inequality of expression in the two sexes is incomplete. However, sex-limitation has been fully established both in a form of oligophrenia and in the Laurence-Moon-Biedl syndrome (Csik and Mather, 1938). In the families studied, recessive oligophrenia occurs about twice as often in the male as in the female. The Laurence-Moon-Biedl syndrome, due to a single gene recessive, in effect involves a series of features varying relatively in their intensity from one case to another. Rather less than twice as many men as women are affected.

It should be noticed that such results as these could not be produced by sex-linkage, whether total or partial. With recessive total sex-linkage the excess of affected males over females is, for rare conditions, immense; the ratio being as $q : q^2$ or as $1 : q$. That is to say, a disease affecting one male in a thousand appears only in one female in a million. Partial sex-linkage may, on the other hand, result in any degree of association with sex, depending upon the distance of the gene concerned from the non-pairing region of the X-chromosome. However, owing to crossing-over, affected individuals will be more frequently males in some families and more frequently females in others: there is no consistent tendency in the population as a whole for the gene to affect one sex more often than the other, as with sex-limited inheritance.

Allergies

The sex-limitation of the allergies has special importance clinically. It is of the semi-dominant type resembling, on the whole, the behaviour of early baldness. At least the majority of allergic conditions are due to a variety of environmental stimuli operating on those individuals which carry a single gene producing general susceptibility to them. When homozygous, the effect appears before puberty; when heterozygous, it first develops later in life or may never do so at all. Individuals of the latter type act as normal " carriers" . Moreover, manifestation is sex-limited in the heterozygotes, but apparently not in the homozygotes, about twice as many men as women being affected (Wiener, Zieve and Fries, 1936).

We have not yet sufficient data to determine the genetic relationships of all the various forms of allergy: asthma, hay-fever, urticaria, light-sensitized skin, the food allergies, migraine, angioneurotic oedema, and others. However, it is clear that in some instances at least the form taken by the allergy is due to other genes modifying the action of the single controlling one already mentioned.

Thus asthma, for example, may be inherited for some generations in a family, then to be replaced by hay-fever in one individual of the pedigree, among whose descendants that particular allergic form may be perpetuated on the same genetic basis.

It should be stressed that the evidence for the genetics and partially sex-limited inheritance of these various allergies is not all of equal value, and there is much danger in generalizing in regard to conditions insufficiently studied or even due to distinct genes having similar effects. Of this latter possibility we here have a clear warning, for a non-allergic form of angioneurotic oedema also exists. This is inherited as a simple heterozygous condition (usually, though incorrectly, described as a dominant in the literature); it does not appear to be sex-limited. Indeed, one of the outstanding needs of human genetics is the study of a sufficient number of pedigrees to make possible statements in regard to the frequency of manifestation of the genes, both their penetrance and expressivity, and their differential effects in the two sexes.

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CHAPTER 6

POLYGENIC INHERITANCE

KENNETH MATHER

MAN is a difficult animal for genetical research. His families are small, his generations slow and his mating is uncontrolled—except, of course, for certain traditional prohibitions, such as the forbidden degrees of relationship in marriage in western civilization, which eliminate matings of types which are frequently among the most informative from the genetical point of view. Attempts have been made, notably by Galton and the biometrical school which followed him, to use man as a subject for primary genetical research, but these all failed. Our understanding of the nature, transmission and action of genes has come from experimental work on plants and other animals. Of these the most outstanding has been the fruit fly, *Drosophila melanogaster*, in which control of mating is easy, the generation time as short as two weeks at 25°C, families so large as often to run into hundreds or even thousands from a single pair, and culture so unexacting that several hundreds of flies can be raised in a half-pint milk bottle.

The rules of genetical behaviour have been gradually established by experiment with these more tractable species, and they have proved to show a remarkable similarity in all the great groups of the living kingdom, with the possible exception of bacteria which have yet to be tested adequately. Armed with this knowledge we can return to man, and even though we could not hope to elucidate the rules of genetics from his study, once knowing them we can show that he also conforms. Indeed, in view of the virtually universal validity of these basic principles, it would be very surprising if man did not behave in the same way.

Even, however, the demonstration that man's genetical behaviour conforms to principles fully elucidated from other species is far from simple. We must generally infer the genetical constitution of parents from their offspring, and such inference must often be highly uncertain where the families are so small. To take an example, individuals showing the effects of a recessive gene will generally occur in the offspring of apparently normal parents. Having seen such an individual we can infer that the parents were both heterozygous for the gene. But only one child in four is expected to show the character. So with families of, say, two, an affected child will fail to appear in nine-sixteenths of cases. Thus we shall miss over half of the families of two which would be of interest to us. We shall obtain in fact a biased sample in-so-far as we must rely on finding an affected child in order to detect carrier parents; and in the families we actually find more than one-quarter of the children will show the affection. Only by the use of suitably elaborate mathematics and statistics can we show that the segregation does in fact conform to the mendelian expectation of $\frac{3}{4} : \frac{1}{4}$ of all children from such parents. And with more complex phenomena like linkage the necessary mathematics become more elaborate still.

Thus man is, and indeed must remain, to a great extent, what might be called an object of secondary genetical study. There are exceptions to this rule. Our knowledge of blood group determination and of the properties of twins springs largely from human studies, but by and large the human geneticist must rely on observations of other species for his general guidance and his basic principles. At present this is perhaps more strikingly true of the study of polygenic systems than of any other branch of genetical science; for the real attack on the genetics of continuous variation, from which the theory of polygenic inheritance directly derives, is very recent. Although continuous variation was first considered in relation to man, and although much of the early work on its analysis related to man, the recent investigations have been on other species and their results have still to be applied to man himself. That they will apply can hardly be doubted.

CONTINUOUS VARIATION AND POLYGENIC SYSTEMS

Mendelian genetics has been concerned with discontinuous variation. Mendel could classify his pea plants as talls or dwarfs, as having coloured flowers or white. The classes did not merge: the tallest shorts were clearly shorter than the shortest talls. Such discontinuous variation allows the mendelian method of experiment to be used, since the genotypes are easily inferable from the sharply distinct phenotypic classes. The situation is different, however, with continuous variation, such as, for example, that in human stature. There are tall people and short people, but every intermediate grade is also to be found and indeed the medium heights are the most common (Fig. 8). No sharp dividing line exists between tall and short people as it does between Mendel's tall and short peas.

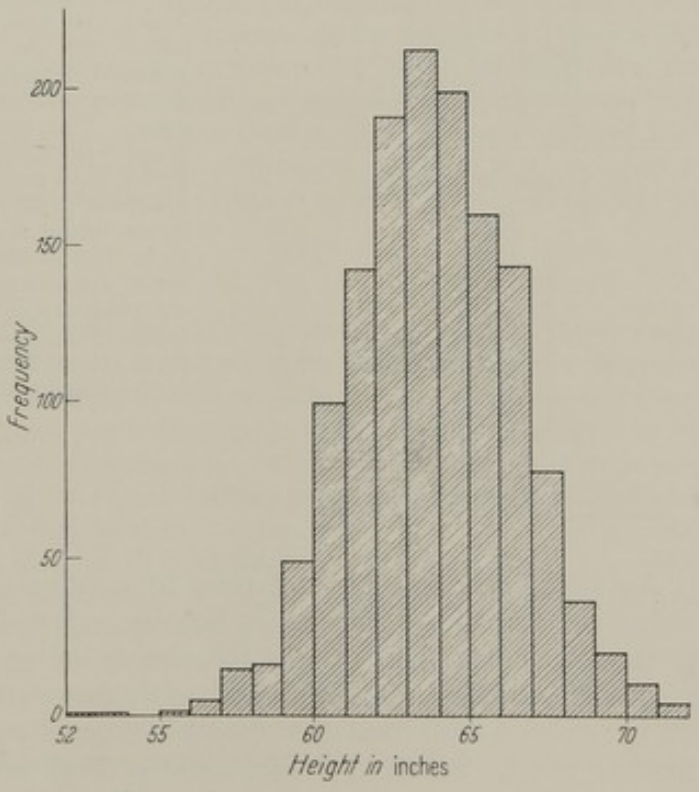

FIG. 8.—Continuous variation. The frequency distribution of stature in 1,376 women. All grades of stature occur between wide limits, the central heights being the most common. The data are grouped into 1 inch classes in order to facilitate representation as a histogram. This grouping is purely artificial: the character shows a smooth gradation of expression. (*Data from Fisher, "Statistical Methods for Research Workers". London: Oliver & Boyd.*)

Now such continuous variation has been known since the time of Galton to be in part heritable, though clearly its heritable differences cannot be traced to genes of large effect. Rather we must refer them to genes whose differences produce only small variations of the phenotype, variations as small in fact as the very fine gradations we can detect in the expression of the character. Since extreme phenotypes are to be found, these must differ in large numbers of genes, whose small effects must therefore be capable of supplementing each other. The genes of continuous variation are thus acting in swarms, or as we say in polygenic systems. The member genes of a system are interchangeable in effect, and intermediate expressions of the character are due not to the action of specific genes of intermediate effect, but to the simultaneous actions of intermediate numbers of genes all of like, or nearly like, effect.

Thus in a polygenic system we are concerned less with the individual gene, and more with the number acting in a given direction in the individual. The intermediate phenotypes can therefore be produced by several, often many, different genotypes. With, for example, a system of only 4 genes lacking dominance, the phenotype given when 4 of their total of 8 allelomorphs act together in one direction, the other 4 acting in the other direction, would be produced by 19 different genotypes (Fig. 9). Clearly the mendelian method of experiment and analysis must break down with continuous variation, for we cannot infer a particular genotype when a particular phenotype is found.

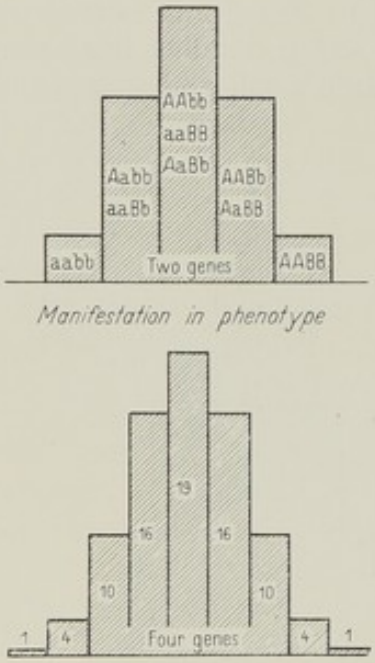

FIG. 9.—The genetical theory of continuous variation. The upper histogram shows the frequencies to be expected for the five phenotypes, where character expression is under the control of two genes *A*—*a* and *B*—*b*, of equal and additive effect and without dominance. The phenotype is thus proportional to the number of capital letters in the genotype. The genotypes giving each phenotype are indicated. The frequencies are those to be expected in a randomly breeding population where *A* is as common as *a* and *B* as common as *b*. The lower histogram shows the same where four genes are involved in the system. The numbers are the numbers of genotypes giving each of the phenotypes. Not all of the genotypes in any one phenotypic class are, of course, present with the same frequency. Non-heritable variation is omitted for simplicity.

As soon, therefore, as we turn to continuous variation governed by such polygenic systems, our genetics becomes statistical, somewhat in the way that physics becomes statistical in the theory of gases. We must devise statistical means of detecting, measuring and analysing segregation, linkage, dominance and all the other phenomena that mendelian genetics has taught us to associate with nuclear genes. We need in fact more general methods of genetical investigation.

These have been achieved over the last thirty years or so. Progress was slow at first, but has been much more rapid in the last decade. We have learned how to show statistically that genes which cannot be followed as individuals in experiment are nevertheless just as surely borne on the chromosomes as those that can.

THE TESTS OF NUCLEAR INHERITANCE

Since the assumption of nuclear, or as we might say mendelian, behaviour of these genes is basic to our methods of analysing the continuous variation mediated by polygenic systems, it is worth considering the evidence upon which our confidence in the validity of the assumption rests. Nuclear genes have three essential properties by which they can be recognized (Mather, 1949 a and b). (1) They are equilinear in transmission, that is, they are handed on equally by father and mother to offspring, apart from special cases of which sex-linkage is the most important. (2) They segregate at gametogenesis in heterozygotes. (3) They show linkage.

Wherever these properties are shown, nuclear genes borne on the chromosomes can be inferred with confidence.

Equilinearity in transmission

The property of equilinearity in transmission is tested by the comparison of reciprocal crosses. If mother and father are contributing equally to the genotype mediating a particular character in the offspring, it does not matter which way round a cross is made. Reciprocal crosses will give similar families. Many examples are recorded of reciprocal crosses between true breeding lines of both plant and animal species differing by continuous variation. In a very few cases differences were found between the offspring of the reciprocals where none would be expected on the basis of nuclear transmission; but these are exceptional. In the vast majority of experiments the reciprocal families did not differ. Genic transmission was equilinear. Furthermore, reciprocal differences do occasionally occur in mendelian experiments with discontinuous variation. We are thus in a position to say from the evidence of reciprocal crosses, that although extra nuclear genes may play a small part in the mediation of continuous variation it is no larger a part than they play in discontinuous variation. Nuclear genes are as predominant in one as in the other.

Segregation

When we turn to our next test, of segregation, the evidence is equally clear. Individuals of true breeding lines may vary continuously in respect of the manifestation of a character by reason of non-heritable, or environmental, effects. The F_1 of a cross between two such lines, which though heterozygous, not homozygous, is as genetically uniform as its parents, can show the same non-heritable variation. But in F_2 the genetical segregation which took place at gametogenesis of the F_1 will become apparent as genetical differences between the individuals. These will be added to the non-heritable variation, so that the variation should be larger in F_2 than in F_1 and parents. Furthermore, F_3 families should again show variation due to segregation in gametogenesis of F_2 individuals, but this should be on the average only half that of F_2 since individuals of the F_2 are on the average heterozygous for only half as many genes as those of F_1. Thus the average variance within F_3 families should lie midway between that of F_2 on the one hand and those of parents and F_1 on the other. Furthermore, the means of the F_3 families should differ from one another and should be correlated with the expression of the character

in the F_2 parent individuals, for these F_2 individuals will differ in the various genes for which they are homozygous.

The predictions which follow from the principle of segregation are, therefore, many and precise. They have been confirmed wherever adequately tested in both plants and animals. There can be no doubt that the genes mediating continuous variation segregate in just the same way as the major genes of mendelian experiment.

Linkage

The third test, of linkage, can be applied in a variety of ways. The polygenes of continuous variation must show linkage with mendelian genes borne on the same chromosomes. They must also show linkage with one another. Linkage with major genes has been tested by observing the continuous variation of a character in classes separated by the segregation of major genes affecting other characters. We find that these classes commonly differ in their mean expressions of the continuously varying character just as would be expected. We also find that the association is not a final one, that is, it can be changed and even reversed, just as it should if it were the outcome of linkage and not of a multiple, or pleiotropic, action of the major gene. The linkage of polygenes with one another is best tested by selection experiments. These tests are, however, complicated, and it will suffice to say that they regularly yield evidence of linkage wherever it would be expected to show clearly.

The phenomenon of linkage can also be used in *Drosophila*, where many special tester stocks exist, to assay the contributions of the various chromosomes to the control of continuous variation. Such assays are, for various technical reasons, unlikely to trace every determinant of continuous variation that is carried on the chromosomes; but even so, it has proved possible to show in a comprehensive experiment that some 90 per cent of the heritable portion of continuous variation for a hair character in *Drosophila melanogaster* must be referred to genes in the chromosomes (Mather and Harrison, 1949). There can be little doubt that the remaining 10 per cent are subject to nuclear determination but have escaped detection because of the technical difficulties just mentioned.

There can therefore be no doubt not only that nuclear genes play their part in the mediation of continuous variation, but also that they play as predominant a role here as they do in the determination of the major differences used in mendelian experiments.

Applications to man

This evidence is all from species other than man: species in which the complex experiments needed for the tests are possible. We have little hesitation in applying these findings to man, because of the uniformity of the various plant and animal species tested in respect of the control of their continuous variation, and of the uniformity of man with other species in his general genetical make-up. We have, however, various pieces of evidence from man himself which must go far to strengthen our confidence in the importance of nuclear genes in mediating his continuous variation.

Regression

The first of these pieces of evidence shows that transmission in man is equilinear as it is in other species. We cannot of course test equilinearity within a population such as our own by producing inbred and therefore true breeding lines whose behaviour on crossing could be observed. We can, however, use Galton's technique of regression to ascertain the contributions of father and mother to the determination of continuously varying characters in their offspring. In doing so we find the paternal and maternal contributions to be substantially equal. Sex linkage which can upset equilinearity is not expected to produce any serious

complication in man as the sex chromosomes constitute only 1 of 24 pairs in the human nucleus.

Race Crosses

Race crosses can also supply evidence of equilinearity since, although not true breeding in all respects, whites and Negroes for example are true breeding in respect of the genes leading to the basic colour difference. This difference we also know not to be ascribable to a simple mendelian gene: rather it must be referred to a polygenic system of unknown complexity, for many shades of colour are possible in the generations derived from such race crosses. I am not sufficiently familiar with the evidence from race crosses to make a fully positive statement, but I have yet to hear that the colour of the offspring is in any way affected by whether the mother is the dark parent and the father the light or *vice versa*. In other words, so far as I know, the evidence, such as it is, accords with equilinearity of transmission.

These race crosses also allow the test of segregation to be applied. We should expect the first generation from such crosses to be as uniform in colour as the two parental types; but when the hybrids breed, whether in crosses *inter se* or in crosses back to the parental stocks, a range of colours should arise from the segregation of the colour genes in their gametogenesis. This expectation is, so far as I am aware, fully borne out by the facts.

THE ANALYSIS OF CONTINUOUS VARIATION

We have seen that the heritable component of continuous variation is referable to nuclear genes, genes whose transmission in heredity is the same as that of the more familiar major genes of mendelian experiments. The two types of gene differ in their action. The action of each major gene is unique in the nucleus; it is also generally drastic so that its mutation has a markedly deleterious effect from the selective point of view. The members of a polygenic system, on the other hand, have actions similar to one another and capable of supplementing one another. Their effects are also small relative to the non-heritable variation, or at least relative to the total variation. These genes cannot therefore be isolated in genetical experiments of the mendelian kind: their effects are too small for individual detection and too much alike for individual recognition. The genes owe their special importance, in fact, to their effects being small and interchangeable, as we shall see later.

Since continuous variation mediated by a polygenic system cannot be analysed by the mendelian technique, we must devise a new and biometrical analysis. This we are able to do because, as we have seen above, we can confidently assume nuclear transmission for these genes as for major genes. Our task must be to discover how segregation and linkage, dominance and interaction contribute to the means, variances and co-variances which can be calculated from, and used to characterize, the distributions of a continuously varying character, just as in mendelian experiments we discover these phenomena from their effects on the

Components of variation

frequencies of the discontinuous classes.

Six components of variation can be recognized as contributing to variation in

a character, namely (1) the additive part of the heritable variation, which largely rests on differences between individuals differing by being homozygous for the opposite allelomorphs of the various genes; (2) the contribution from dominance, that is the departure from additiveness in effect of allelomorphs; (3) the contribution from genic interaction, that is the departure from additiveness in effect of non-allelomorphic genes; (4) any cytoplasmic or maternal effect, that is the departure from equilinearity in transmission of parental effects; (5) the non-heritable contribution made by differences of environment; and (6) interactions in effect of genotype and environment. This exhaustive list is so long as to be unmanageable in experiment. We must therefore reduce it before an analysis, sufficiently simple to be practicable, becomes possible.

The cytoplasmic or maternal effect can be tested by comparison of reciprocal crosses. If, as is commonly the case, these are alike we can neglect this component. If they are not we can calculate, from the difference observed, a correction for departure from equilinearity.

The two interaction components (3) and (6) are complex in their determination and possible effects. They are therefore unmanageable in analysis and are best omitted if possible. Generally their effects can be minimized, often eliminated, by choice of a suitable scale on which to represent the manifestation of the character. Thus genes which show interaction when the character is measured on a natural scale may fail to do so on a logarithmic scale (*see* Table). Rescaling by transformation of the metric is thus a powerful ally in reducing the complexity of the analysis. And if a scale is inadequate in this respect, evidence of the inadequacy can often be obtained from a simple analysis made on the assumption that interaction is absent.

TABLE

THE USE OF TRANSFORMATION OF SCALE TO GIVE ADDITIVENESS OF GENE EFFECTS

	aa	*Aa*	*AA*
bb	1	2	3
Bb	2	3	4
BB	3	4	5

Additive

	aa	*Aa*	*AA*
bb	1	4	9
Bb	4	9	16
BB	9	16	25

Additive on scale of square roots

1	2	3
2	3	4
3	4	5

	aa	*Aa*	*AA*
bb	1	3·2	10
Bb	3·2	10	32
BB	10	32	100

Additive on scale of logs

0	0·5	1
0·5	1	1·5
1	1·5	2

	aa	*Aa*	*AA*
bb	0·30	0·48	0·60
Bb	0·48	0·60	0·70
BB	0·60	0·70	0·78

Additive on scale of antilogs

2	3	4
3	4	5
4	5	6

The upper square shows the degree of manifestation of the character with the nine genotypes distinguished by two genes. When transformed as shown, the effects of the two genes become additive.

N.B.—For simplicity the present examples have been chosen so that dominance vanishes when the effects of non-allelomorphic genes become additive. This will not, however, be the case in general.

This leaves us with three components of variation for explicit incorporation in the analysis: the additive genetic variance (D), the effect of dominance (H), and the non-heritable or environmental contribution (E). Full accounts of the effects and constitutions of these components will be found elsewhere (Mather, 1949 a and b), and it will be sufficient for our present purpose to note their general properties. Where a gene *A-a* has the effect of producing a difference of $2d_a$ between the homozygotes *AA* and *aa* in their manifestations of the character, gene *B-b* the effect $2d_b$ and so on, we can define D as $S(d^2)$ in the absence of linkage and with the gene frequencies of *A* and *a* equal. Linkage, if operating,

introduces certain other terms in $d_a d_b$ and so on into D, and it can be detected by changes of the value of D from generation to generation in controlled crosses. Changes in gene frequency also affect the constitution of D in characteristic ways.

In the same way we can define H, the dominance component, as $S(h^2)$ where h_a is the departure of manifestation in the heterozygote *Aa* from the average, or mid-point, of *AA* and *aa*. Again H changes characteristically with linkage and with departure of gene frequency from equality. Again these changes like those of D can be used to detect linkage and change of gene frequency. Furthermore, variation in D and H over statistics in which their values should be alike, even with linkage and unequal gene frequencies, can be used to detect genic interactions arising from inadequacy of the scale, or irremovable by scaling, should these be present.

The non-heritable component E is of course composite, but we are concerned to break it down only in so far as this will promote genetical analysis. In general no such breakdown is necessary and we may content ourselves with noting that the value of E will obviously vary according to whether we are measuring the variation of the character among individuals or among the means of groups of related individuals. Finally, E will not contribute to the co-variance of related individuals in properly designed experiments, though it may do so in populations where related individuals tend to have environments more alike than are those of unrelated individuals, as happens in man.

Human stature as an illustrative example

The applications of this general theory to the understanding and analysis of continuous variation are many and varied. We will take one illustrative example from man. A wealth of data exists on the correlations between human relatives in respect of continuously varying characters. Pearson and Lee for example record that parent and offspring show a correlation of 0·4180 in respect of the cubit measurement, whereas full sibs show a correlation of 0·4619. Now it can be shown that, when measured as the mean square deviation from the mean in the customary statistical fashion, the variance of a randomly breeding population, to which man approximates, is built up as $\frac{1}{2}D + \frac{1}{4}H + E$. The co-variance of parent and offspring is simply $\frac{1}{4}D$, and the co-variance of full sibs is $\frac{1}{4}D + \frac{1}{16}H$. Then the parent/offspring correlation ($r_{p/o}$) and the sib correlation ($r_{s/s}$) are respectively

$$r_{p/o} = \frac{\frac{1}{4}D}{\frac{1}{2}D + \frac{1}{4}H + E}$$

$$\text{and} \quad r_{s/s} = \frac{\frac{1}{4}D + \frac{1}{16}H}{\frac{1}{2}D + \frac{1}{4}H + E}$$

These will have maximum values of 1 when $H = E = O$, that is when there is no dominance and no non-heritable variation. Non-heritable variation will reduce them almost equally, but dominance will reduce $r_{p/o}$ more than $r_{s/s}$. Given the values of these two correlations we can detect both non-heritable effects and dominance and even measure them, not of course in absolute values but relative to the value of D, for we have only two equations. If we had the actual values of the variance and the two co-variances we could go further and estimate the absolute values of D, H and E, for we should then have three equations.

In the present case where $r_{p/o} = 0{\cdot}4180$ and $r_{s/s} = 0{\cdot}4619$ we find $H = 0{\cdot}4201\ D$ and $E = -0{\cdot}0069\ D$. A negative value for E, which must be a quadratic quantity, is of course impossible. The present result must therefore arise from sampling error, and it is indeed small enough for this to be a reasonable interpretation. E may well be under-

estimated through the relatives, parent and offspring or full sibs, whose co-variances were calculated having environments more alike than those of the unrelated individuals from observations on whom the variance ($\frac{1}{2}D + \frac{1}{4}H + E$) was found. We can, nevertheless, be confident that E is not large within these families.

Thus the variation in cubit length is very largely genetical in this human sample. Dominance, on the other hand, is making a sizeable contribution to it. Now if all the genes were of the same effect and showed the same dominance, the fraction $\frac{H}{D}$ would be a measure of $\frac{h^2}{d^2}$ so that $\sqrt{\frac{H}{D}}$ would estimate the degree of dominance. We cannot, of course, be sure that the genes are all alike in magnitude of effect and dominance. Any differences in these properties will however lead to underestimation of dominance when estimated as $\sqrt{\frac{H.}{D}}$ Thus we can say that in the present case the average degree of dominance is at least $\sqrt{0{\cdot}4201}$ or 0·65.

THE PROPERTIES OF POLYGENIC SYSTEMS

The study of methods of analysing continuous variation is in its infancy, but it is commanding increasing attention. Plant and animal breeders and students of evolution need these methods because much of the variation with which they are concerned is of this kind. For the same reason the human geneticist also needs them, developed in ways suited to his peculiar material. He must, however, have another interest in polygenic systems if he is to understand the genetical structure of human populations, since these systems have properties which are remarkable in several ways (Mather, 1943; Darlington and Mather, 1950).

Prior to Mendel it was generally thought that inheritance was blending: that on coming together in the offspring the hereditary contributions made by mother and father blended like ink and water. Thus, it was supposed, hereditary variation was continually being destroyed at a great rate by crossing, for, once mixed, heredity could not be unblended. This Mendel showed not to be the case. True, when we cross two contrasting types their offspring may be uniform, so that the differences between the parents have vanished in the hybrid offspring. But the loss is only apparent. Being particulate, the genes segregate when the F_1 forms its gametes, and the parental differences reappear among a proportion of the individuals in the second, or F_2, generation. The variability must thus still have been present in the F_1, but present in a latent or potential form. The free variation, visible as differences between the parent's phenotypes, had been converted by crossing into the potential variation hidden as differences inside the F_1's genotype. This potential variability is freed, or partially freed, by segregation to express itself in the phenotypes of F_2. And such of it as remains potential in F_2 can be freed in later generations by inbreeding. Thus no loss of variability is in fact consequent on crossing. Heritable variability, like energy, is conserved, apart at least from the action of selection; though, again like energy, it can exist in potential as well as operative states.

Where a character is showing a difference governed by a single gene, the variability is hidden after crossing owing to the presence of two unlike allelomorphs of the gene in the F_1 individual. Such potential variability, depending on unlikeness

of allelomorphs, is the property of heterozygotes and is released by segregation of the allelomorphs when they pass separately to the gametes, each of which carries but one of them. Where a polygenic system is operating, however, the possibilities of potential variation are much more elaborate.

Potential variability

It is characteristic of a polygenic system that its member genes have similar and supplementary, as well as small, effects. Thus, suppose we have in the system several genes each of two allelomorphs, *A-a*, *B-b*, *C-c*, and so on, acting so that *A*, *B*, *C* and so on pull the character in one direction and *a*, *b*, *c* and so on pull it in the opposite direction. The extreme expressions of the character will be produced by individuals of genetic constitution *AA BB CC* and so on and *aa bb cc* and so on. Intermediate phenotypes will be found when the genes designated by capital and small letters are mixed: when in fact the genes are acting against, or balancing, one another. Furthermore, *B* or *C* can balance *a* just as *a* or *b* can balance *C* and so on. There thus exists in a polygenic system a type of potential variation which depends on dissimilarity, not of the allelomorphs of one gene, but of the allelomorphs of different members of the system. This potential variation can exist even in homozygotes; for example, *AA bb CC dd* and *aa BB cc DD* could have the same phenotypes while carrying between them genetical variation. The wide variety of this type of balance shows that it will generally be much more important in storing variability than will the heterozygotic state.

The first kind of potential variability, that of the heterozygotes, is built up by crossing and lost by segregation. The second, or homozygotic, kind is, however, built up from the first kind by segregation and turned back into it by crossing. And it can be turned into the free variation of phenotypes only *via* the heterozygotic potential state (Fig. 10). Thus the heterozygotic potential is the channel of interchange between the free state and the homozygotic potential state, in which most variability will be found. The frequency of heterozygous individuals, and with it both the size of the heterozygotic pool and the rate of flow from free to homozygotic potential and back, is dependent in any population on the breeding system of the species, which governs the frequency of outcrossing or inbreeding. We can thus see the advantage to the species concerned of the wide range of devices controlling the breeding system, devices as varied as the separation of the sexes on to different individuals, so common in animals, the cyclical production of male and female gametes as seen in the oyster, and the incompatibility of pollen and style to be found in many plants. These devices control the flow of variability between the potential state in which selection, natural or artificial, cannot operate on it to change the character, and the free state where, being expressed in the phenotype, it is the available raw material of selective change, of adaptation and evolution, and of selective improvement in crops and stock.

Now crossing and segregation are not in themselves sufficient to turn heterozygotic potential into free variability. The genes must also recombine. We can produce a heterozygote *Aa Bb* by crossing the balanced types *AA bb* and *aa BB*, whose gametes must be also of the balanced constitutions *Ab* and *aB* respectively. But the freeing of the variability by the occurrence of say *AA BB* and *aa bb* offspring requires that the gametes produced by the heterozygote include the recombinant

types *AB* and *ab*: mere segregation of *A* from *a* and of *B* from *b* is not enough. The frequency of such recombinant gametes depends on the linkage relations of the genes, which reflect their spatial distribution on the chromosomes. With loose linkage they will match the balanced *Ab* and *aB* types in frequency. Thus the linkage properties, or to put it another way, the chromosome organization, also helps to determine the flow of variability from the potential to the free state (Fig. 10).

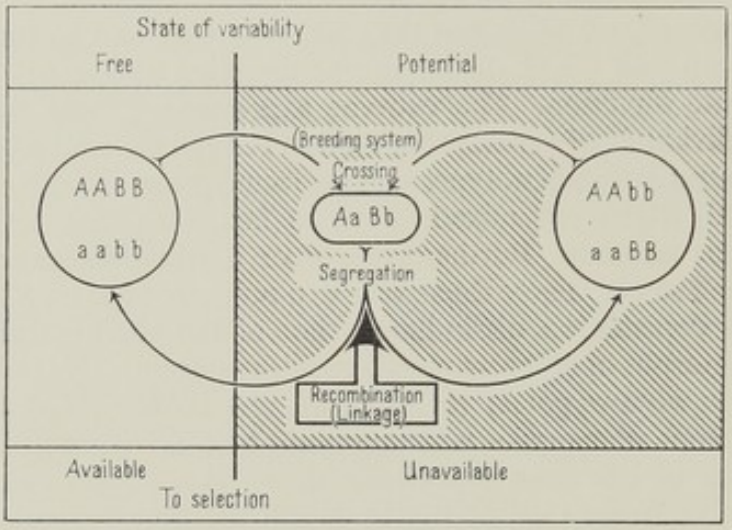

FIG. 10.—The chief states of genetic variability. Most variability is hidden in the genotype, but some expresses itself in the phenotype where it is exposed to the action of selection. The rate of flow of variability is governed by the frequency of crossing, which itself depends on the genetically controlled breeding system. The distribution of the variability emerging by segregation from the heterozygotic pool is governed by the frequency of recombination, which reflects the linkage relations of the chromosome organization. The genotypes shown indicate the types of difference involved in each state of variability —they are not exhaustive lists.

Experiment has provided us with good evidence of a vast reservoir of variability lying hidden in tightly linked, balanced combinations in wild species—a reservoir much vaster than the free variation detectable in the phenotypes. We can hardly doubt that the same will be true of man; that his genetical potentialities are vastly greater than would appear at first sight.

THE IMPORTANCE OF POLYGENIC SYSTEMS

The properties of polygenic systems show us why plants and animals have elaborately controlled breeding mechanisms and chromosome organizations. By way of the chromosome organization, they show us also how selection for one character can change another, often unpredictably and adversely, upon which no selection is being practised, for linkage affects genes of unlike systems as well as of like. They show how vast stores of genetic variability can be maintained beneath a cloak of phenotypic uniformity, and how this reservoir can provide the raw material for great changes in evolution and, properly used, in plant and animal improvement. These properties of polygenic systems also bring us to a

conception of variability as existing, like energy, in different states between which it ebbs and flows according to definite rules and by mechanisms which can be controlled and adjusted. They show us, in fact, a new field of what might even be called biological thermodynamics, whose quantitative study has hardly yet begun.

Polygenic systems in man

The study of polygenic systems is of no less importance for our understanding of man. Mendelian genetics, concentrating as it does on genes of major, often pathological effect, gives us a false idea of the genetical structure of man as of other species. We are led to see human populations as consisting essentially of a large core of genetically normal individuals, the " wild-type " as the drosophilists would call it, with a fringe of unfortunates who are abnormal by reason of their carrying some mutant gene or genes, whose effects are often pathological and almost always a handicap. Some genic variation, such as that controlling our blood groups, might not be fairly viewed in this light, but such genes constitute a small and exceptional class, the greater part of the major genic variation being pathological.

When we turn to consider continuous variation we get a very different, if less precisely delineated, picture. With a few exceptions, of which the antigenic properties are the chief and perhaps the only example, all characters in man would seem to show continuous variation, partly genic and partly non-heritable. In some cases, especially physical characters such as stature, the evidence is clear. In others, disease resistance, mental capacity and so on, the information available is less final. But taking all in all, and giving due weight to analogy with other better explored species, it would appear safe to assert that no two human beings, monozygotic twins excepted, are genetically alike. Far from there being a homogeneous standard type, even the " normals " are seen to be different when we turn to their polygenic systems. They differ one from another in the very genic systems upon which depend the smooth changes of adaptation and evolution, and which have the remarkable properties of variability storage already outlined.

We are thus led to picture human populations as systems of genetic variation, held in check, if we may once again argue by analogy with other species, by the selective forces to which they are subjected. Indeed, we know that variation in such diverse characters as stature and intelligence is associated with differences of fertility, just as is variation in other species. This being true, it will follow that any strengthening or relaxation of the selective forces, which operate on it, must quickly lead to a readjustment of the genic constitution of the population. How rapid and how drastic these changes are will depend on the flow of variability within the population, on the freedom of interchange of genes (that is, on the frequency of mating) between the different groups into which our complex society is more or less clearly determinated by genetic, social, cultural and religious agencies. To understand our genetic potentialities requires therefore that we learn something of the genetical structure of our society—a task which has only recently been envisaged, still less attempted.

At the same time we must seek to discover something of the changing impact of selection on us. It is often implicitly assumed that these forces will change

only in so far as we deliberately change them, as by sterilization of the unfit and similar measures. This might well be true, at least up to a point, provided we considered only the pathological effects of major gene differences. But continuous variation, mediated by polygenic systems, is so much more widespread and so much more sensitive to changes of selective force that virtually every alteration in the organization and management of our society will have its effect on the genetic constitution. Every law we pass, every breaking down of old barriers and building up of new, will alter us genetically, for it will affect the darwinian fitness, the contribution in progeny to the next generation, of the immense variety of genetic types which makes up our population. These changes may be slow and small, desirable or deleterious; but they are inescapable.

So much is obvious. In recognizing the possibilities and problems as they appear in man we have, however, only cleared the ground for much patient observation and research which will be necessary before human genetics comes to include not only the study of the abnormal but that of the normal too; not merely the genetics of the hospital, but also that of society. This is akin to, and will be aided by, the modern genetical study of populations of both wild and domesticated plants and animals. Much of the observation, and all of the experiment, on continuous variation and the underlying polygenic systems, must come from these other species; but as we apply, and verify, their findings in man, we shall begin to form a truer picture of the genetic structure, possibilities and dangers of our own species.

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vide the selective agencies with a more abundant choice and so speed the evolutionary progressive process itself. But this would be mistaken. According to current theory each species has a specific mutation frequency which has been so regulated by natural selection that it is now neither too high nor too low. Natural selection has worked to conserve and perpetuate those genes which, in their action, have appropriate affects, plus or minus, upon the spontaneous mutation frequency. The result has been that new genes appear in numbers in conformity with the species' capacity to cope with them. Any considerable increase in the mutation frequency would therefore not accelerate the evolution of a species ; it would embarrass and retard it.

At the present time it would seem that the incidence of abnormality due to new mutation is of the order of 2 per 1,000 births. If this rate were tripled through the exposure of individuals to mutagenic agents in moderate amount, this would not seriously affect the total defect and derangement in the population as a whole unless the individuals so exposed constituted a large proportion of the whole population and their contribution and that of their descendants was disproportionately large. The exposure of a large proportion to large amounts could be serious since it could increase the number of dominant mutants by a few hundred per million births and could induce several thousand lethal recessives which could gain expression in several thousands of years.

Most of the long-term damage caused to the body by radiation, apart from malignant growths, would seem to result from the effects of the radiation upon the chromosomes of dividing somatic cells. Since the effect is proportional to the dose, and since the effect is cumulative over an indefinitely long period, it follows that most of the existing measurements of safety, for example changes in the blood count, erythemá, loss of sperm motility, are by no means reliable since grave damage to the individual can result from the repetition of doses far too small in themselves to produce any obvious effect.

It has been estimated that in human populations that live in a state of approximate genetic equilibrium mutation as a cause of human disease must be responsible for between one-fifth and two-thirds of all deaths and failure to reproduce on the part of such as are not killed by acquired disease before reaching the age of reproduction or who are prevented from reproduction by other and purely extrinsic causes.

The improvement in living conditions, the application of medical knowledge and so forth, have resulted and will result in a saving for reproduction of a large proportion of those who under former conditions would, because of their genetic disability, have been eliminated or incapacitated. There has been a progressive mitigation of the effects of the genetic disabilities of the great majority of the population. The result of this saving for reproduction, if current genetical theory is correct, must mean that the mutant gene frequency must gradually be rising in the direction of a new level. At the new level, despite all ameliorative measures, as large a proportion will again suffer genetic elimination or incapacity as formerly. If this is so, it follows that the only means by which the effects of the genetic load of disability can be lightened permanently and securely is by the protection of the population from radiation hazards and by coupling the ameliorative procedures of medicine with a rationally directed guidance of reproduction.

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CHAPTER 9

BIOMETRIC EVALUATION OF FINDINGS

GUNNAR DAHLBERG

THE PROBLEMS of human genetics may be divided into two groups, social and individual. (1) The social type of problem deals with the characters of populations and tells us when and why their gene frequency is changing in one direction or another or remains constant. (2) The individual type of problem has to do with a certain trait or character and concerns the chances that a given person possesses that trait or that his children or other relatives will inherit it. The most important problems met with in human genetics belong to the social group, but these naturally cannot be worked out without some knowledge of the problems of the second group. We shall here chiefly discuss the method of how to deal with the individual problems. It should merely be emphasized that the genes of a people do not change without cause and that changes may originate from five conceivable causes.

The genes may change by selection and by mutation, although the latter is not particularly important if the populations are considered at short sight. Without going deeply into the matter, it should be mentioned that selection has a very slight effect also, so far as rare characters are concerned; it is only on fairly common properties that the process is appreciably effective.

Furthermore, the genes may be sorted out into pairs in various ways by intermarriages, assortative mating and isolate-action. These three processes do not affect the number of genes but cause the genes to coincide more or less often. On the whole they tend to increase the homozygotes and reduce the frequency of heterozygotes.

Classification of human characters

Human characters may be classified as follows.

Purely hereditary or genetic characters.—These occur when a certain inherited factor, a gene or gene combination is present and its action cannot be changed appreciably by ordinary environmental factors.

Purely environmental characters.—These arise in any individual as a result of a certain environmental factor or factors.

Constellational characters.—These occur when environmental and specific genetic factors co-operate. The genetic factors are *per se* predisposing to the character in question, but the trait will not manifest itself unless one or more specific environmental factors are present as well. If the genetic factors are absent, the environmental factors are of no avail.

These three different types are not sharply differentiated. It is sometimes a matter of taste to which group a character should be assigned. The classification of the character depends, furthermore, on the frequencies in the population. For

example, on good grounds it may be assumed that only in those who are infected with syphilis can general paresis (dementia paralytica) develop, which might be due to an inherited disposition. The latter character is consequently constellational and due to syphilis infection and a coincident factor which probably is genetic and brings out a peculiar reaction that gives rise to general paresis. However, if the incidence of syphilis in a population were 100 per cent, the existence of general paresis would be wholly dependent on the hypothetical genetic factors.

Any particular character is actually due to both genetic and environmental factors. Without genetic factors there would, of course, be no individuals. Nor can an individual live in an excessively abnormal environment which, for instance, is too hot or too cold. Within the limits set by death genetic and environmental factors may combine in many different ways. The classification suggested here is an attempt to create some order in this muddle.

It should be noted, furthermore, that we are used to think of characters as normal or pathological. What we mean by " normal " is not quite clear. Actually we mean different things in different situations. The normal, generally speaking, is equivalent to the usual. From the genetic point of view normal characters are said to be complexly inherited, whereas the pathological as a rule seems to depend on a simple genetic factor. Naturally, though this process is the usual one it is not necessarily the only one, and it must not be assumed that pathological characters never can be complexly inherited. This is well illustrated by the simple fact that there is no sharp and definitive frontier between normal and pathological. Besides, small deviations from the normal are usually called anomalies, provided that they are not accompanied by any marked functional disorder.

INHERITANCE IN THE PEDIGREE

The older medical literature, but also a few recent works, often specified the existence of " inheritance in the pedigree " of a certain trait. The implication of the term is that the character occurs in the person's relatives, chiefly his ancestors. Such data are not particularly useful by themselves. The situation is better and more satisfactory if figures are given for a control group with the character lacking in the initial persons. A considerable difference would then carry some force of proof. It should be kept in mind, however, that persons with a given disease are particularly interested in finding the same disease in members of their family or amongst their relatives. Merely for this reason they should get higher figures, that might suggest the existence of inheritance in the pedigree, than the controls without the character. A difference may naturally be due also to random variation, especially if there are few persons in the group.

It should finally be noted that some genetic characters appear at an earlier age than others. Consequently the groups to be compared must have fairly similar age distributions. It is also necessary in both groups to study persons of the same kind of relationship. It will seem that these facts are seldom appreciated. The worst is that often it is impossible to tell whether they have been.

If a character has the frequency p in the population and if data are available for an average of 10 relatives, it is easy to calculate how often the character should

be present if it is due only to random accumulation. The character is absent in $(1 - p)$ and its absence in 10 persons can be expected in $(1 - p)^{10}$ cases. Hence it should be present in the rest, that is, in $1 - (1 - p)^{10}$ cases.

On the other hand, if 20 relatives are studied the corresponding expression will be $1 - (1 - p)^{20}$ cases. Let $p = 2$ per cent, then the figures for these two instances will be 18 and 35 per cent, respectively. Thus, if 100 initial persons are explored for disposition, respectively 18 and 33 of them will lack the character in the pedigree.

The object of this computation is to illustrate the great importance of investigating an equal number of relatives to each person if the groups are to be comparable. Geneticists are inclined to shrug their shoulders at investigations along these lines, because of the criticism now made. However, even if they can be criticized on good grounds they do provide evidence of a certain value, at the same time as they naturally reveal that the investigator has not made himself acquainted with the methods of modern genetics.

SELECTED PEDIGREES

When mendelian laws first were applied to problems of heredity in human genetics attempts were made, in a manner of speaking, to copy the methods of experimental genetics. Pedigrees were constructed for the purpose, namely, setting out from a given person, his relatives, that is, parents, sisters, brothers, children, and so on were described. Obviously it was impossible to go very far back because complete data were not available. It is equally obvious that the pedigrees had to be rather small and could not embrace very many individuals. In other words the result was highly characterized by randomness. It is even more serious that such pedigrees mostly are selected to some extent and include too many possessors of the character of interest. The starting point is apparently an individual with a certain character but the rest of the pedigree is to some extent selected, and is published for the very reason that it happens to include an unexpectedly large number of character-carriers. It might be said that the pedigree itself is really the starting point, not an initial person. The danger that a pedigree is misleading is naturally greater if it is small than when it is big and embraces many generations. On the other hand, pedigrees do undeniably supply some valuable information. It may be concluded, however, that published pedigrees contain a more or less misleading over-representation of persons with the character.

Distinction is usually made between pedigrees and ancestries. The first ones start from a given ancestor, who may be selected more or less arbitrarily, and give his progeny. The second ones start from a selected person and give his parents, grandparents, and so on. The published genealogical table or family tree is probably in most cases a combined ancestry and pedigree with a more or less arbitrarily limited number of persons who chiefly have been selected from the viewpoint of the relevant factor, that is that the character occurs fairly often.

A published pedigree should, of course, always show which of the individuals were examined by the investigator and for which the information was second-hand and hence more or less unreliable.

The risk that the pedigree by chance will show a reasonably mendelian pattern

is, of course, greater if the character is common in the population than if it is rare. If we require an investigation that satisfies high standards it is desirable to have a fairly exact conception of the incidence of the character in the population. We shall therefore discuss this problem briefly.

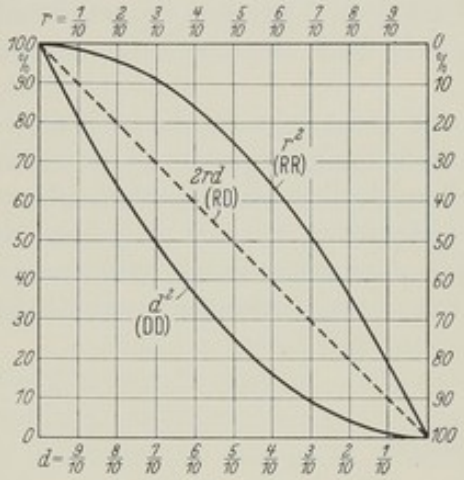

FIG. 15.—Diagram showing the types of zygotes in a population with increasing gene proportion (broken line). The numerical values are read off in vertical direction. (*After Dahlberg and Hultkrantz, (1927). Arch. Rassenbiol.*, **19,** 9.)

Composition of a population

Suppose that we have one pair only of genes in a population. Let the genes R and D have the frequencies r and d. Then $r + d = 1$ and, if panmixia prevails in the population the combinations will be $RR = r^2$, $RD = 2rd$ and $DD = d^2$. The distribution is shown in Fig. 15 and Table 1. We shall point out only one other detail, namely, the relationship between heterozygotes and homozygotes.

TABLE 1

PERCENTAGE OF HETEROZYGOTES WITH SOME DIFFERENT GENE PROPORTIONS IN A POPULATION

RR zygotes $100r^2$	RD zygotes 100 2rd	DD zygotes 100 d^2	RR zygotes 100 r^2	RD zygotes 100 2rd	DD zygotes 100 d^2
0·01	1·98	98·01	1	18	81
0·05	4·37	95·58	2	24·28	73·72
0·1	6·12	93·78	3	28·64	68·36
0·2	8·54	91·26	4	32	64
0·3	10·35	89·35	5	34·72	60·28
0·4	11·85	87·75	6	36·99	57·01
0·5	13·14	86·36	7	38·92	54·08
0·6	14·29	85·11	8	40·57	51·43
0·7	15·33	83·97	9	42	49
0·8	16·29	82·91	10	43·25	46·75
0·9	17·17	81·93			

This relation is characterized by the expression :

$$\frac{\text{heterozygotes}}{\text{homozygotes}} = \frac{2rd}{r^2} = \frac{2(1-r)}{r}$$

If r is a very small number the expression approaches infinity, which implies that heterozygotes will be much commoner than homozygotes if a gene is rare.

It follows that sterilization of recessive homozygotes would be practically ineffective if the character is rare. More significant from the point of view of this chapter is that under this condition most of the recessive homozygotes would be born in marriages between heterozygotes.

Calculation of the standard error

In most cases we know little or nothing concerning the frequency of genetic characters of a population. If the data refer to a rather limited population, the figure will, of course, be unreliable. It may be a little too high or too low at random. In order to evaluate the order of such inaccuracies it is usual to calculate the standard error. If the frequency is p per cent, the standard error $\epsilon(p)$ will be equal to $\sqrt{\frac{p\,(100 - p)}{n}}$, where n is the number of individuals in the observed population.

The formula shows that the size of the standard error is proportional to the square root of the number of individuals. Hence four times as many observations will be required to reduce the standard error by half. The reader is referred to ordinary text-books on statistics for the deduction of the formula (Dahlberg, 1940). It should be mentioned here only that the deduction is made with the aid of the theory of probability. Nevertheless, in order to illustrate the reasoning behind the formula, we shall illustrate the idea from the distribution obtained when a red or a black card is drawn from a pack of ordinary playing cards. If only one card is drawn, the probability of obtaining a red card is the same as the probability for a black card. If two cards are drawn (a card must be replaced in the pack before the next card is drawn), we can expect two red cards in one case, a black and a red card in two cases, and two black cards in one case. Continuing thus, we will obtain the following series of numbers:

Combination	1 draw	1 + 1	total 2	draws
,,	2 draws	1 + 2 + 1	,, 2·4	,,
,,	3 ,,	1 + 3 + 3 + 1	,, 3·8	,,
,,	4 ,,	1 + 4 + 6 + 4 + 1	,, 4·16	,,
,,	5 ,,	1 + 5 + 10 + 10 + 5 + 1	,, 5·32	,,

This pyramid of figures, which is called Pascal's Pyramid, is obtained with the aid of the binomial theorem. Each horizontal row consists of the coefficients in the expanded expression $(a + b)^2$ for consecutive values of n. Thus:

$(a + b)^1 = 1a + 1b$
$(a + b)^2 = 1a^2 + 2ab + 1b^2$
$(a + b)^3 = 1a^3 + 3a^2b + 3ab^2 + 1b^3$
$(a + b)^4 = 1a^4 + 4a^3b + 6a^2b^2 + 4ab^3 + 1b^4$
$(a + b)^5 = 1a^5 + 5a^4b + 10a^3b^2 + 10a^2b^3 + 5ab^4 + 1b^5$

Such a distribution is called a binomial distribution. The same distribution can be obtained also with an apparatus which was designed by Francis Galton (Fig. 16). Balls are put in at the opening in the top and, striking the pegs standing out from the wall, fall down and collect in slots at the bottom (a form of the pinball gambling machines). The distribution is seen in Fig. 17 which shows the paths the falling balls may take. Let us suppose now that the apparatus is infinitely large and the balls infinite in number. Then the distribution would seem continuous, just as a polygon with an infinity of sides that is inscribed in a circle may be said to coincide with the circle. It is possible thus to calculate the curve

that theoretically would be produced by Galton's apparatus. It is represented by the function:

$$y = \frac{1}{\sqrt{2\pi}} \cdot e^{-\frac{\chi^2}{2}}$$

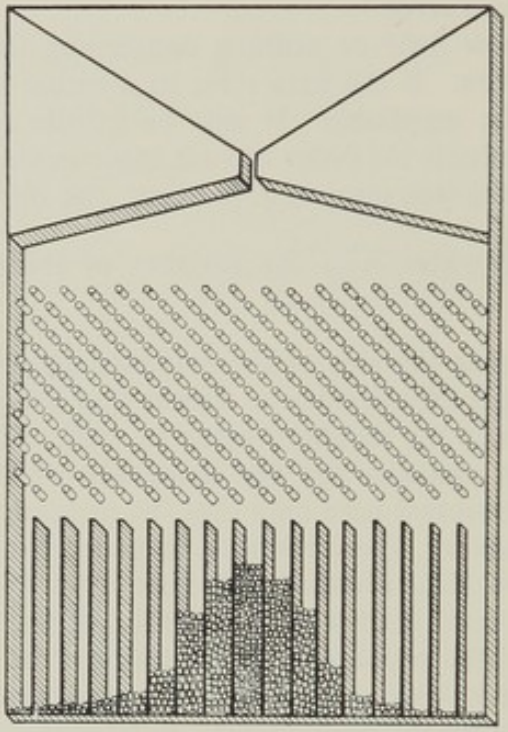

FIG. 16.—Galton's apparatus.

This equation is generally said to be the equation for a normal curve in which there is a constant, σ, that can assume different values. The curve may in other words be more or less steep or flat and it consequently represents a family of curves. σ is the point where the curve turns from concave to convex, and between $+\sigma$ and $-\sigma$ will lie about two-thirds of the observations. Practically no ball will

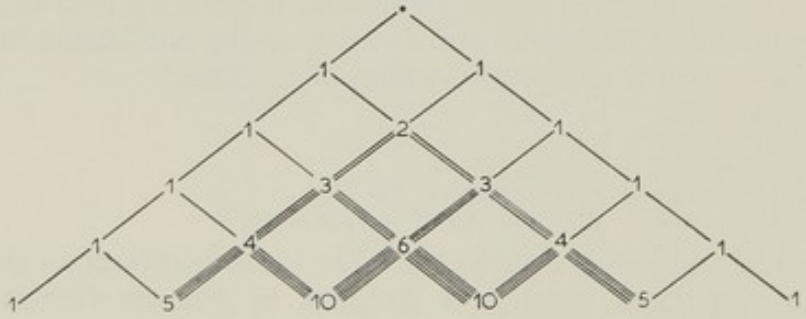

FIG. 17.—Pascal's pyramid. The lines indicate the paths the balls are travelling in Galton's apparatus.

fall outside $+ 3\sigma$ and $- 3\sigma$. It is maintained, therefore, that 6σ is the range of variation. The highest top on the curve, which represents its mean, will naturally be more exactly determined for a small number, if σ is small than if σ is large. The accuracy is in point of fact proportional to the square root of the number and the standard error of the mean $= \epsilon(p)$, which in terms of per cent is the very same formula as the above. Because for a binomial distribution

$\sigma = \sqrt{npq} = \sqrt{np(1 - p)}$, where p and q are the probabilities of drawing a red or a black card, respectively.

The French term for standard error is *écart-type* for the very reason that it can be deduced in this way by drawing cards. When the group studied is large the standard error is without importance, but it assumes increasing importance as the group becomes smaller. Particularly when the observed group is large, so-called systematic errors play a greater role. These arise because the observations are not absolutely accurate. The frequency of the character may not be the same in all age-groups. Thereby complications and difficulties arise which are not so easy always to surmount. Moreover, the character may be more or less noticeable, and then the least marked cases will easily be overlooked.

NON-SELECTED PEDIGREES

Particularly with regard to characters that are not extremely rare it is usual to construct pedigrees by commencing with persons who have the character without having pre-selected them in accordance with their ancestry. In such cases it may be necessary to take into consideration the qualities of the population from which the observed individuals were drawn.

FIG. 18.—The figure illustrates how the genes of the initial person are more and more mixed with the genes from the population in the ancestral generations.

If one starts from persons with the given character one expects to find in their ancestors the same genes as in the initial persons but diluted with the genes of the population (Fig. 18). If we start from homozygotes with the character RR, and if the frequency in the population of the gene is r, we can apply the general formula for the gene content among ancestors in the n: th generation:

$$\frac{1 + (2^n - 1)r}{2^n}$$

On the other hand, for heterozygotes with trait RD the formula will be:

$$\frac{1 + (2^{n+1} - 2)r}{2^{n+1}}$$

Some gene combinations being impossible because of restricted gene mobility, this formula does not give directly the ancestral frequency of the character. From the initial persons the genes can be traced in separate directions, to father and to mother, in which respect they are bound. The formulae in Table II have been deduced to cope with this.

Thus, unless it is very low, the gene content of the population must be taken into account. Table II reveals what figures are to be expected; and, besides, it also shows that the difference between the frequency of the character in the population and its frequency amongst the initial person's relatives is highest when the gene is infrequent in the population. For very common traits the difference vanishes more or less.

TABLE II

Frequencies of Recessive and Dominant Characters

Frequency of the recessive character (RR)					Frequency of the dominant character (RD, DD)				
In the population	In the following groups of relatives of persons with the character				In the population	In the following groups of relatives of persons with the character			
	1. Sisters and brothers	2. Parents and children	3. Grand-parents, grand-children and sibs of parents	4. Greatgrand-parents, greatgrand-children and first cousins		1. Sisters and brothers	2. Parents and children	3. Grand-parents, grand-children and sibs of parents	4. Greatgrand-parents, greatgrand-children and first cousins
1	2	3	4	5	6	7	8	9	10
r^2	$\frac{(1+r)^2}{4}$	r	$\frac{r(1+r)}{2}$	$\frac{r(1+3r)}{4}$	$1-r^2$	$1-\frac{r^2(3+r)}{4(1+r)}$	$1-\frac{r^2}{1+r}$	$1-\frac{r^2(2+r)}{2(1+r)}$	$1-\frac{r^2(4+3r)}{4(1+r)}$
%	%	%	%	%	%	%	%	%	%
0	25	0	0	0	0	50	50	25	12·5
0·1	26·60	3·16	1·63	0·86	0·1	50·04	50·04	25·07	12·58
0·2	27·28	4·47	2·34	1·27	0·2	50·09	50·08	25·14	12·67
0·5	28·67	7·07	3·79	2·14	0·5	50·21	50·18	25·34	12·92
1	30·25	10	5·50	3·25	1	50·44	50·38	25·69	13·34
2	32·57	14·14	8·07	5·04	2	50·88	50·75	26·38	14·19
3	34·41	17·32	10·16	6·58	3	51·32	51·13	27·07	15·03
4	36	20	12	8	4	51·76	51·52	27·76	15·88
5	37·43	22·36	13·68	9·34	5	52·20	51·90	28·45	16·73
6	38·75	24·49	15·25	10·62	6	52·64	52·29	29·14	17·57
7	39·98	26·46	16·73	11·86	7	53·07	52·65	29·82	18·41
8	41·14	28·28	18·14	13·07	8	53·52	53·04	30·52	19·26
9	42·25	30	19·5	14·25	9	53·97	53·43	31·22	20·11
10	43·31	31·62	20·81	15·41	10	54·41	53·82	31·91	20·96

Corrective procedures

When non-selected pedigrees are obtained, it is impossible to include in the data all families which have a potentiality of producing the genetic trait under observation. Only those families in which at least one child with the trait occurs will be eligible. For instance in simple recessive inheritance due to chance alone no homozygotes may appear among the children of two heterozygotes, especially if the number of children is small. Obviously there is no way to include these families in our data but from a statistical point of view they are as important as those leaving one or several children with the trait. Therefore, the data will always be biased and include too many individuals with the trait. Many different methods of eliminating this source of error have been published. The first method was formulated by Weinberg and is called Weinberg's propositus method.

Weinberg's propositus method

When this method is used the initially selected test persons, that is, the propositi, must be rejected. Moreover, the family must be counted as many times as it contains persons with the character. The formula will therefore be:

$$p = \frac{\Sigma x(x-1)}{\Sigma x(s-1)},$$

where p is the required probability, x the number of persons with the character in the families, and s the number of children of the individual families. The origin of this method is that Lundborg once felt he found too many carriers in a group of myoclonic families. He found a ratio of 17: 54, that is, 31·5 ± 6·3 per cent. He asked Weinberg about the reason for the excess, and was given the following method of calculation (Weinberg, 1912).

TABLE III

COMPUTATION ON LUNDBORG'S MATERIAL ACCORDING TO WEINBERG'S PROPOSITUS METHOD

Family No.	Size of family s	Number of recessive children x	x(s − 1)	x(x − 1)
1	6	3	3·5 = 15	3·2 = 6
2	8	1	1·7 = 7	1·0 = 0
3	6	2	2·5 = 10	2·1 = 2
4	9	3	3·8 = 24	3·2 = 6
5	9	1	1·8 = 8	1·0 = 0
6	5	2	2·4 = 8	2·1 = 2
7	6	2	2·5 = 10	2·1 = 2
8	4	2	2·3 = 6	2·1 = 2
9	1	1	1·0 = 0	1·0 = 0
Total	54	17	Σx(s − 1) = 88	Σx(x − 1) = 20

Thus, the calculated content of recessive homozygotes is:

$$\frac{20}{88} = 22{\cdot}7 \text{ per cent.}$$

The figure is lower than the expected 25 per cent, which Weinberg thought plausible, since homozygotes occur also among sibs who will not exhibit the disease until later; the standard error is quite large, so the deviation may also be accidental.

The standard error must be based on the total number of persons involved in the calculation. Thus:

$$\varepsilon(p) = \sqrt{\frac{p(100 - p)}{\Sigma(s - 1)}} .1 + r + pr(s - 3),$$

$$\text{where } r = \frac{\Sigma \text{ secondary propositi}}{\Sigma \text{ secondary cases}}$$

We shall illustrate the formula by taking an elementary example.

Suppose that two heterozygotes are married and that we are studying their offspring. The probability for a recessive character will then be 1/4, and if every family has two children, the expected family composition will be:

One family with 2 recessives, 6 families with 1 recessive and 1 non-affected child, and 9 families with no recessive and 2 non-affected children (Fig. 19).

FIG. 19.—The ideal distribution of characters in families with each 2 children. The probability of a character is 1/4 (in marriages between heterozygotes). Dark symbols = character; open symbols = non-affected children.

Obviously the latter 9 families cannot be included when the data are collected: we are only considering homozygous individuals. Therefore, in all the families studied, 8 out of a total of 14 children will have the character, which gives too high a probability, namely 8/14 = 57·1 per cent. On the other hand, if we follow the previously given procedure—that is, to discard the probands and count families with two recessives twice over—the figure will be 2/8, that is, the expected 25 per cent, which is correct.

The calculation just described is a special case of the propositus method, called Weinberg's sibling method. It is correct to use this method provided that all the persons with the character in a certain population have been included in the data. If this is not the case but we are dealing with an unselected series of propositi from a special sample, for example, to take the most common type, a clinical sample, we must apply another modification. This is the propositus method of Weinberg in the strict sense. In such cases only those persons with the character who have been selected according to the same principles agreed upon at the start of the research work are treated as propositi. All other cases who may be found later among sibs, parents or other relatives are called secondary cases and must not be counted as propositi. For example, if in a series of sibs we have b propositi, the formula for the calculation will be:

$$p = \frac{\Sigma b(x - 1)}{\Sigma b(s - 1)}$$

The difference between the sibling method and the propositus method is, one may say, that when all who have the character can be regarded as propositi the sibling method is applied, whereas by the propositus method only some of the persons with the character can be counted as propositi.

Dahlberg's later sibling method

Another corrective procedure is the later-sibling method which the present author has formulated (Dahlberg, 1930). The theory behind it is that if we take ordinary dice and special dice marked 2–7, mix them up, throw them into a room,

pick up the dice showing a 7, throw these dice into another room, and now count the proportion of the 7's, then we will directly get the expected probability for getting a 7 with dice at all capable of showing a 7. When we wish to find the probability for persons with the character, we actually are looking for the probability for them in marriages which are at all capable of having children with the required character. The procedure then is to disregard all births up to and including the character and to consider only births after that of the initial person with the character. Then a correct result will be obtained directly. Of course, if the sample does not include the whole population but only a more or less large part of it, it is necessary to weigh the families with several characters with the figures for the character in the family. This because the families with several characters have a greater chance to be included in the sample than a family with only one character. The figure thus obtained can be used in calculating the probability for a non-affected child before the person with the character. Let this probability be called p and its contradictory opposite q, then $p + q = 1$. The probability of getting a non-affected child will accordingly be q, the probability of getting 2 consecutively will be q^2, and the probability for 3 consecutive non-affected children will be q^3, and so on. After this fashion it is possible to estimate the probability of getting a non-affected child before a child with the character is born and the found and the expected figures can be compared. Such a computation utilizes the materials more fully and provides, as noted, a means of checking the first values. The standard error is found by means of the aforementioned formula for the standard error of percentages. This method, however, can be used also for quantitative characters.

The method just given is not based on a given probability; the required probability is instead obtained from the computations.

Aprioristic procedure

A method of another type makes use of an expected probability which is then related to the ultimate result. Such procedures are consequently called aprioristic. The tentative probability is usually that to be expected in recessive heredity in homozygous matings, namely, 1/4. According to the size of the family the probability of families without the character will decrease more and more, which is shown in Table IV.

TABLE IV

PROBABILITY OF FAMILIES WITHOUT THE CHARACTER AND FAMILIES WITH THE CHARACTER AND WITH THE FOLLOWING NUMBER OF CHILDREN

Number of children in the families	*Families without the character* %	*Families with at least one child with the character* %
1	75	25
2	56·25	43·75
3	42·19	57·81
4	31·64	68·36
5	23·73	76·27
6	17·80	82·20
7	13·35	86·65
8	10·01	89·99
9	7·51	92·49
10	5·63	94·37

Those who are non-affected have been excluded from these families in advance. Thus, by dividing the number of persons with the character by the number of children, a quotient will be obtained which can be compared with the figure to be expected in families of the given size. This method has been recommended before now by Weinberg, Apert (1914), Bernstein (1931), Hogben (1931), Haldane (1932), Macklin (1938) and others.

It is, of course, not very important which method is used, but it is necessary to correct for the unavoidable loss of families without affected children. Whatever method is used the results will not be appreciably different; besides, the ultimate results must obviously be expected to be scattered haphazardly about the expected result, and it is therefore necessary to calculate standard errors. Another source of error, which is important also, is that if all individuals are not very carefully observed persons with the character will be missed if their characteristics are such as cannot be found except by very careful examination. The gene may have a very slight manifestation in heterozygotes; but then, of course, the mechanism of inheritance is intermediary instead of recessive.

Often we have no opportunity ourselves to examine the healthy individuals in the population. Consequently it is not surprising that clinically less important symptoms of the character are often overlooked.

Variations in penetrance

It must be remembered, finally, that a gene can manifest itself more or less often, that is, it may have a varying degree of penetrance. This possibility must always be taken into account, and when it exists special calculations should be made.

Penetrance is a diffuse concept. It implies that the character is not present when it should be present. The reason for this might sometimes be that the character is prevented from developing by other genes, sometimes that the character is concealed by the absence or presence of special environmental factors. Such characters may be lacking during either foetal or postnatal life. In most cases it is assumed that the weak penetrance is due to the absence, or presence, of intra-uterine factors. If we now dare to suppose that the penetrance is equally effective in all families, it may be assumed that the following expressions are applicable to recessively inherited traits, if p = penetrance and r = the frequency of the gene:

$$\begin{aligned}
&\text{The frequency in the population} && = pr^2 && = k_1\\
&\text{The frequency among siblings} && = p\frac{(1+r)^2}{4} && = k_2\\
&\text{The frequency among parents} && = pr && = k_3\\
&\text{The frequency among grandparents} && = p\frac{r(1+r)}{2} && = k_4
\end{aligned}$$

These expressions yield:

$$p = \frac{k_3}{r} = \frac{k_1}{r^2}$$

We further get:

$$r = \frac{2k_2 - k_3 \pm 2\sqrt{k_2^2 - k_2k_3}}{k_3}$$

The figures theoretically to be expected in different kinds of family groups can be found by means of the latter formulae. Let us suppose, on the other hand,

that we are dealing with a dominant monohybrid gene with the frequency d and the penetrance p. Then we have the following expressions:

$$\begin{aligned}
&\text{Population:} && pd(2-d) && = k_1\\
&\text{Siblings:} && p\left(1-\frac{(1-d)^2(4-d)}{4(2-d)}\right) && = k_2\\
&\text{Parents:} && p\left(1-\frac{(d^2-2d+1)}{(2-d)}\right) && = k_3\\
&\text{Grandparents:} && p\left(1-\frac{(d^2-2d+1)(3-d)}{2(2-d)}\right) && = k_4
\end{aligned}$$

These expressions give rise to the following equation:

$$p = \frac{4k_2(1+d)}{6+3d-d^2}$$

Suppose $\frac{k_2}{k_3} = c$

and further $\frac{64c^3}{27} - 8c^2 + \frac{20c}{3} - 1 = A$

and $$-\frac{320c^4}{27} + \frac{1408c^3}{27} - \frac{2191c^2}{27} + 52c - \frac{316}{27} = B$$

Then

$$d_1 = \frac{6-4c}{3} - \sqrt[3]{A+\sqrt{B}} - \sqrt[3]{A-\sqrt{B}}$$

$$d_2 = \frac{6-4c}{3} - \frac{i\sqrt{3}}{2}\left(\sqrt[3]{A-\sqrt{B}} - \sqrt[3]{A+\sqrt{B}}\right) + \tfrac{1}{2}\left(\sqrt[3]{A-\sqrt{B}} + \sqrt[3]{A+\sqrt{B}}\right)$$

$$d_3 = \frac{6-4c}{3} - \frac{i\sqrt{3}}{2}\left(\sqrt[3]{A+\sqrt{B}} - \sqrt[3]{A-\sqrt{B}}\right) + \tfrac{1}{2}\left(\sqrt[3]{A-\sqrt{B}} + \sqrt[3]{A+\sqrt{B}}\right)$$

TABLE V

OBSERVED AND EXPECTED FREQUENCY OF STRABISMUS IN RELATIVES OF THE PROPOSITUS WHEN STARTING FROM A CALCULATED PENETRANCE OF ABOUT 7 PER CENT IN DOMINANCE AND 30 PER CENT IN RECESSIVENESS AT A FREQUENCY OF 2 PER CENT IN THE POPULATION, AND A CALCULATED PENETRANCE OF 35 PER CENT AT A FREQUENCY OF 3 PER CENT IN THE POPULATION

Relatives of the propositus	Frequency in the population			
	Monohybrid dominance		Monohybrid recessiveness	
	2%	3%	2%	3%
Siblings – –	3·6	3·6	11·4	10·3
Parents – –	3·6	3·6	4·9	5·2
Grandparents –	1·8	1·9	2·8	3·0

However, it is possible that the penetrance varies in different families and that the above expressions consequently cannot be used, which makes them doubtful. It is even worse that the basic material itself may be heterogeneous from a genetical point of view, because it happens not rarely that one and the same character may be inherited in different ways in different pedigrees, that is, it may be caused by genes of different types. Many examples of this exist. Theoretically, therefore, the obtained figures may be considered rather unsatisfactory, but they

do provide an estimate of the risk for affected persons getting children who are similarly affected. They provide an empiric prognosis of inheritance. The different pedigrees of the data must therefore be studied to see whether the mechanism of gene transmission is variable. It may be assumed that disposition for hereditary diseases has been brought about by mutation, not only once but several times. Indeed, mutations may be of different types and produce genes of different nature, although the subsequent characteristics seem to be alike. On close examination, though, one might discover small differences between the characters. In other words we may not deal with absolutely identical characters. Here we have one reason for the very great importance of careful clinical examinations in hereditary studies. Severe diseases are as a rule inherited recessively, whereas mild types often are inherited dominantly. From these aspects it is necessary to examine the affected persons very carefully and, given an adequate number of cases, to classify them according to age and severity of the disease (*cf.* Dahlberg, 1952).

With regard to the age at which the character becomes manifest, it may be necessary to calculate risks for different ages and in the study use the cumulative risk at a given age, but such computations require a great number of data and cannot, consequently, often be carried out.

Comparison of standard errors

It should be noted, lastly, that when the standard errors of several frequencies are to be compared the methods developed by Fisher (1925) should be adopted.

We use the χ^2 (chi square) test, that is, we calculate the sum of the quotients of the squares of the differences between observed and expected figures and the number of cases as shown in Table VI.

TABLE VI

OBSERVED AND EXPECTED FREQUENCY OF STRABISMUS IN RELATIVES OF THE PROPOSITUS WHEN STARTING FROM A CALCULATED PENETRANCE OF ABOUT 7 PER CENT IN DOMINANCE AND 35 PER CENT IN RECESSIVENESS AT A FREQUENCY OF 3 PER CENT IN THE POPULATION

Relatives of the propositus	Observed frequency	Monohybrid dominance, expected frequency = e	(Diff.)² divided by expected value, e	Monohybrid recessiveness, expected frequency = e	(Diff.)² divided by expected value, e
Siblings – –	10·0	3·6	11·4	10·3	0·01
Parents – –	5·7	3·6	1·2	5·2	0·05
Grandparents –	1·5	1·9	0·1	3·0	0·75
Total – – –	—	—	12·7	—	0·81

If χ^2 is small, obviously the agreement is good, but if it is large, the agreement may be dubious or non-existent. To obtain the probability, p, of this, we use a special table in a statistical text-book. Then we must know the degrees of freedom, that is, the number of independent values: p for $\chi^2 = 12{\cdot}7$ is found to be less than 0·0027, which signifies that the probability of agreement is very small. In fact

the difference is significant. For $\chi^2 = 0{\cdot}81$, p is 0·7, which signifies very good agreement.

CONSANGUINITY

Consanguinity among parents is particularly important for the recessive inheritance of rare characters. In consanguineous matings the genes have a higher probability of coinciding in double dose. As a matter of fact, if the gene arises as a single mutation, intermarriage is the only possibility for the character to manifest itself. Conversely, if we begin with affected persons, their parents should exhibit a higher frequency of intermarriage. Cousin marriages are, however, practically the only important type of consanguineous matings to be found in man. Closer degrees of intermarriage are, of course, prohibited, and even cousin marriages are not allowed in some countries.

As early as 1919 Lenz deduced an equation for calculating the expected incidence of cousin marriages in relation to a monohybrid diallelous character occurring with different frequencies in the population. The deduction is only approximate, however. Lenz only considered the heterozygotes and disregarded homozygotes and he also disregarded the fact that a number of marriages between cousins are to be expected out of pure chance in panmixia. The correct equation for large populations has been given by the present author (Dahlberg, 1929).

Let us assume that the gene has the frequency r and the marriages between cousins the frequency c. The frequency of marriages not between cousins will then be $1 - c$. If we assume the population to be very large, so that in panmixia there would be, practically speaking, no marriages between cousins, c then implies an increase of such marriages beyond what is to be expected in panmixia.

For marriages between cousins the frequency of the character is obtained from the following expression:

$$\frac{cr}{16}(1 + 15r)$$

In the population there are persons with the character with the following frequency:

$$(1 - c)r^2 + \frac{cr}{16}(1 + 15r).$$

The ratio of persons with the character derived from marriages between cousins to that of the total number of persons with the character k, will be:

$$k = \frac{\frac{cr}{16}(1 + 15r)}{(1 - c)r^2 + \frac{cr}{16}(1 + 15r}$$

$$\therefore k = \frac{c}{c + \frac{16(1 - c)r}{1 + 15r}}$$

If c is a very small number in this equation, we can put $1 - c = 1$, and if we also venture to put $1 + 15r = 1$ (which is very doubtful), the equation will be as follows:

$$k = \frac{c}{c + 16r}$$

This is the approximate equation that Lenz deduced.

If we now assume that marriages between cousins actually do occur with a

certain frequency, c_1, and are to be expected in panmixia in a certain frequency, c_2, persons with the character from marriages between cousins will have the following frequency:

$$\frac{c_1 r}{16}(1 + 15r).$$

In the population we should, in panmixia, expect persons with the character with the frequency r^2; but we get an increase of their frequency by

$$(c_1 - c_2)\frac{r}{16}(1 + 15r).$$

In all, then, the frequency of persons with the character in the population will be:

$$(1 - c_1 + c_2)r^2 + (c_1 - c_2)\frac{r}{16}(1 + 15r).$$

Therefore, the ratio of persons with the character deriving from cousins to the total number will be:

$$k = \frac{\frac{c_1 r}{16}(1 + 15r)}{(1 - c_1 + c_2)r^2 + (c_1 - c_2)\frac{r}{16}(1 + 15r)}$$

$$\therefore k = \frac{c_1}{c_1 - c_2 + \frac{16r(1 - c_1 + c_2)}{1 + 15r}}$$

If $c_2 = 0$, that is, if the population is so large that the random frequency of cousin marriages to be expected is small enough to be ignored, we get the formula $k = \frac{c}{c + 16r}$, if we also set $1 + 15r = 1$, which implies a very doubtful approximation. If $c_1 = c_2 = c$, that is, if the marriages between cousins occur in the frequency to be expected in panmixia, the equation will be:

$$k = \frac{c(1 + 15r)}{16r}.$$

TABLE VII

PROPORTION OF PERSONS WITH THE CHARACTER (PER CENT) DERIVING FROM MARRIAGES BETWEEN COUSINS = k, IN DIFFERENT FREQUENCIES OF A RECESSIVE, MONOHYBRID CHARACTER RR AND IN DIFFERENT FREQUENCIES OF MARRIAGES BETWEEN COUSINS IN A POPULATION = c

RR	k when			
	c = 0·1%	c = 0·25%	c = 0·5%	c = 1%
0·000001 – –	6·344	15·860	31·721	63·439
0·00005 – –	0·978	2·444	4·888	9·776
0·0001 – –	0·719	1·797	3·594	7·188
0·0005 – –	0·373	0·933	1·866	3·733
0·001 – –	0·291	0·729	1·457	2·912
0·0025 – –	0·219	0·547	1·094	2·188
0·005 – –	0·182	0·455	0·911	1·821
0·01 – –	0·156	0·391	0·781	1·563
0·05 – –	0·122	0·304	0·609	1·217
0·1 – – –	0·114	0·284	0·568	1·135

Table VII gives the percentages of persons with the character deriving from marriages between cousins at different frequencies of a recessive monohybrid diallelous character and of such marriages. The approximate formula $k = \frac{c}{c + 16r}$ gives slightly lower values than the correct formula $k = \frac{c(1 + 15r)}{16r}$, if we assume that marriages between cousins occur to the same extent which one would expect in panmixia. For very rare genes and particularly in small populations with a high frequency of cousin marriages, the difference is not negligible. For instance, if the ratio for the gene is 1: 10,000 and the proportion of cousin marriages 1 per cent, we find by the approximate equation that the number of cousins among parents of persons with the character is 5·88 per cent, whereas the true figure is 7·19 per cent. The difference can thus sometimes be substantial. As a matter of fact, at most the increased frequency of cousin marriages among the parents with children with the character is found to be less than 30 per cent. The reason for this is given in Dahlberg, 1938.

In this connexion it should be mentioned that a similar increase is to be expected in more complicated forms of inheritance. (In dihybrid dominance, if the two genes are equally common, the increase is maximally equal to that of monohybrid recessivity; when one gene is common and the other one rare, we have an extremely slight increase of marriages between cousins in the parents.) If we want to test whether hereditary factors play a part in the appearance of such characters as diseases and the like that are relatively rare, we can pursue two lines. We can demonstrate an increased frequency of the character in near relatives of the persons with the character (brothers and sisters, parents, children, and so on), and we can also look for an increased frequency of consanguineous marriages between the parents of the individuals with the character. This latter line has been followed to a certain extent, but should be used still more since an increased frequency among the relatives may be connected with environmental factors. That tuberculous parents have children suffering from tuberculosis may, for example, be due to infection. On the other hand, an increase of the intermarriage frequency in parents of tuberculous children may not be connected with anything else than hereditary factors, and is therefore of greater value as proof.

It may finally be asserted that if the inheritance mechanism and the frequency of cousin marriages amongst the parents of persons with the character is known, the equations submitted here can, of course, be used to calculate the frequency of the genes. If, for example, 15 per cent of the persons with the character are cousins, and the general frequency of marriages between cousins is 2 per cent, the gene will have the frequency 1/105, and if the general frequency of cousin marriages is 1 per cent the gene will have the frequency 1/225, or 0·44 per cent. If the general frequency of cousin marriages is 0·5 per cent, the corresponding figures will be 1/465, or 0·22 per cent. With knowledge of the mode of inheritance, the frequency of persons with the character, and the proportion of these latter deriving from cousins, it is, of course, also possible to calculate the frequency of the marriages between cousins in the population.

One reason why the frequency of intermarriage has not been very extensively investigated nor used in genetic research is the difficulty of getting normal figures. There are official figures from a number of countries (*see* Dahlberg, 1938). But they

cannot by themselves be used for comparison with materials collected in other populations, even though they may be thought to provide an approximate starting point. We can probably assume that the frequency of intermarriage seldom exceeds 1 per cent, and, at present, probably not infrequently keeps well below 0·5 per cent.

OTHER METHODS

In genetics one often uses monozygotic and dizygotic twins to decide the effect of genes and environment. These problems are treated in the chapter on twin studies (Chapter 4). Some problems regarding penetrance and detection of heterozygotes are also treated in Chapters 2 and 3.

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CHAPTER 10

EXPERIMENTAL METHODS

I.—CYTOGENETICS

P. C. KOLLER

THE PHYSICAL bases of heredity which underlies mendelian inheritance are the genes, borne on the chromosomes. They comprise the nuclear material of the cell, which is evenly distributed during mitosis between the two daughter cells. If the segregation of chromosomes is abnormal then as a consequence abnormal and often non-functional cells are produced. When this occurs during gamete formation in the testes or ovaries the genetical repercussions can be observed in family pedigrees, showing irregularities in the transmission of particular heritable characters. The fact that the chromosomes carry the genes which determine and control the inheritance of morphological, physiological or mental characters, emphasizes the significance of the cytological aspect of heredity in all organisms, including man.

THE NORMAL CHROMOSOME MECHANISM

Number

Though the constancy of the somatic chromosome number is a characteristic property of a species, variation can be encountered in many tissues of individuals. In human testis about 3 per cent of the spermatogonial cells contain more than the normal 48 chromosomes; they are *polyploid* instead of being *diploid* (Koller, 1937). Other very rapidly proliferating tissues, for example, the allantoic membrane, intestinal mucosa, uterine endometrium and especially malignant growth, usually display a wide variation in chromosome number (Fig. 20). In these tissues, adjacent cells depend on each other and very often undergo mitosis at the same time (Fig. 21); by virtue of this interdependence cells with fewer or more than the normal 48 chromosomes are nevertheless able to divide, though the chromosomes display various abnormalities (Fig. 22) (Koller, 1947 a, 1947 b). The high frequency of functional cells in somatic tissues with irregular chromosome number suggests that the nucleus, which normally controls cell behaviour, can occasionally play a secondary role. This condition may be a regular feature during embryonic development before cell or tissue differentiation takes place (Timonen and Therman, 1950).

Size and shape

The human chromosomes differ in size and shape. The longest is about 7 μ, and the smallest about 1·5 μ in length. Some are V-shaped with equal or unequal arms, others are rod-shaped. Their shape is determined by the position of the centromere, which is the dynamic centre of the chromosomes and is responsible

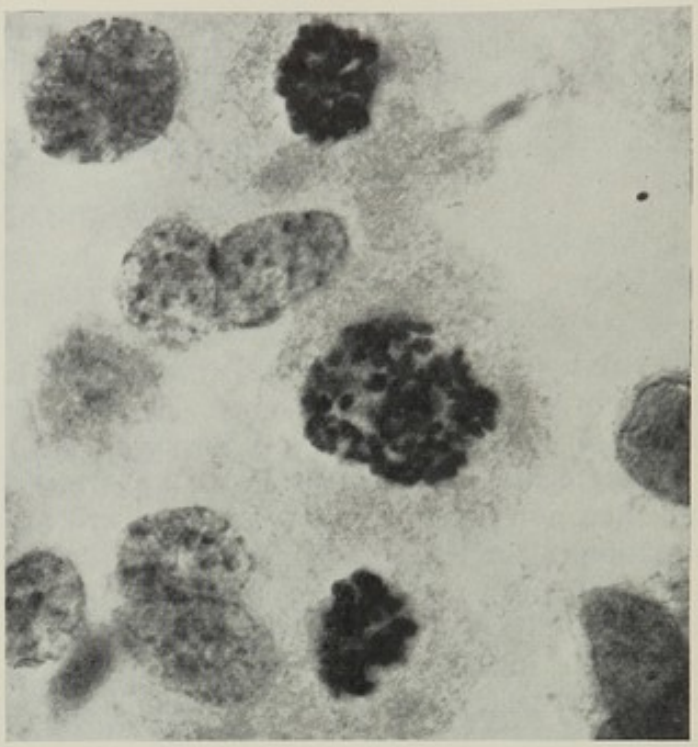


FIG. 20.— Dividing cells in a squamous-cell carcinoma of the skin, two with diploid, one with polyploid chromosome number. ×1800.

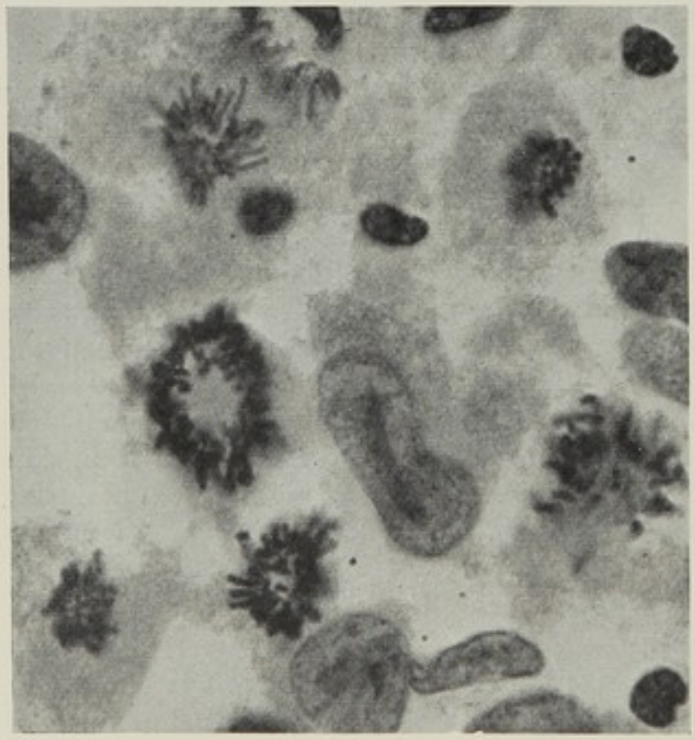
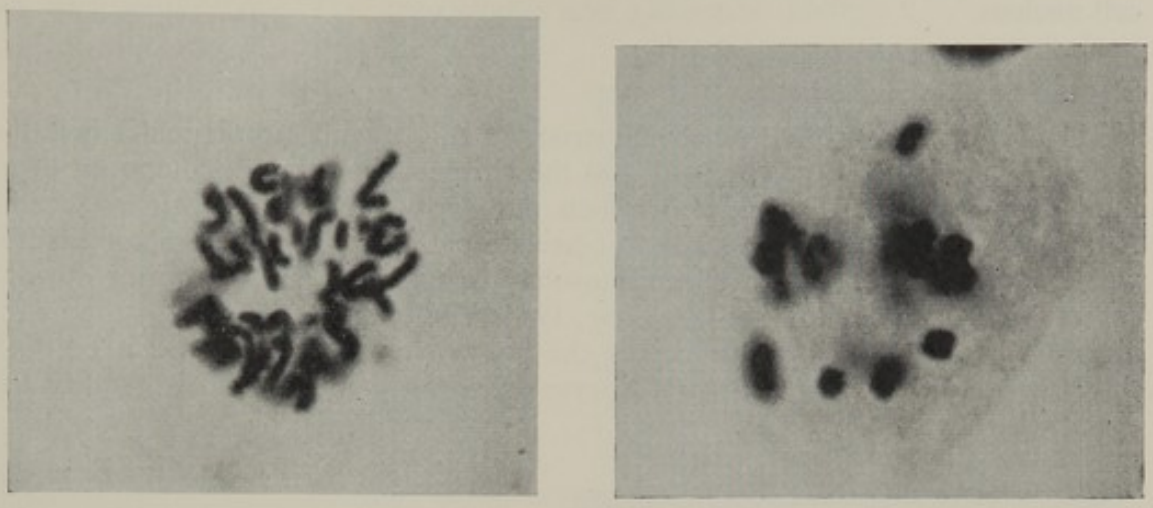
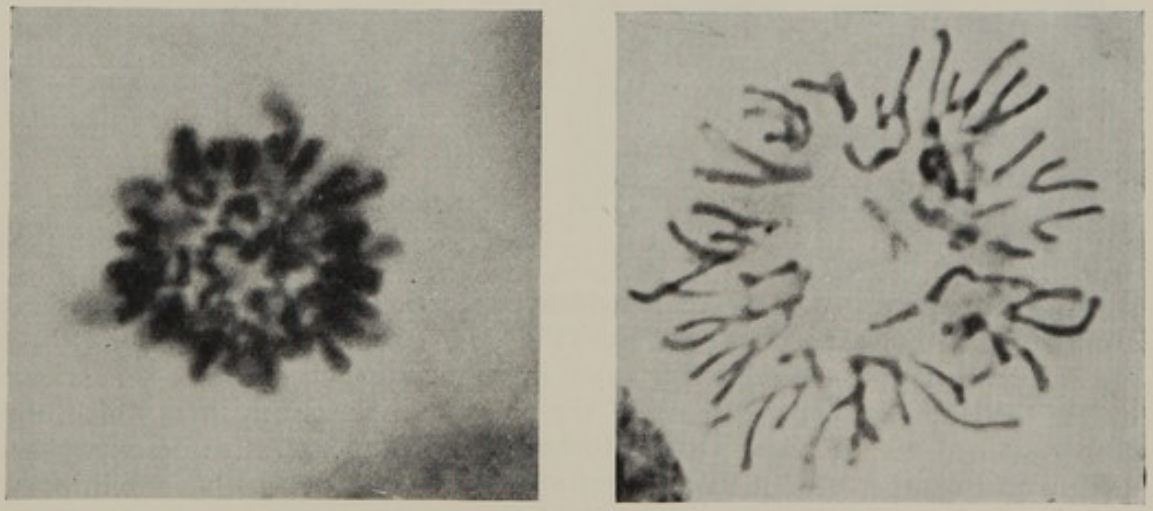


FIG. 21.—Synchronous division in a squamous-cell carcinoma of cervix. The dividing cells differ in chromosome number and behaviour. ×1800.



(*a*) (*b*)

FIG. 22.—Two tumour cells from an adenocarcinoma of the large intestine showing (*a*) normal contraction and (*b*) super-contraction of the chromosomes; the number of chromosomes is less than the diploid number. ×2500.



(*a*) (*b*)

FIG. 23.—Dividing blood-cell precursors in the bone marrow: (*a*) pro-erthyrocyte; the chromosomes are short and thick and heavily charged with desoxyribosenucleic acid; (*b*) promyelocyte; the chromosomes are long and thin and their nucleic acid charge is much reduced. (*Fig. 23b by kind permission of Mr. L. La Cour.*) ×2800.

for their movement within the cell during division. One, possibly two pairs of chromosomes are associated with the nucleoli, which are present in the resting cell nucleus.

Structure and organization

The chemical basis of chromosome structure and organization is under investigation. The view is now accepted that the chromosome fibre is composed of a bundle of polypeptide chains to which desoxyribosenucleic acid is attached. Attempts have already been made to correlate pathological conditions of tissues with abnormalities observed in chromosome organization and behaviour during cell division or differentiation (La Cour, 1944; Thorell, 1947). Thus, in the bone marrow of man the chromosomes of the pre-myelocyte precursors can be distinguished from those of the erythrocyte series by a much reduced ability to

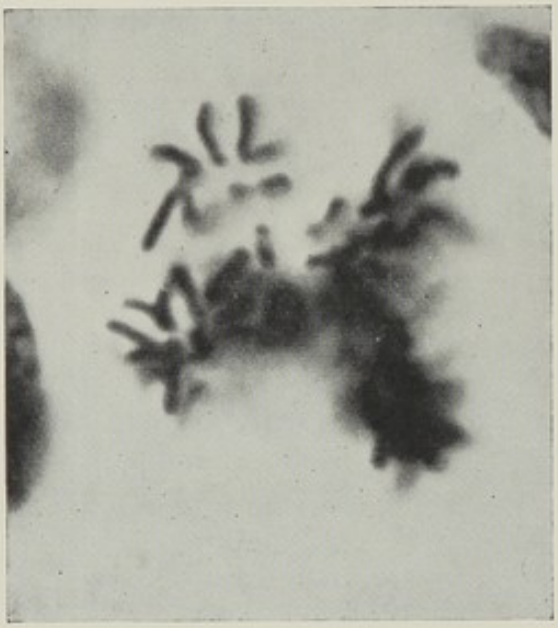


FIG. 24.—A red-cell precursor undergoing abnormal mitosis in a case of pernicious anaemia. (*By kind permission of Mr. L. La Cour.*) ×2800.

stain when they are treated by Schiff's aldehyde reaction for nucleic acid, indicating a difference in nucleic acid metabolism (Fig. 23). According to La Cour (1944), the difference is much more exaggerated in pernicious anaemia and it is shown by the fact that the chromosomes of the pre-erthyroblasts are short, thick and deeply stained with Feulgen's basic fuchsin, due to an excessive desoxyribosenucleic acid charge. About 95 per cent of the pre-erythroblasts have multipolar mitotic spindles (Fig. 24) and exhibit other abnormalities, which cause death and lead to their elimination.

Owing to the high number of chromosomes in man, it is almost impossible to identify individual chromosome pairs by their morphological features, except in the case of the sex chromosomes. Cytological maps, based on the topography of the chromosomes, are very valuable for the detection of structural rearrangements; therefore, any investigation into the detail of chromosome structure in

man would be a rewarding undertaking. Recently a promising start has been made in this direction and the chromomere-pattern of the nucleolar chromosome has been worked out (Fig. 25) (Schultz and Lawrence, 1949).

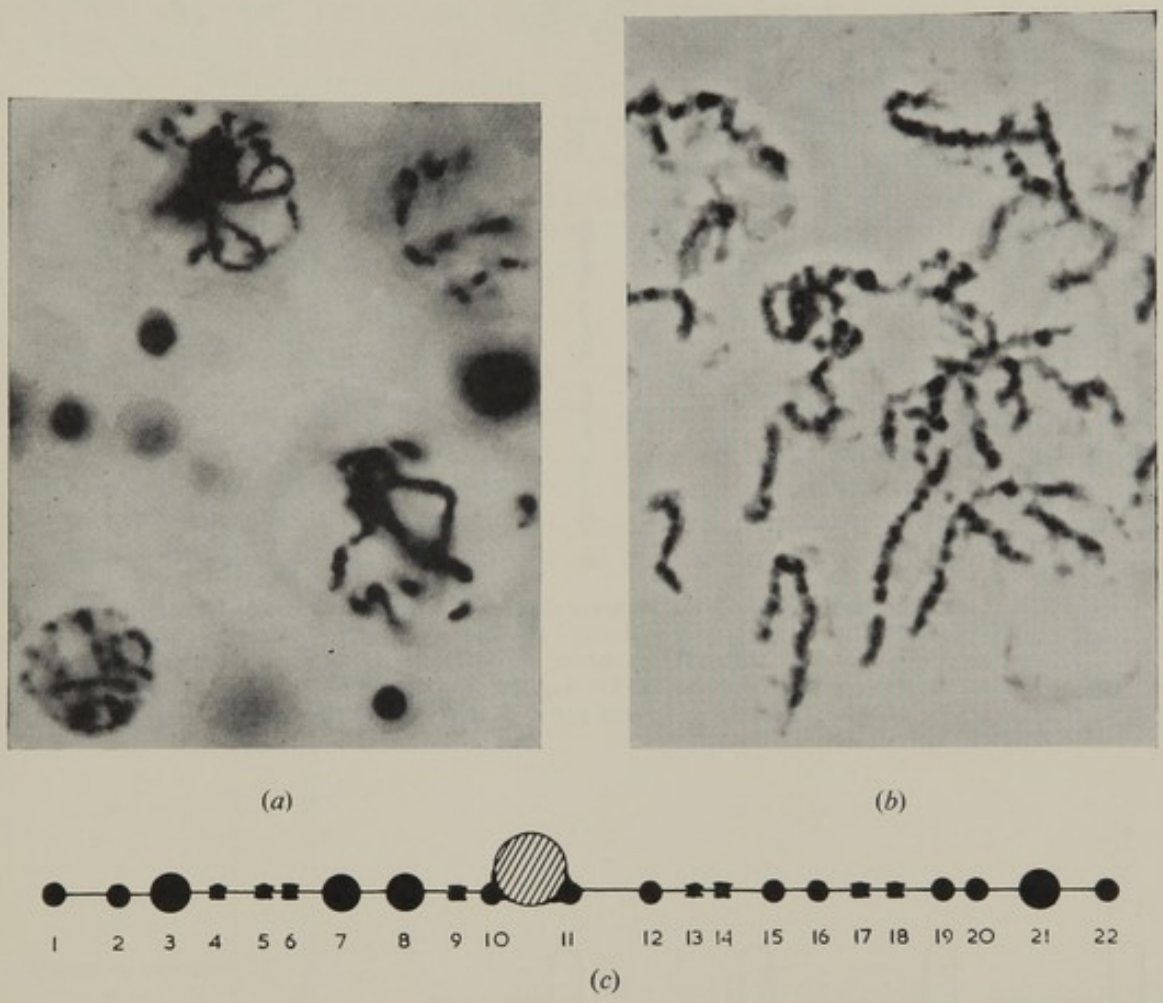


FIG. 25.—The chromomere-pattern of chromosomes. (*a*) During meiotic prophase the paired (*b*) homologous chromosomes show a bead-like structure × 2000. These are seen clearly in squash preparations × 2600. Each " bead " corresponds to a chromomere, which contains a group of genes. The topography of the nucleolus-associated chromosome is illustrated diagrammatically in (*c*). (*Fig. 25b by kind permission of Dr. I. Schultz. Fig. 25c is modified from T. Schultz and P. S. Lawrence, 1949.*)

Meiosis

Segregation, genetic ratios, or the recombination of heritable characters are determined during *meiosis* (Fig. 26), a process which takes place in the testis and ovary. At meiosis, the maternal and paternal homologous chromosomes associate and pair, forming a double thread; after that event each chromosome splits into two *chromatids*. The configuration is called the *bivalent* and it is composed of two chromosomes or four chromatids. At the end of the first meiotic division the two members of the bivalent move to opposite poles undivided. Chromosome

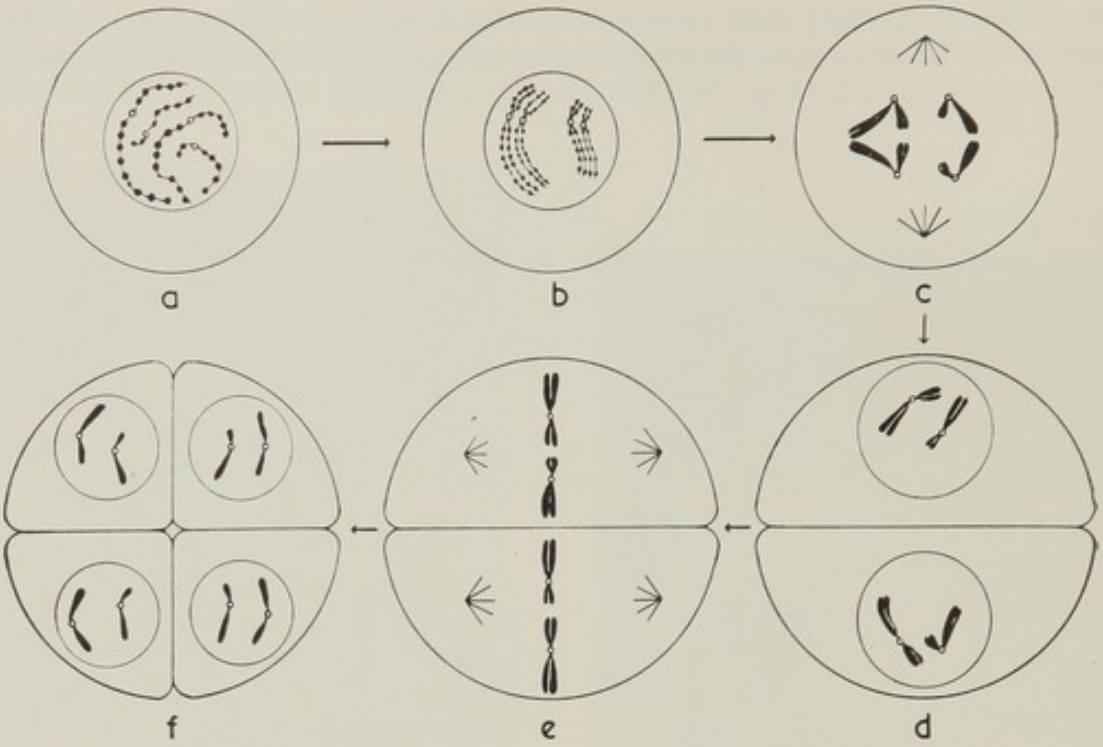


FIG. 26.—Diagram illustrating the various stages of meiosis or gamete formation. (*a*) A resting cell with four chromosomes. (*b*) The homologous chromosome pair and each member split into two daughter chromatids. (*c*) One daughter nuclei contain only two chromosomes. (*e*) During the second meiotic division the chromosomes undergo division. (*f*) Four gametes are formed, each with half of the original chromosome number.

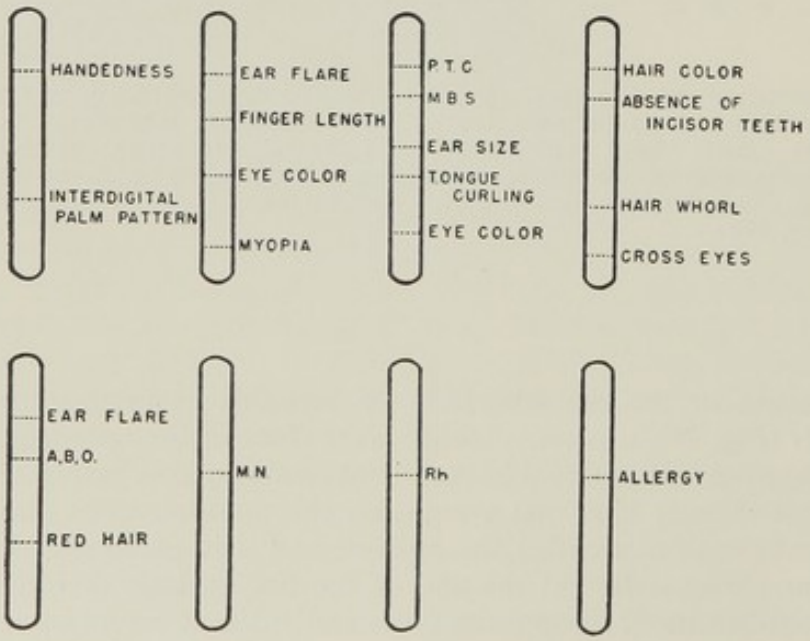


FIG. 27.—Maps of some of the human autosomes, based on the work of Burks, Kloepfer, Penrose, Rife, Snyder, Wiener and Zieve. (*From Snyder, L. H. (1946.) The Principles of Heredity. Boston; D. C. Heath and Co.*)

division or the separation of the daughter chromatids into different gametes occurs during the second meiotic division. Thus, meiosis is a process by which the cell divides twice, while the chromosomes divide only once, and the result is a numerical reduction or halving of the chromosome number in the gametes (sperms and ova). The somatic diploid number is restored again at fertilization, when the sperm and ovum fuse.

Because during the first meiotic division the arrangements of the different chromosome pairs are independent of each other, and obey only the law of chance, the maternal and paternal set of chromosomes undergo free recombination. Their free re-assortment forms the physical basis of the 3 : 1, 1 : 2 : 1, and other mendelian ratios. It is obvious that interference with the chromosome mechanism during meiosis results in abnormal genetic ratios.

Linkage

Those heritable characters whose genes are in the same chromosomes are transmitted together, that is, they belong to the same linkage group. Experimental investigation on the fruitfly *Drosophila*, sweet-pea, maize, mice, and so on, has shown that the number of linkage groups is the same as the number of chromosome pairs in somatic cells. In the fruitfly we have 4 linkage groups, in maize 10, in

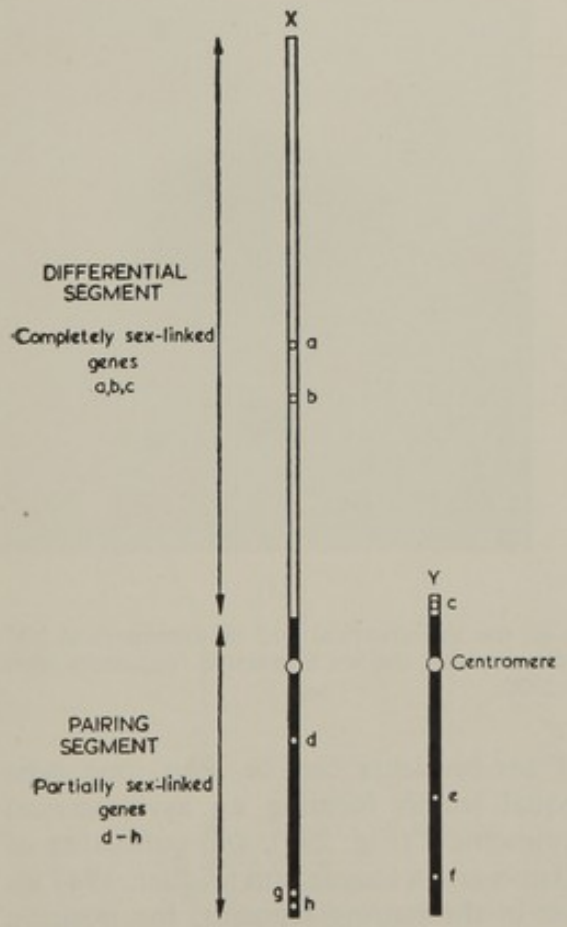
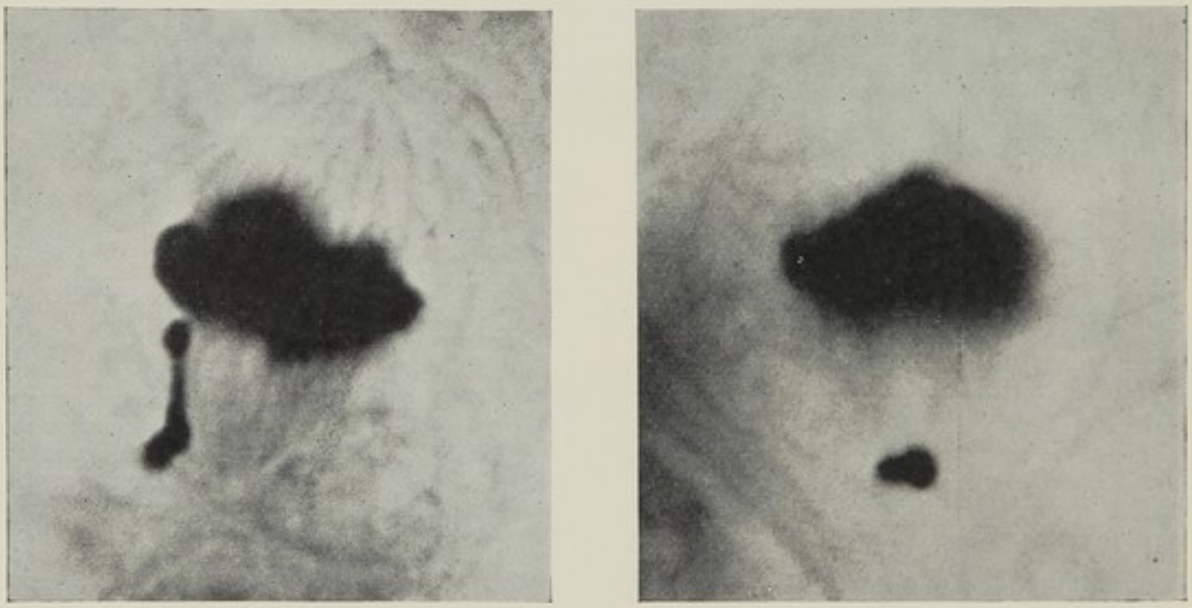


FIG. 28.—Diagram showing the structure of sex chromosome in man. Both are composed of two parts: one is the pairing segment which carries the centromere and the partially sex-linked genes; the other is the differential segment which carries the completely sex-linked genes. While the pairing segments of X and Y are of the same length, the differential segments differ greatly in size.

mice 20. On this ground in man we can expect 23 linkage groups besides the group of those genes which are located in the sex chromosome. Owing to the high number of chromosome pairs in man, up to the present only 8 autosomal chromosomes or linkage groups (Fig. 27) have been identified. The clinical implications, the effects of crossing over, and the possibilities in constructing chromosome maps are discussed in Chapter 7.

The sex-chromosomes

The X and Y chromosomes of the male greatly differ in size; the former is about 3–4 times larger than the latter. The X contains a large segment which is lacking in the Y chromosome, and during meiosis when X and Y pair, about two-thirds of the large X has no corresponding partner; this part is called the *differential segment*, because it carries the sex-differentiating genes, and is distinguished from the *pairing segment*. There is definite genetical evidence to show that not only the X but the Y chromosome also has a differential segment. It is, however, relatively very small and not always possible to identify cytologically. The centromere of the sex chromosomes has been located in the pairing segment (Fig. 28).



(*a*) (*b*)

FIG. 29.—Two spermatocytes in meiosis showing (*a*) the asymmetrical and (*b*) symmetrical XY bivalent respectively. Owing to the structural peculiarities, the sex bivalent is frequently seen placed apart from the autosomal bivalents. ×2800.

During spermatogenesis, two kinds of sex-bivalents can be seen, one type composed of two chromosomes of unequal length forming an asymmetrical configuration (Fig. 29*a*), and the other symmetrical (Fig. 29*b*), and consisting of a short, thick and deeply stained terminal knob and a longer arm (Koller, 1947 a). These types are the result of crossing-over in the pairing segment, the position

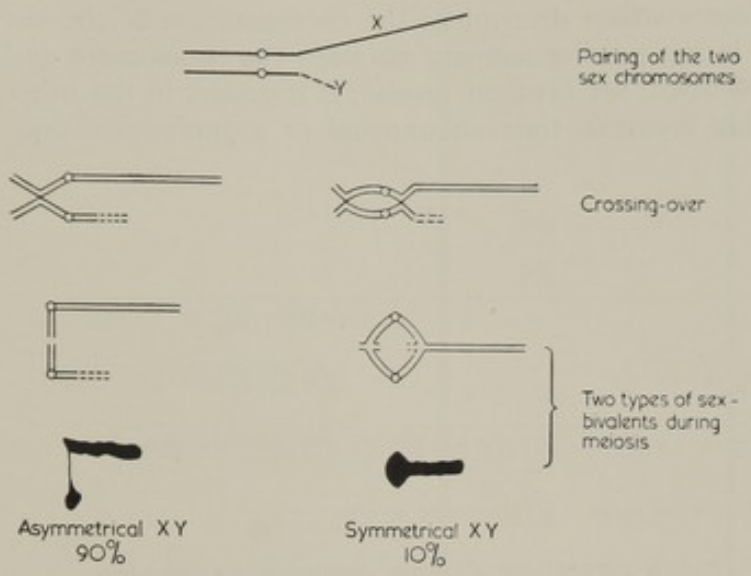


FIG. 30.—Diagram to illustrate the method of origin of the two types of sex-bivalents in man. The frequency of the asymmetrical and symmetrical XY is given.

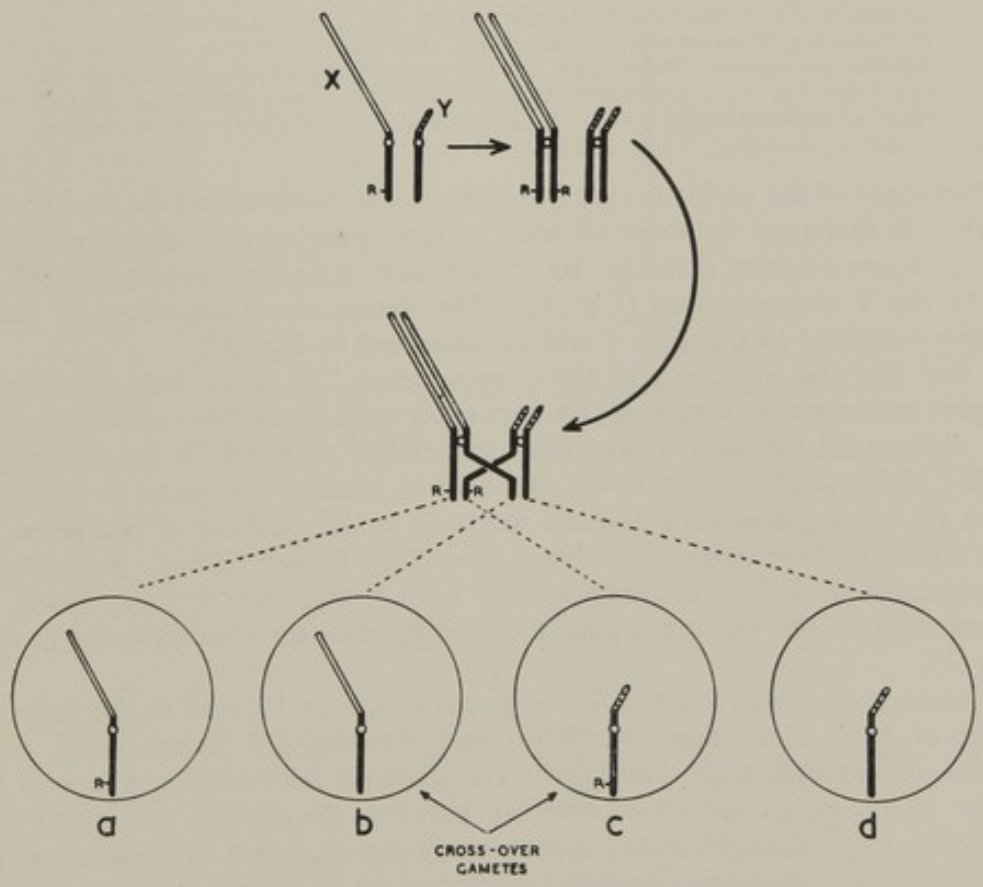


FIG. 31.—Diagram illustrating the result of crossing-over in the pairing segments of X and Y. It is shown that gene R (retinitis pigmentosa) is transferred from the X to the Y chromosome, and there are now two types of gametes with new chromosome constitution (b and c).

of crossing-over being the factor which determines the configuration of the sex bivalent (Fig. 30). If it lies in the pairing segment between the centromere and differential segment the symmetrical sex-bivalent results; if it occurs in the other or distal region of the pairing segment, then an unequal or asymmetrical configuration is formed.

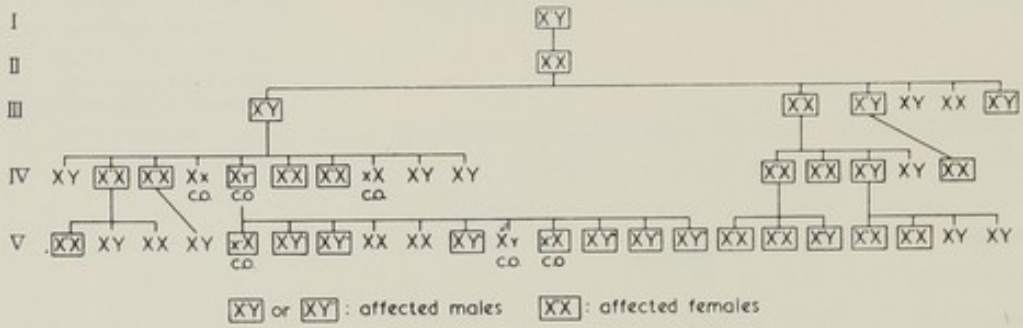


FIG. 32.—A pedigree of retinitis pigmentosa showing dominant sex-linkage and the result of crossing-over. The male of the first generation carried the gene in the X· chromosome and transmitted the ailment to his daughter (X·X). She handed the gene down to sons and daughters (III. 1, 2, 3, and 6). Amongst the children of the eldest son (III. 1), two non-affected daughters (IV. 3 and 8) and one affected son (IV. 5) could only be explained by assuming crossing-over between the X and Y chromosomes of the father. Similar explanation holds true for the appearance of affected daughters (V. 5 and 12) and a non-affected son (V. 11) in the next generation derived from an afflicted father (IV. 5). (*After Haldane, J. B. S. (1941). New Paths in Genetics*. London; Allen and Unwin.)

The presence of the various types of sex-bivalents in man indicate that crossing-over, that is exchange between sections of the homologous pairing segment of X and Y, occurs during meiosis. By this process genes can be transferred from the X to the Y chromosomes (Fig. 31). The genetical consequences of such an event are discussed in Chapter 7 and summarized in Fig. 32.

The fact that the frequency of the " unexpected " or cross-over individuals in a pedigree indicates the distance of a particular gene from the terminal end-point of the differential segment makes the localization of partially sex-linked genes possible. Haldane (1936 and 1940) was able to localize six genes in the pairing segment by using ingenious statistical methods in the analysis of pedigrees. The loci of some of these genes have been altered by Fisher (1936). Recently, two more partially sex-linked characters have been found (*see* Snyder, 1946). The genetical map of the pairing segment of the human sex chromosome is shown in Fig. 33.

The number of *completely sex-linked* genes which are located in the differential segment of X is more than 30. The most familiar are haemophilia, colour-blindness and myopic night-blindness. The distance between the first two genes is about 10 crossing-over units, whereas between the second and third it was found to be more than 50 units; consequently the sequence of these three genes in relation to the centromere cannot be determined at present.

Five genes are known which are transmitted only in the male line, on account of which it is believed that they are located in the differential segment of the Y chromosome. One trait is *ichthyosis hystrix gravior*; it consists of bristly outgrowth on the whole body

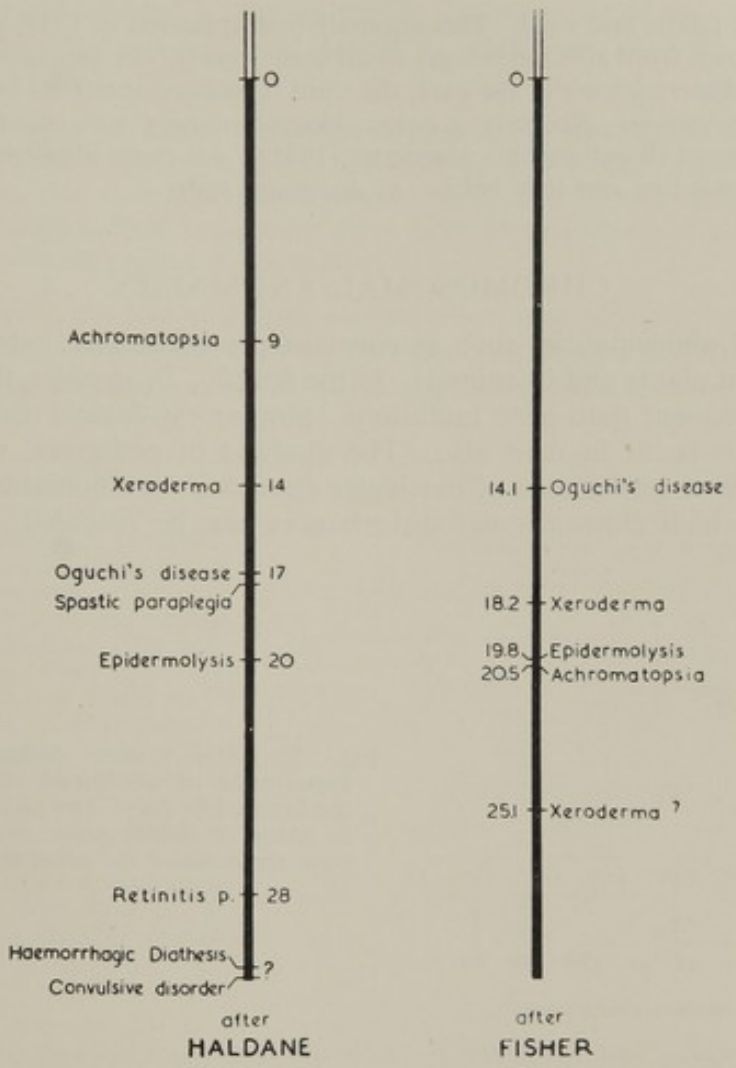


FIG. 33.—The genetical map of the pairing segment showing the loci of the partially sex-linked genes according to Haldane and Fisher.

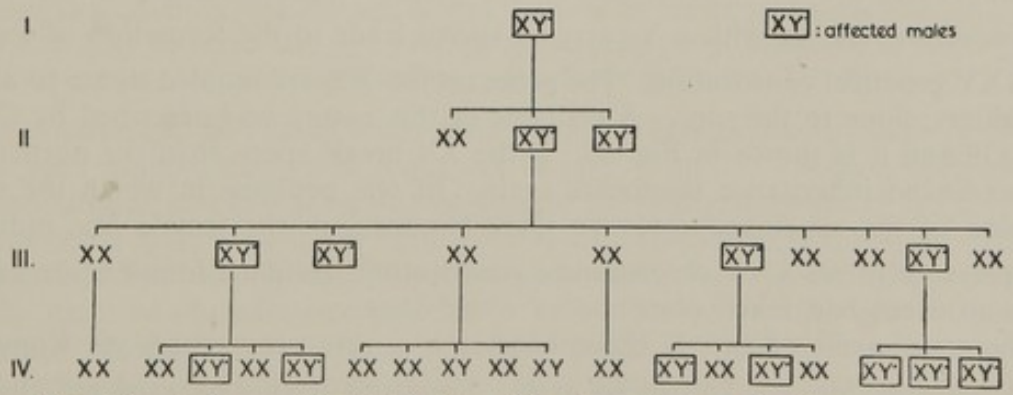


FIG. 34.—Pedigree of webbed toe. The transmission of this anomaly is restricted to the male line, which indicates that the gene responsible is located in the differential segment of the Y chromosome. (*After Schofield, R. (1921.) J. Hered.*, **19**, 400).

except the face, palms and soles. This anomaly first appeared in 1717, and the gene has been handed down from affected fathers to all their sons for six generations. The second abnormality is *hypertrichosis* of the ears, the third is webbed toe (Fig. 34) and the fourth is *keratoma dissipatum*. Recently a colour-vision anomaly was reported to show Y-linked transmission (Reed and his associates, 1951). All these abnormalities are transmitted in the male line and they behave as dominant traits.

CHROMOSOMAL ANOMALIES

Chromosomal abnormalities such as constant presence of an extra chromosome are common in plants and in animals. In the fruitfly, *Drosophila*, they were found to be more frequent than gene mutations. Similar cytological abnormalities can be expected to occur in man also. The analysis of pedigrees, which show an irregular mode of inheritance of particular characters or anomalies, is one of the methods by which chromosomal disturbances can be revealed.

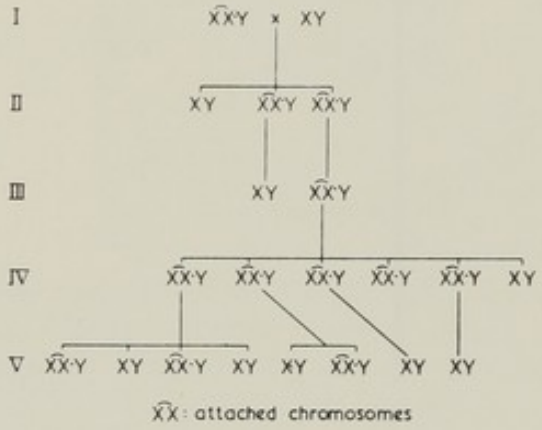


FIG. 35.—The Cunier pedigree showing the appearance of sex-linked colour-blindness in the female line only. The pedigree is interpreted in terms of chromosome constitution to illustrate the basis of the anomalous inheritance.

Haldane (1932) drew attention to various pedigrees, in which anomalies, known to be completely sex-linked (for example, colour-blindness) were transmitted in the female line only. Such a behaviour is consistent with the view that two X chromosomes are attached so that they segregate together during meiosis. The fusion of an $\widehat{XX}$ egg with a Y-carrying sperm leads to the formation of females of $\widehat{XX}Y$ genetical constitution. The genes on the $\widehat{XX}$ are handed down to all the daughters, none to the sons. A pedigree of this nature was described by Cunier in 1839 and it is shown in Fig. 35. If the X's break apart, then the normal line of sex-linked inheritance reappears again. In one pedigree in which the transmission of the sex-linked recessive night-blindness in the female line indicated the presence of an $\widehat{XX}Y$ chromosome constitution, Haldane found evidence that such an event had taken place.

The attachment of two X chromosomes is a rare occurrence, yet women of $\widehat{XX}Y$ constitution are known to exist. Therefore it can be expected that the number of women with an XXY constitution (when the X's are free) ought to be much higher. It is very likely that this is the case, but the detection of such a chromosome constitution by genetical analysis alone would be extremely difficult.

The evidence of *trisomy*, a case in which the presence of an extra autosomal chromosome may be inferred, was found by Haldane (1932) in a pedigree by Haselhorst and Lauer.

These authors described a family in which the mother belonged to the AB and the father to the O blood groups. Their son was found to have O blood. Haldane argues that it is very unlikely that A and B simultaneously mutated to O, and suggests as the most reasonable explanation that there must have been three instead of two blood group carrying chromosomes present in the mother.

Deletion, that is, the loss of a chromosome piece, is another type of chromosome abnormality which has been reported by Race and Sanger (1950). The pedigree with the genetic constitution of the particular individuals is shown in Fig. 36.

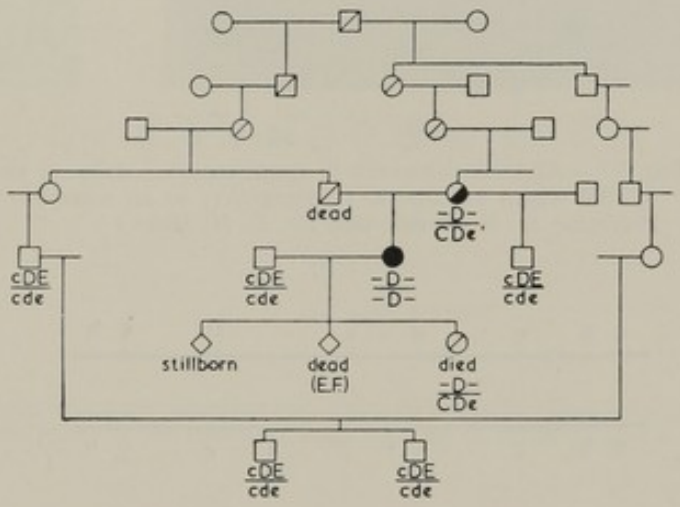
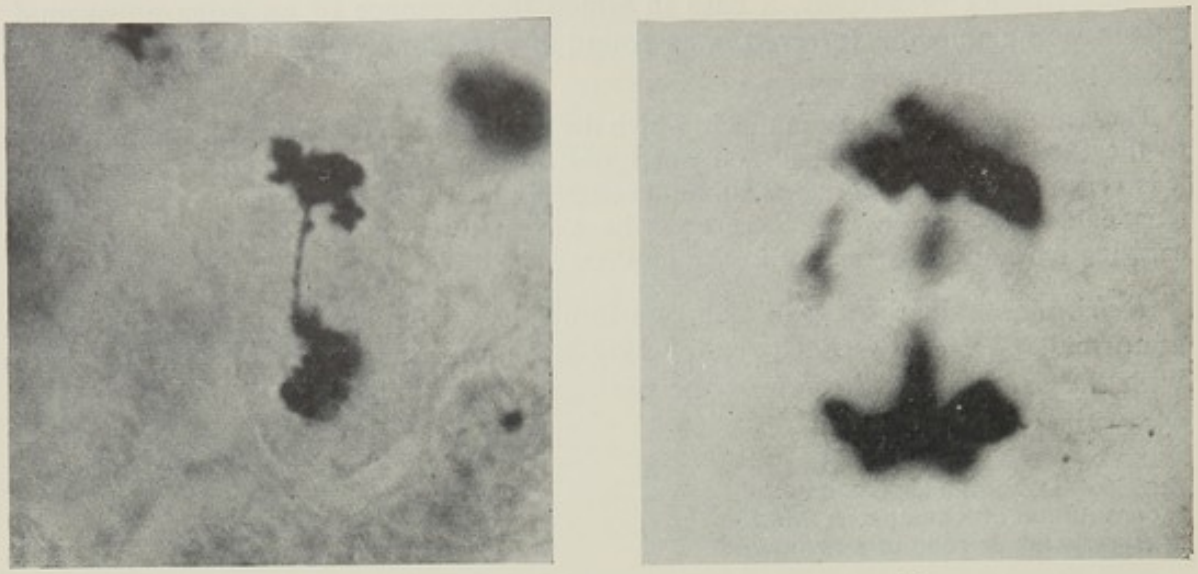


FIG. 36.—The pedigree of an unusual constitution of Rh-antigens, which suggests the deletion of a chromosome section carrying the genes of the C and E antigens. The donor (●) is considered to be homozygous for the deletion. The antigen constitution of her third child was determined and found to be similar to that of the maternal grandmother. The squares and circles struck through, as also the half blacked out circle indicate those relatives and ancestors whose Rh-antigens were not tested but presumed to be heterozygous for deletion. (*After Race, R. R., and Sanger, R. (1950). Nature*, **166**, 520.)

Serological test has disclosed that the blood of the donor had antigen D but lacked C and E antigens, which strongly suggests a genetic constitution of -D-/-D-, the dashes representing the absence of the C and E series. It is known that the absence of genes, due to the deletion, results in spurious dominance of the alleles in the corresponding normal chromosome. The pedigree described by Race and Sanger has another merit. Because two deletions, one on each side of the gene D, are extremely unlikely, this particular case may be taken also as a proof that the sequence of the genes is DCE instead of CDE, so that the genetic constitution of the donor is given as D- -/D- -.

Chromosome or chromatid bridges and fragments during the first meiotic division have been observed by various authors in man (Fig. 37). Such a chromosome abnormality is known to be due to one or two crossings-over in an inversion chromosome loop causing the formation of chromosomally unbalanced gametes. When an individual is heterozygous for an inversion, that is, one of the members of the parental chromosome pair has a section in which the order of genes is reversed—abcdefg : normal gene-sequence; abedcfg : inverted gene-sequence—then during meiosis various anomalies, such as chromosome bridges and fragments, can be expected (Fig. 38).

The genetical consequence of an inversion is shown by a reduction in the number of cross-over individuals due to the fact that embryonic development does not occur if



(*a*) (*b*)

FIG. 37.—Abnormal meiosis in spermatocytes showing single (*a*) ×1800 and double bridges (*b*) ×2400 which are due to crossing-over in an inversion loop. (*Fig. 37a by kind permission of Professor H. W. Beams and Dr. E. H. Slifer.*)

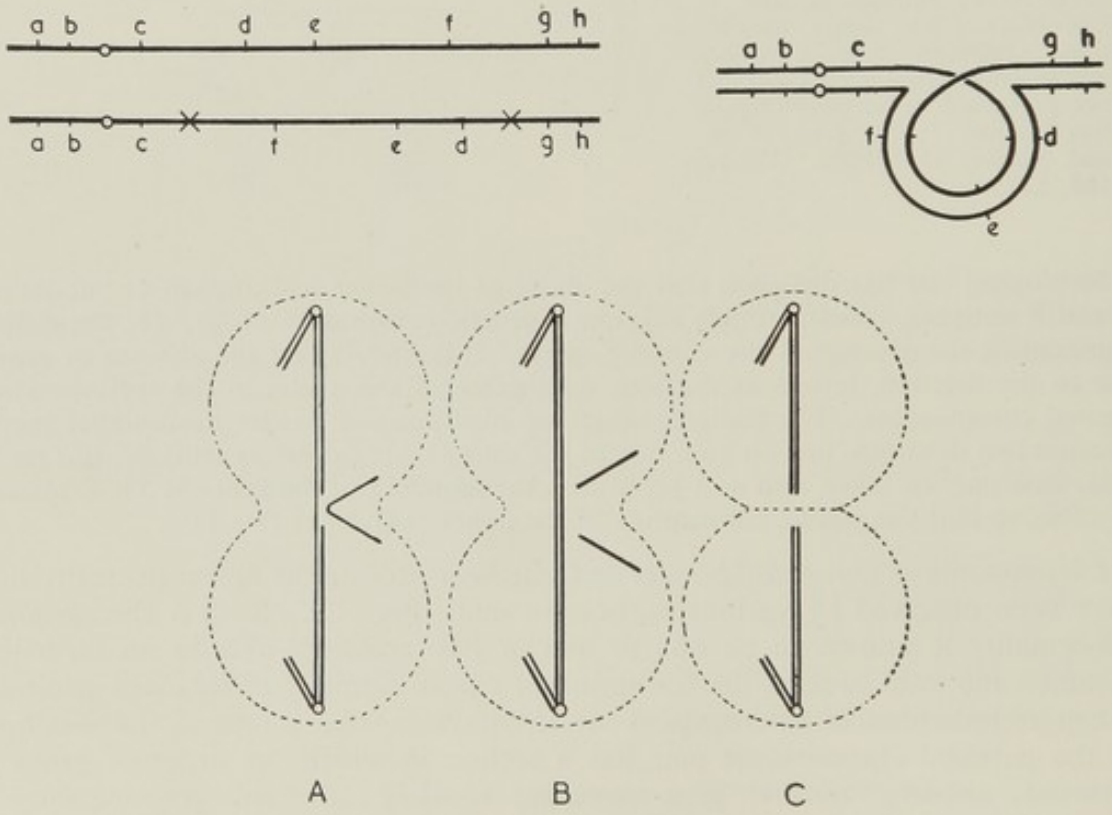


FIG. 38.—Diagram showing the pairing of homologous chromosomes, one of which has an " inverted " section (indicated with X—X). Single or double crossing-over in the inversion loop produces chromosome or chromatid bridges and fragments and leads to the formation of abnormal gametes.

normal ova are fertilized by sperms having abnormal chromosome constitution. Reduced fertility is one of the criteria which suggests the presence of chromosome anomalies.

Position effect.—Another type of chromosome anomaly has been found in a pedigree of *xeroderma pigmentosum*, which is a partially sex-linked condition (Koller, 1948) (Fig. 39).

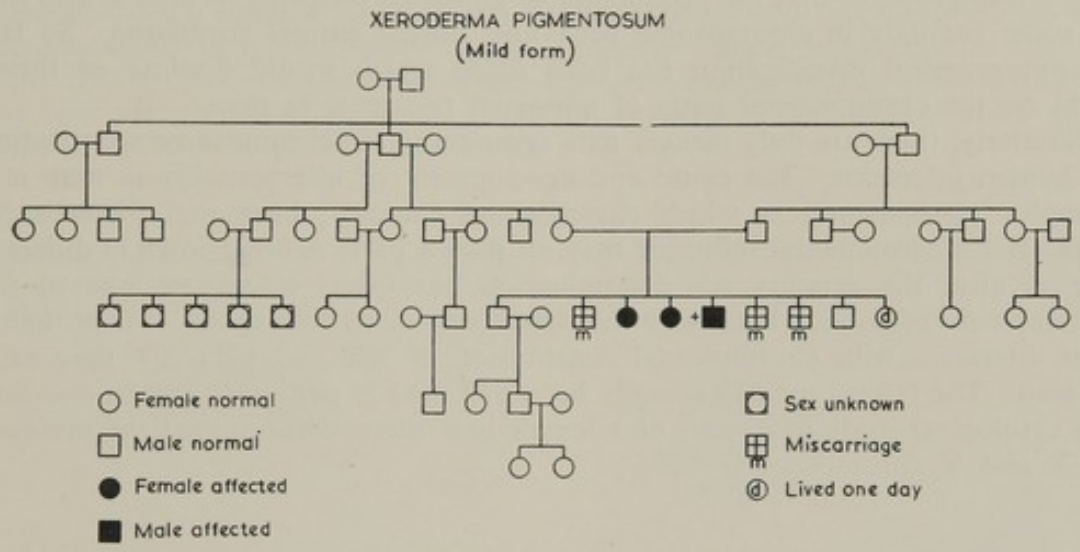


FIG. 39.—Pedigree of xeroderma pigmentosum, showing two unusual features. One is the late onset of the anomaly, the other is the relatively high number of cross-overs amongst the affected members.

The chromosome abnormality has been suggested by two unusual features observed in the history of the particular family: one is the late onset and mild manifestation of the disease, which normally appear a few weeks or months after birth and is always lethal; the other feature is the high frequency of cross-over individuals amongst the affected members; they are more numerous than expected on statistical grounds. Both these conditions are explained on the assumption that the gene of *xeroderma* has been transferred to a more distant region of the pairing segment. The increased distance between the gene and the differential segment would explain the higher crossing-over frequency in respect of sex, and the altered position of the gene would account for in the lower degree of malignancy.

" Position effects " have been described in the fruitfly, *Drosophila*, and in some plants, and attributed to a shift in the position of the gene. The result of such a change is a new inherited phenotype.

Sex ratio, unisexual pedigrees and intersexuality

The primary sex determination of an individual takes place at fertilization. Fusion of an X-carrying egg with an X-carrying sperm results in females, that of an X-egg and Y-carrying sperm results in male offsprings. Because an equal number of X-carrying and Y-carrying sperms are formed during spermatogenesis, the number of males and females at the time of conception could be expected to be equal. However, it has been found that the primary sex ratio

differs from the expected equality and estimated to be 130 males to 100 females. The greater number of males strongly suggests that in man the fertilization of eggs with Y-carrying sperm is more common than with X. At present no explanation for this fact can be given.

Few pedigrees are known which contain only males, or only females. In view of the fact that in *Drosophila* an abnormal behaviour of the sex chromosomes during meiosis is known to be responsible for the elimination of all male offspring, it is not improbable that the production of unisexual offspring in man is also due to some anomaly in chromosome behaviour during gamete formation. So far, no cytogenetical investigation has been made which would disclose or throw light on the chromosomal basis of unisexual pedigrees in man.

Similarly, there are only meagre data concerning the chromosome constitution of human intersexes. The cause and development of intersexuality in man is a complex phenomenon in which chromosome anomaly, hormonal disturbance, genic and environmental influence may all play a part. A breakdown in differentiation after the primary sex determination has taken place can lead to the development of an individual with the characteristics of both sexes. It is probable that intersexes with chromosomal constitution of XX and with XY may exist in man. The latter type has actually been observed in pedigrees and in one case the cytological study of a testis of a female-like intersex has proved the presence of X and Y chromosomes.

THE GENETIC CONSEQUENCE OF SPONTANEOUS AND INDUCED CHANGES IN THE CHROMOSOMES

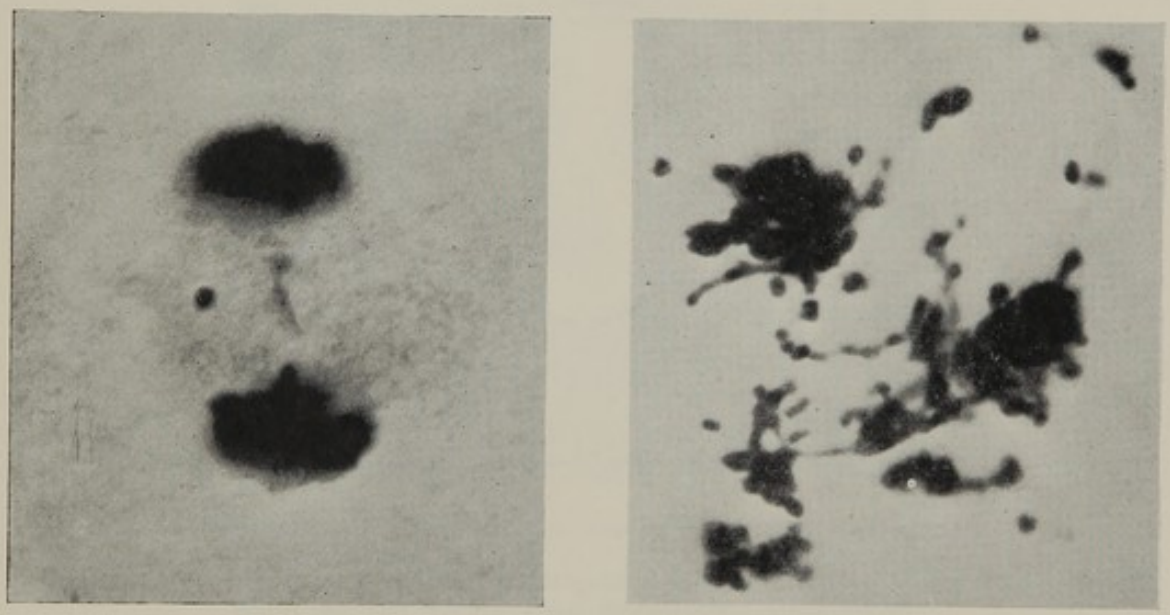
Two kinds of changes can be induced in the chromosomes: (1) gene mutation; and (2) structural or numerical alteration (inversion, deletion, translocation, polyploidy and so on). Both types occur naturally. The cause, responsible for the naturally occurring or " spontaneous " gene or chromosome mutations, is manifold and far from clear at present. Though their rate of occurrence is low, it has been possible not only to detect their existence, but also to estimate the frequency of many mutations, as was seen in Chapter 8.

The occurrence of chromosomal mutations is at least as frequent as gene mutations if not more so. Examples have been found in pedigrees showing irregular transmission of some abnormality, and the presence of a few chromosome mutations has been indicated by direct cytological observation. Some of these instances have already been described above.

Radiation as a mutagenic agent

The most important amongst the mutagenic agents is ionizing radiations: x-rays, *gamma*-rays, neutrons and so on. These produce minute and gross chromosome injuries; the latter cause the death of cells in mitosis, and can therefore be employed for the treatment of malignant growth. It was found that the amount of chromosome injury in a cell is closely related to the dose (Fig. 40). When the mutations are induced in the chromosomes of the gonads, they can then be transmitted to the descendants of the exposed individual and lead to serious genetical implications in future generations.

Radiation-genetics has accumulated an impressive amount of experimental data which show that the frequency of new mutations induced by ionizing radiations is related to the dose and independent of the intensity at which it was delivered. This fact has a serious aspect in human affairs because nowadays an increasing proportion of the population is being employed in medical practice and in industry, in occupations which involve a certain amount of radiation hazard. The " tolerance dose " is 0·5 roentgen per week; very small indeed, yet it does not eliminate radiation hazards completely. Recently it was reported that cells with nuclear abnormalities were found in the blood of personnel associated with a 130-inch cyclotron after exposures which were well below the accepted tolerance levels (Ingram and Barnes, 1951). Although safeguards and rigorous measures are devised to protect the individual directly exposed to radiation, so far too little attention has been paid to the genetic consequences and especially to those effects which would come to light only in the far distant future.



(*a*) (*b*)

FIG. 40.—Two dividing cells of carcinoma of the cervix uteri showing chromosome injuries 24 hours after irradiation with x-rays: (*a*) dose 25 roentgens, (*b*) dose 2,500 roentgens. The amount of chromosome-fragmentation is related to the dose. ×2000.

While gene mutations, being mostly recessive, will need to spread far and wide in the human population throughout many generations before their existence can be registered, there are major genetic changes, induced by radiation, which can be detected in the first generation. One of these changes consists of an interchange of segments between non-homologous chromosomes (Fig. 41). Due to such a structural change, not two but four chromosomes will associate into one configuration during gametogenesis. Various arrangements of chromosomes are possible in the ring formed by the four chromosomes. When the alternate members of the ring go to the same pole, normal gametes are produced. Two other arrangements are also possible, in both of which the adjacent members of the ring go to the same pole. If the orientation of chromosomes in the ring is at random,

then the frequency of the six kinds of gametes is the same, but only two of these types contain a complete chromosome set, the other four having one segment present in duplicate while at the same time lacking another segment. These types are abnormal in respect of their chromosomes and when they fertilize a normal egg, the zygote or embryo dies. One result of an interchange is a great reduction in fertility; theoretically only 33·3 per cent of the gametes produced are viable. Another genetic consequence of such structural alteration in the chromosomes is the change in genetic linkage; genes which are normally located in different chromosomes will behave as those which belong to the same linkage group.

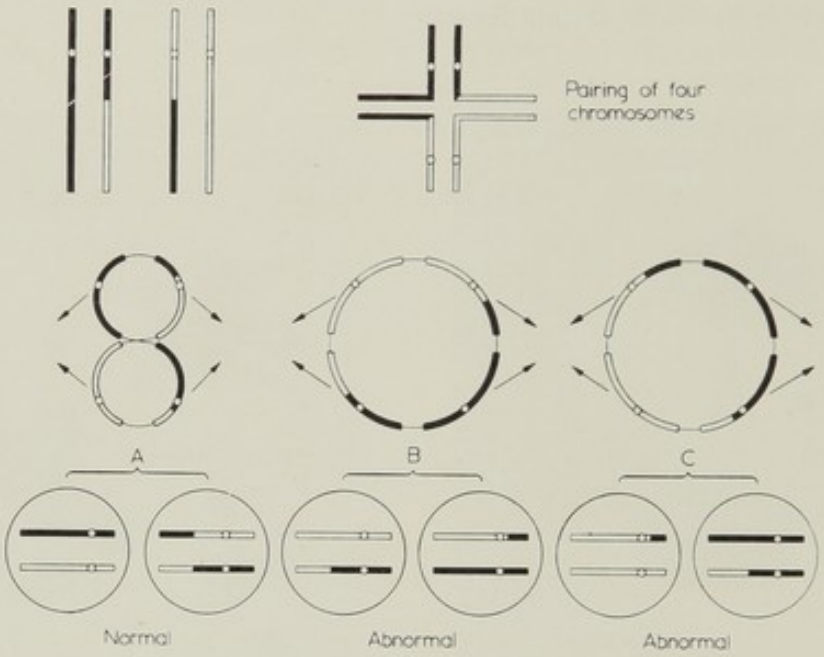


FIG. 41.—Diagram illustrating the behaviour of two non-homologous chromosome pairs during meiosis which have interchanged segments. The orientation of the chromosomes in the " ring-of-four " is at random, as a result of which six types of gametes are formed, each with different chromosome constitutions. Only two gametes are normal, the others are chromosomally abnormal.

The repercussions of radiation-induced chromosome interchange have been studied in mice (Koller, 1944). There is no doubt that the chromosomes of the germinal cells in man if not protected from x-rays can also undergo similar structural change. The consequence is greatly reduced fertility in the descendants of the individual irradiated.

In view of the vast expansion of research in the field of atomic energy which has been taking place recently, it can be expected that the genetic hazards of radiation will increase. Hence investigation into the fertility rate of descendants whose progenitor has been exposed to ionizing radiation would be a convenient, easy and at the same time very promising undertaking which could yield important data to estimate the magnitude of the genetic implications involved.

Other mutagenic agents

Some chemical compounds—a few of which have already found employment in the chemotherapy of various human ailments, such as the nitrogen mustards in the treatment of leukaemia and Hodgkin's disease (Fig. 42)—can also produce gene and chromosome mutations. They carry more potential danger of affecting the germinal tissues in man than the use of x-rays, for the gonads cannot be shielded effectively.

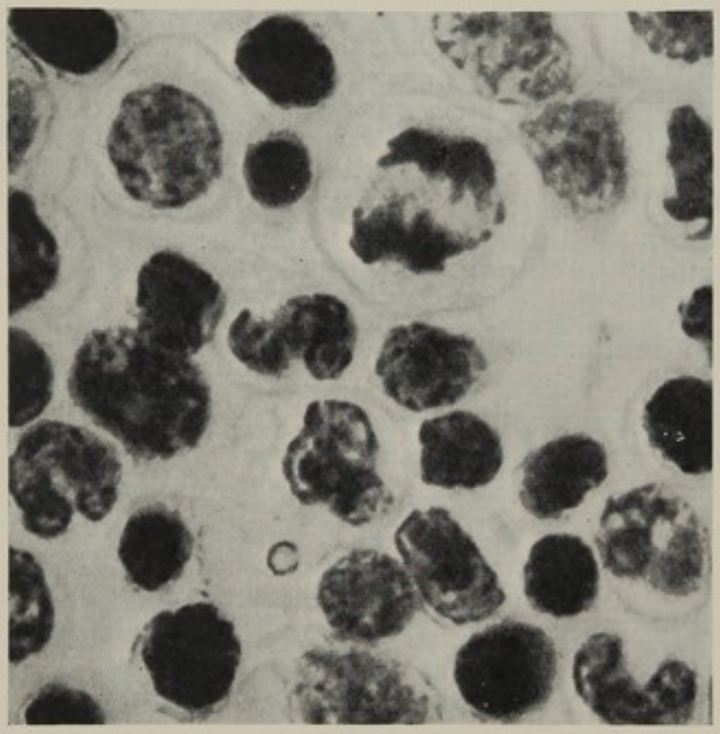


FIG. 42.—Microphotograph showing cells taken from the sternal bone marrow of a patient treated with nitrogen mustard. The presence of a "micronucleus" or chromosome fragment in a resting cell and bridges in a dividing cell are the effects of nitrogen mustards on the chromosomes. ×1800.

The potential dangers of radiotherapy and chemotherapy

The potential genetic consequences which may follow treatment with particular chemotherapeutic or radiotherapeutic agents should therefore be weighed before their use becomes general. The magnitude of the genetic effects for the next and future generations must be considered from an individual as well as from a population point of view. Gene mutations are almost always deleterious and if they are produced with high frequencies, they will, throughout future generations, kill more people whose germ plasm is contaminated with the mutated genes than could be killed directly by the explosion of the atom bomb.

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CHAPTER 10

II.—Chemical Genetics

D. G. Catcheside

The means by which the genes determine particular characters is the subject matter of physiological genetics. It is anticipated that it may become possible to describe this in completely chemical or biochemical terms, but at present the connexion between gene and character is still largely unknown. A fruitful approach is a careful analysis in chemical terms of the changes in character wrought by a change in one or more genes. This subject of chemical genetics has made use of the most varied biological material, from the pigments of flowers (Lawrence to the metabolic derangements in some congenital human diseases (Garrod, 1923).

Alkaptonuria in man is a classic in chemical genetics, being the first instance in which a particular gene was related to a specific and known biochemical reaction. One characteristic symptom is the blackening of the urine on exposure to air, a reaction due to 2·5-dihydroxyphenylacetic acid, also known as homogentisic acid and alkapton. Soon after the rediscovery of Mendel's work in 1900, it was recognized that alkaptonuria behaved in inheritance as a simple mendelian recessive. Some time later it was found that the blood serum of normal individuals contains an enzyme capable of catalysing the breakdown of homogentisic acid and that this enzyme was apparently absent from the sera of alkaptonurics. Thus it was established that a single gene change resulted in the absence or inactivity of a specific enzyme and that this in turn led to the failure of a particular biochemical reaction. Several other inherited metabolic defects involving the metabolism of the amino acids tyrosine and phenylalanine are now known and are discussed elsewhere (Chapter 11). They all support an interpretation of gene action in terms of a one gene-one reaction hypothesis.

Many of these materials suffer from some experimental disability or other, and in almost all respects the work on the chemical genetics of mould fungi, especially that on *Neurospora*, commenced by Beadle and Tatum, is the most promising. This fungus may be gorwn under completely defined conditions and a great range of chemical characters may be analysed genetically. It is proposed to confine the rest of this account to the principles of chemical genetics as illustrated by the *Neurospora* work.

CHEMICAL MUTANTS OF *NEUROSPORA*

This work began with the hypothesis that any mutation which interfered with an essential process of intermediate metabolism would render the strain carrying it incapable of growth on a medium sufficient to support the normal wild type, and that it should be possible to obtain growth of the mutant strain if the deficient

substance could be supplied from the medium. In practice, the wild type mould will grow if supplied with mineral salts, an inorganic source of nitrogen (such as potassium nitrate), sugar (15–20 grammes per litre) and biotin (1–4 γ per litre). Mutants are sought amongst stocks isolated on a medium consisting of these mineral requirements supplemented by various materials, such as malt or yeast extract or by individual substances in special cases. The mutants are those stocks which do not grow on the minimal medium but will grow on a supplemented medium. Further tests by exclusion technique will usually discover the particular defect and the nutritional remedy for it.

The loss of a specific metabolic step as a consequence of mutation of a specific gene shows that the wild type allele is uniquely concerned in controlling the specific metabolic step. Its particular contribution is not duplicated by any other gene in the array. Where two different mutants, which will each grow with the same supplement, are shown genetically not to be allelic it is evident that each results in the blockage of a different step in the same metabolic sequence. If two such mutants are caused to form a heterocaryon, in which the two different kinds of nuclei inhabit the same mycelium, the heterocaryon will usually grow on minimal medium. This shows the two deficiencies are mutually complemented in the heterocaryotic organism. Thus we are led to postulate a stepwise process in the synthesis or metabolism of vital substances in the organism and to postulate a one-to-one relation between gene and step in metabolism in the organism.

A considerable number of different nutritionally deficient mutants of *Neurospora crassa* are now known. In Table I the better known of these are listed according to their different growth factor requirements, the number of mimics that are genetically different being noted. In many cases, a given mutant type has appeared repeatedly, but no attempt is made in the table to indicate which mutants have recurred in this way. Sometimes the recurrences have differed from one another in their characters, and further reference will be made to the comparative properties of such multiple alleles. There are several other kinds of mutants indicated by recent work, including requirements for peptides, though the precise kinds are not yet known. These are interesting as indicating genetic control of peptide synthesis.

TABLE I

Neurospora crassa Chemical Mutants Listed According to Growth Factor Requirements

Vitamins	*Amino acids*	*Nitrogen bases*	*Various*
Thiamine 4	Arginine 10	Adenine 7	Amino group 2
Riboflavine 1	Tryptophane 5	Cytidine or uridine 4	Reduced nitrogen 2
Pyridoxine 2	Isoleucine$^+$ valine 2		Succinate 2
Pantothenic acid 1	Leucine 2		Acetate 1
p-Aminobenzoic acid 1	Lysine 5		Fat 2
Inositol 1	Methionine 7		Sulphonamide 1
Choline 2	Homoserine 1		Quinic acid 1
Nicotinic acid 5	Cysteine 3		Shikimic acid 1
	Threonine 2		
	Proline 1		
	Valine 1		
	Serine or glycine 2		
	Phenylalanine 1		
	Tyrosine 1		
	Histidine 4		

PATHWAYS OF BIOSYNTHESIS OF GROWTH FACTORS

One of the first uses of biochemical mutants is to discover the pathways of biosynthesis of the various growth factors required by different mutants. To a first approximation, we may suppose that the synthesis of a given growth factor G is sequential, such that A→B→G, the substances A and B being precursors. The first step is the attempt to identify these substances. If two genetically different blocks in the biosynthesis of G were known, it might happen that one blocked the stage A→B and the other the stage B→G. In this case we should expect to be able to find a substance B which could substitute for G as a growth factor for the first mutant, but not for the second one. This would specify B as a precursor of G and it is conceivable that the process could be extended by means of still other mutants.

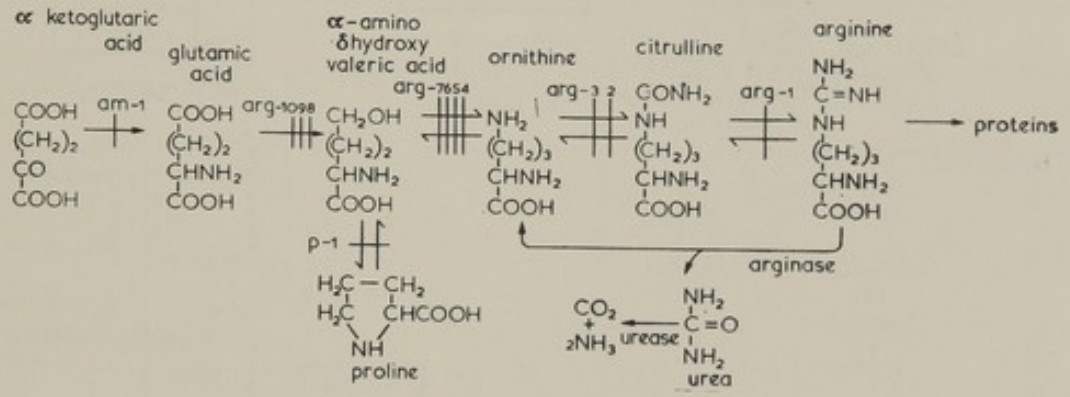

FIG. 43.—Pathway of arginine synthesis in *Neurospora crassa*.

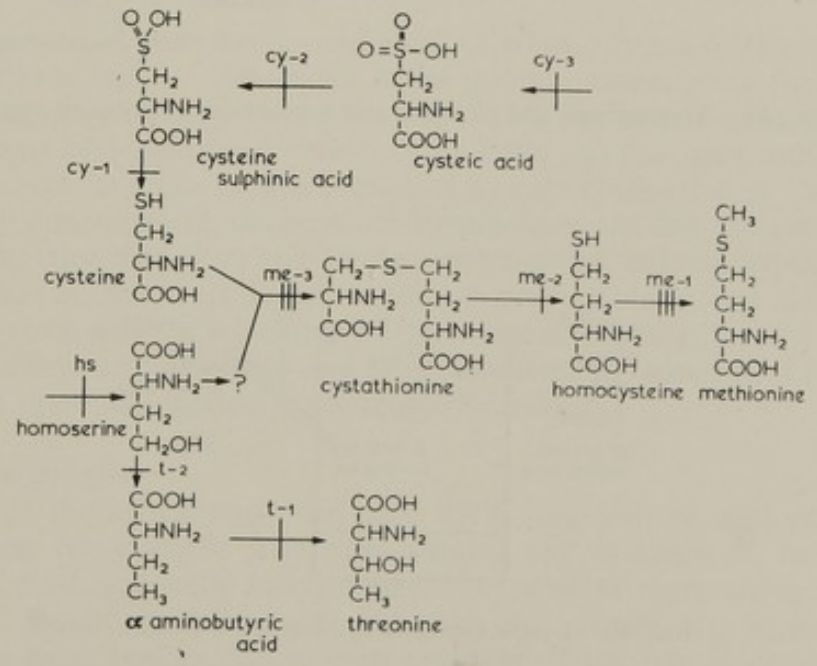

FIG. 44.—Methionine and threonine synthesis in *Neurospora crassa*.

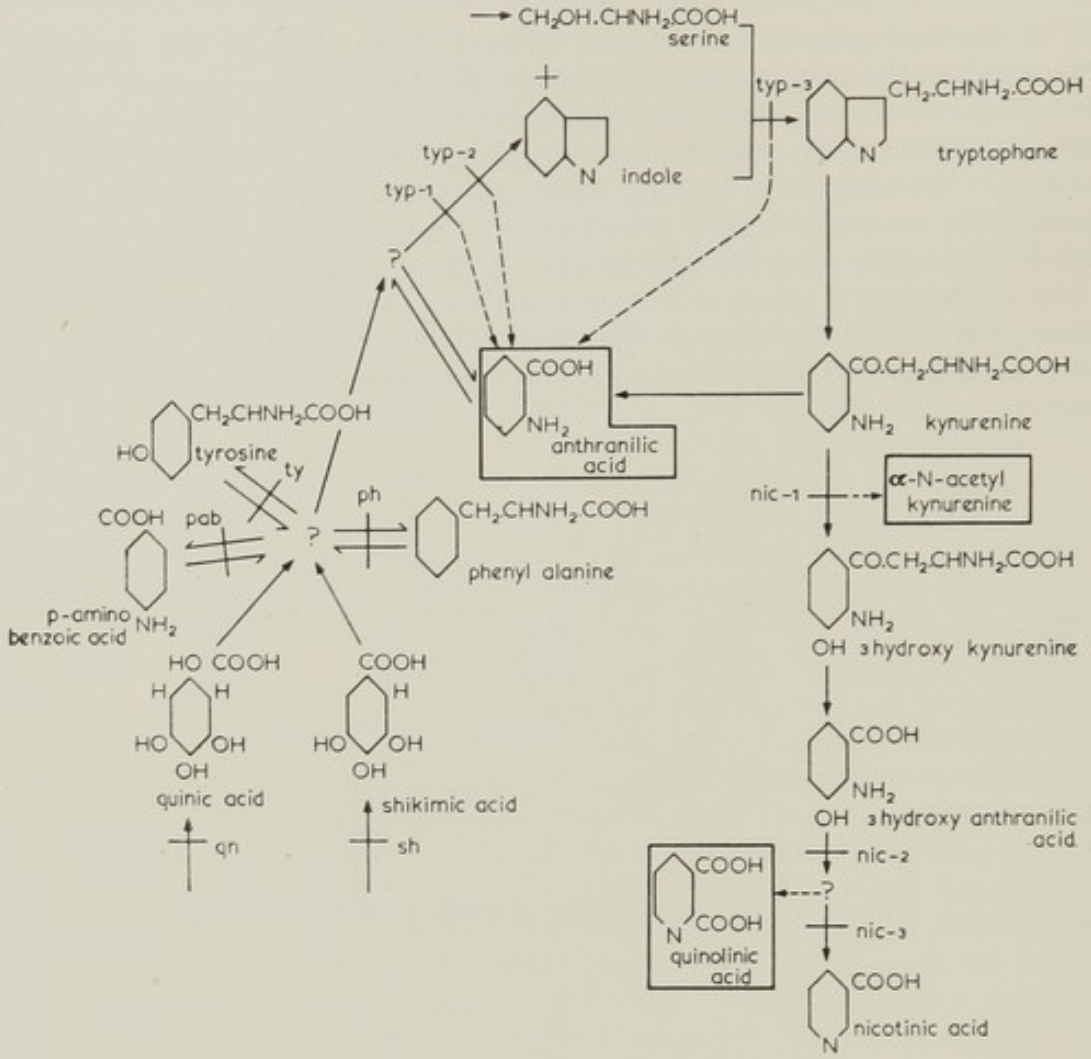

FIG. 45.—Tryptophane and nicotinic acid synthesis in *Neurospora crassa*.

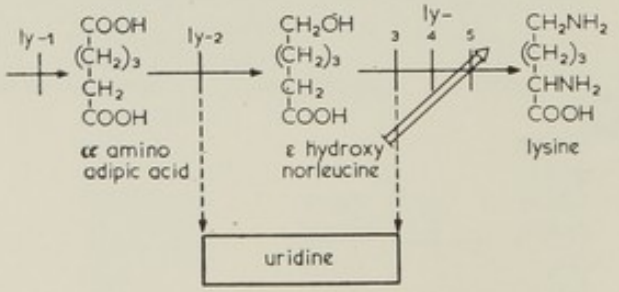

FIG. 46.—Lysine synthesis in *Neurospora crassa*.

In the first case analysed, that of arginine synthesis (Srb and Horowitz, 1944), the selection of substances for trial as possible precursors was aided by the prior knowledge of the ornithine cycle in animals and the presence of a similar cycle was demonstrated in the mould. Since then several other mutants affecting the biosynthesis of related substances have been found. Their growth responses to the various intermediates is summarized in Table II and the relations between the genes concerned and the stages in synthesis of arginine are shown diagrammatically in Fig. 43. More or less extensive schemata have been constructed for the syntheses involving methionine and threonine (Fig. 44), tryptophane and nicotinic acid (Fig. 45), lysine (Fig. 46) and several other natural compounds.

TABLE II

SUBSTANCE ADDED TO MINIMAL MEDIUM

Mutant	Arginine	Citrulline	Ornithine	Proline	α—Amino δ–hydroxy valeric acid	Glutamic acid	Ammonia
arg — 1	+	0	0	0	0	0	0
arg — 2, — 3	+	+	0	0	0	0	0
arg — 4, — 5, — 6, — 7.	+	+	+	0	0	0	0
arg — 8, — 9, — 10.	+	+	+	+	+	0	0
p	0	0	0	+	0	0	0
am	+	0 (or —)	+	±	?	+	0

LEVELS OF EFFECT IN GENE MUTATION

In a gene mutation there are several levels of effect. Primarily there is the alteration in the gene itself. Next there is the primary alteration in function, which brings about the alteration in character by which the altered gene is recognized. In many cases of biochemical deficiency mutation, as has been indicated above, there appears to be a loss or dysfunction of a single synthetic step. Now enzymes are directly concerned in intermediate metabolism and the connexion between gene and function has given rise to the one gene–one enzyme hypothesis, which supposes that enzymes are fairly immediate gene products and that each gene controls in some way the formation of one enzyme. Thirdly, there is the array of secondary effects on physiology and other biochemical functions of the organism consequent upon the primary functional derangement.

Alteration in the gene

As regards the alteration in the gene itself, little can be said except that in several cases, for example leucineless (Ryan), the evidence of back mutation shows that the functionally inactive gene is capable of reproducing itself, for, if it may back mutate, the mutant is not a mere loss. It may also be asked whether the inactive gene, besides retaining its property of self reproduction, is likewise still producing in the cell a primary product which is, however, physiologically

inactive. If it were, instances might be expected in which the inactivity was shown only under some conditions while under other conditions activity was shown. The wild type gene, selected as the normal one for the organism, would be one functional about equally over the whole range of conditions, external and internal, natural to the organism. Probable examples of partially inactive mutant alleles are the temperature-sensitive mutants which require growth factors, such as adenine or inositol, only in the upper region of the temperature range possible for the organism.

Primary alteration in function

The published facts on the enzymes of *Neurospora* mutants are rather meagre and not wholly satisfying. Wagner and Guirard in 1948 showed that intact mycelium of a mutant strain which required pantothenic acid for growth was unable to make pantothenate from pantoyl lactone and β-alanine, whereas the wild type could do so. Later Wagner showed that this mutant had an enzyme system for the *in vitro* synthesis of pantothenate from the precursors. This occurred in cell-free homogenates. Wagner's conclusion was that the data rule out the enzyme absence hypothesis for these mutants, assuming that it is this particular step in pantothenate synthesis that is impaired. This conclusion rests however on the assumption that an enzyme system active *in vitro* is also active *in vivo*. It is possible that disintegration of the cells removes some inhibitory influence and that the mutants in fact produce an altered pantothenic desmolase, characterized by *in vivo* inactivity. Mitchell and Lein in 1948 found that a mutant which required tryptophane for growth (*typ*–3, Fig. 45) could not condense indole and serine to produce tryptophane, and, further, that cell-free extracts also would not produce tryptophane from the two precursors. Later, Gordon and Mitchell found evidence which tended to show that the mutant did possess the enzyme tryptophane desmolase, but with the difference that the mutant's enzyme was sensitive to inhibition by various cellular components. The crude cell-free extracts were inactive but, after dialysis and fractionation with ammonium sulphate, the purified ones showed considerable tryptophane desmolase activity. Likewise, if the intact mycelium was thoroughly washed with distilled water considerable activity was demonstrable. However, no mutant enzyme preparation ever had more than half the activity of wild type extracts. The tryptophane desmolase activity of wild type extracts was not inhibited by dialysable or by non-dialysable components of mutant extracts, or by heat-inactivated mutant extracts. A number of compounds, among them ammonium sulphate and certain amino acids, were inhibitory for the inactivated mutant extracts at concentrations which are not significantly inhibitory for wild type preparations. However, there are unpublished reports that these interesting results, which appear to be exceedingly significant, cannot now be repeated.

An absence of glutamic dehydrogenase activity has been found by Fincham (in press) in a mutation unable to aminate α-keto glutaric acid (*am*-1, Fig. 43). Fox and Gray in 1950 reported an absence of tyrosinase activity from one strain and its presence in another, but there is no evidence about the inheritance of this difference. Lastly, it is worth mentioning that Shepherd has studied the succinic dehydrogenase of wild type *Neurospora* fairly completely and found that

some of its physico-chemical properties, notably the *p*H optima and the responses to various inhibitors, show characteristic differences from those of succinic dehydrogenase from other sources.

The status of the one gene–one enzyme hypothesis is that it is still a useful hypothesis and that it will remain so as long as it appears profitable to see to what extent gene substitutions are correlated with enzyme alterations.

Just as an inactive primary product, such as an enzyme, may possibly be activated completely or partially by isolation from the organized cell system, so the reversal may occur by mutation of other genes which thus appear to suppress the mutant character. The best known mutation of this kind is the suppressor of a pyrimidine requirement studied by Houlahan and Mitchell in 1947. The most interesting feature of this case is that the suppressor acts towards three different alleles, each with a characteristic physiology, two being temperature sensitive and the third producing an absolute requirement for pyrimidine at all temperatures. Besides such specific suppressors, there exists the possibility of non-specific suppressors, like some in *Drosophila*, which make two or more non-allelic mutants more or less normal.

Secondary effects on physiology and chemistry

The various biochemical mutants have an obvious utility in efforts to work out chains of synthesis, the process of which has been indicated above. It is more appropriate now to consider in general the kinds of alteration in the physiology and chemistry of an organism consequent upon a gene change in such a reaction chain. Consider a simple synthetic chain $A \xrightarrow{1} B \xrightarrow{2} C \xrightarrow{3} D \xrightarrow{4} E$. A block at reaction 3, in which C is normally converted to D, would result in an absolute or conditional requirement for a growth factor subsequent to the block. Presumably D or E or any compound readily convertible to them in the organism would satisfy the requirement. The requirement would be absolute if the block existed under all conditions suitable for growth of the normal wild type, conditional or partial if it existed only under certain conditions. The former is characteristic of most of the biochemical mutants so far studied, the latter is characteristic of the few which are temperature sensitive and perhaps also of the one or two *p*H sensitive mutants which have been reported.

As regards the relation of the growth response of the mutant to the concentration of the added growth factor, several different patterns are found. Various possible types that might be expected are illustrated in Fig. 47. The response of a lysineless mutant (*ly*–3, Fig. 46) to lysine is, according to Doermann's data of 1944 like the A (or possibly the B) pattern. There is an appreciable response to a small amount of lysine, the magnitude of the response being about linearly related to the concentration of lysine until other factors begin to be limiting, when the curve falls off and becomes steady at about the growth rate of the wild type. The responses of mutants, which require leucine or para-aminobenzoic acid respectively, are similar.

A different type of growth response, namely C, appears to be shown by mutants requiring histidine. Small concentrations of histidine produce little or no growth. Germination of conidia starts, growth is at first rapid and then abruptly ceases. Above a threshold value growth continues, though often at a diminishing rate, to the exhaustion of the medium and above a somewhat greater

concentration no further increase in initial or average growth rate occurs. The maximum growth rate on the highest concentrations of histidine is never more than 60 per cent of that of wild type strains under the same conditions. It appears that the growth responses of certain tryptophaneless mutants and of pink adenineless mutants show a similar pattern with the maximal rate of growth of the mutant under optimal conditions less than that of the wild type similarly treated. The possible explanation of these poor growth responses will be pointed out later.

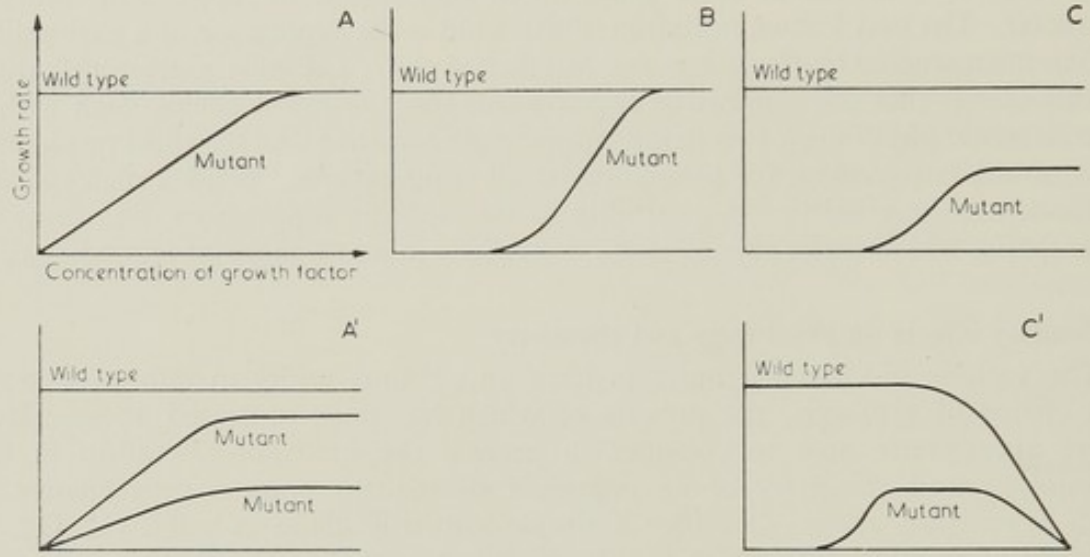

FIG. 47.—Patterns of growth responses of *Neurospora* chemical mutants.

If in the chain A $\xrightarrow{1}$ B $\xrightarrow{2}$ C $\xrightarrow{3}$ D $\xrightarrow{4}$ E, the reaction 3 were blocked, so that compounds D and E will not be formed by the mutant if it is grown with a supply of the growth factor it requires, it might well nevertheless form substances A, B and C. The further conversion of C being blocked, conditions might favour the accumulation of these precursors or some of them to levels above those in the normal wild type. The relative proportions of the precursors are likely to depend on the equilibria of reactions 2, 1 and other antecedent ones. These conditions need investigation. Accumulated precursors may then be found in the mycelium or in the medium as a result of excretion. The first case actually found, by Tatum, Bonner and Beadle in 1944, was of anthranilic acid secretion by a mutant requiring tryptophane (*typ*–1) for growth.

In a given synthetic chain, blocks in two different places may result in the accumulation of the same substance in relatively large amount. For example, among the mutants requiring tryptophane for growth there is a second one (*typ*–2) which also accumulates considerable amounts of anthranilic acid. Thus predominant accumulation is not necessarily of the precursor immediately antecedent to the block in synthesis.

Occasionally it is possible to recognize the accumulation, by one mutant, of two different precursor substances or derivatives of them. For example, in the synthesis of nicotinic acid, which comes from tryptophane through kynurenine, the mutant *nic*–3 accumulates α N–acetyl kynurenine while *nic*–2 accumulates a

considerable amount of 3–hydroxy anthranilic acid and a smaller amount of α N–acetyl kynurenine.

Two different nutritional substances (such as E and N) may have a common precursor (A), as in the branched synthetic chain

$$\begin{array}{l} \overset{1}{\nearrow} B \overset{2}{\rightarrow} C \overset{3}{\rightarrow} D \overset{4}{\rightarrow} E \\ \rightarrow A \\ \underset{11}{\searrow} L \underset{12}{\rightarrow} M \underset{13}{\rightarrow} N. \end{array}$$

Under normal conditions in a non-mutant organism, reactions 1 and 11 would compete for the common substrate, and presumably this competition would be nicely balanced so that suitable proportions of E and N were synthesized.

In a mutant with a block at position 1, or even 2 or 3, the reaction 11 might have an increased amount of available A substrate and as a result N could be formed in excess. In the synthesis of methionine, there are three genetically different mutants (*me*–3, Fig. 44) in which the formation of cystathionine by condensation of homoserine and cysteine is blocked. Each of these mutants, grown with methionine, accumulates a substance of unknown composition which is an intermediate between homoserine and cystathionine. One of them also accumulates excess threonine and perhaps the other two do so also.

In several cases it appears that a precursor, which tends to be accumulated, gives rise to a shunt product that is not a normal intermediate in synthesis, and that this shunt product is accumulated instead of the precursor. Such shunt products have very low activities in supporting the growth of mutants having blocks at positions still earlier in the chain of synthesis. Examples of coloured compounds are the pink pigment in one adenineless mutant and the brown pigment, which appears to be formed from 3 hydroxy anthranilic acid, in nicotineless–3. The α N–acetyl kynurenine of *nic*–3 has an activity about one-tenth that of kynurenine, while the quinolinic acid accumulated by *nic*–1 has a very low activity for *nic*–2 and other nicotinicless mutants (Fig. 45). The amounts of precursors, or of their shunt products, which accumulate are sometimes extraordinarily high (Table III) and may greatly exceed the amounts of the respective growth factors required by the mutants for maximal growth.

TABLE III

Growth factor requirement	γ/ml for maximal growth	γ/ml supplied	γ/ml of precursor accumulated
Pyrimidine – – –	20	17	up to 1300 orotic acid
Choline – – – –	0·2	0·125	3 monomethylamino ethanol
Methionine (*me* — 2) –	50	25	6 cystathionine

Physiological effects may be expected from the accumulation of precursors which are generally not present in appreciable quantities in non-mutant organisms. One readily detectable feature which has already been mentioned is the presence in some cases of coloured compounds. Secondly, a precursor may inhibit the utilization of the growth factor into which it is normally converted. Thus ε–hydroxynorleucine, which is a precursor of lysine (Fig. 46), is inhibitory towards mutants blocked at later stages in lysine synthesis (Good, Heilbronner and

Mitchell; there is no evidence that ε–hydroxynorleucine is accumulated by any of them. This cause appears to underly the limitation of the maximal growth rates of histidineless mutants to a value below that of the wild type. The relative rates of growth in this case are: wild type 100, two histidineless mutants 64 and their heterocaryon 80. Why the heterocaryon also has a lower growth rate than the wild type is unknown.

The same factor appears to be the cause of the poor growth of tryptophaneless mutants on any concentration of tryptophane (Fig. 47C). Indeed, both anthranilic acid and tryptophane inhibit the growth of wild type, its growth rate being depressed to about half by similar concentrations of the two substances, about 70 γ per millilitre in the case of anthranilic acid and about 100 γ per millilitre in the case of tryptophane. The inhibitory effect of tryptophane may be accounted for by the tryptophane cycle (Fig. 45), demonstrated in *Neurospora* by Haskins and Mitchell (1949). A substantial part of the tryptophane disappears from the culture medium within a few hours of a conidial inoculation of a mutation blocked in tryptophane synthesis, prior to appreciable germination and growth, and considerable amounts of anthranilic acid may be isolated from the medium, as well as small amounts of nicotinic acid. The inhibitory effects of anthranilic acid and of tryptophane towards the wild type are additive.

These inhibitory effects mean that any spontaneous genetic or cytoplasmic changes which tended to overcome the inhibition would be selected. Some possible genetic changes are back mutation, suppressor mutation and further mutation at an earlier synthetic step which would cut out the accumulation of the substance that caused the inhibition. The last was reported in a pink adenineless mutation by Mitchell and Mitchell in 1950. Very little is known about the precursors of adenine, but a considerable number of genetically and physiologically different blocks are known, one of which results in the pink pigment as a shunt product. Mutations at a prior block in the pink adenineless result in a white adenineless strain, a double mutant, which grows faster than the pink adenineless strain, though not so fast as the wild type on the same medium.

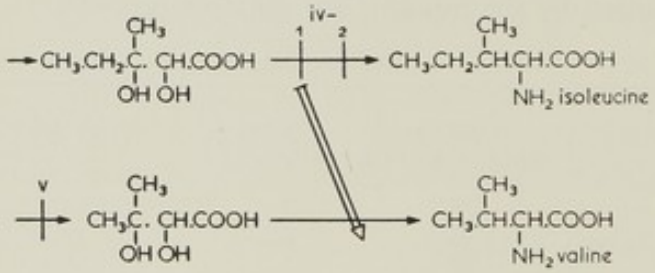

FIG. 48.—Isoleucine and valine mutants in *Neurospora crassa*.

It is also possible that the accumulated precursor may inhibit other normal reactions, in related or unrelated synthetic chains, and so cause an accumulation of a precursor in the different synthetic chain and incidentally result in a double growth factor requirement. A possible case is the mutant (*iv*–1, Fig. 48) which requires a balanced proportion of isoleucine and valine. The two amino acids are similar in structure respectively α-amino β ethyl butyric acid and α-amino β methyl

butyric acid. The mutant accumulates both of the corresponding α, β dihydroxy-analogues in the medium, according to Adelberg and Tatum in 1950.

Finally, it is possible that an accumulated precursor might stimulate an unrelated reaction, though it is not possible to point to a likely example.

Inhibition by growth factors

Attention should also be drawn to the inhibitions of the utilization of growth factors by other normal growth factors. The result of these is often that a mutant will not grow or else grows very poorly in the presence of a mixed supplement, such as malt or yeast extract or casein hydrolysate. For example, a mutant that requires lysine (*ly*–3, Fig. 46) is inhibited by arginine, equimolar proportions reducing the growth rate to half, while a molar concentration of arginine twice that of lysine gives zero growth rate. The lysineless mutant, which will grow if supplied with α aminoadipic acid, is inhibited by arginine if grown on lysine and by asparagine if grown on α aminoadipic acid. Similarly, an argininelessmutant (*arg*–1, Fig. 43) is inhibited by an excess of lysine. The mutant which will grow with homoserine will also grow on a suitably balanced mixture of threonine and methionine, the molar ratio 1 to 0·8 giving optimal growth; on excess methionine growth is depressed and ceases at a molar ratio of 1 threonine to 2 methionine.

In some kinds of mutants it appears that a normal reaction is caused to take place at a higher rate, the increased amount of product proving to be inhibitory towards the organism. The mutant which requires sulphonamide for growth at temperatures above about 33° C. (Emerson, 1950) appears to be of this nature. It appears to have an enhancement of a reaction in which methionine appears to be the substrate. The reaction has a high temperature coefficient and the unknown product is inhibitory. The reaction requires *para*-aminobenzoic acid, the use of which can be antagonized by sulphonamide at concentrations insufficient to disturb the participation of *p*-aminobenzoic acid in other essential reactions. The reaction, or the effects of its product, can also be antagonized by means of threonine.

THE GENE: STRUCTURE IN RELATION TO ACTION

The gene is confined within the nucleus which in general constitutes the minor portion of the bulk of the cell. One possibility to consider is that the reactions might take place upon the surface of the gene itself within the nucleus, but there is evidence that many of the important enzyme systems are located in the cytoplasm. A major outstanding problem is then how the genes influence the enzymes they control, and also to what extent the enzymes are capable of reproducing themselves without the direct intervention of the genes. If any reactions do take place upon the genes themselves it is possible that they might have to be arranged together in proximity upon a chromosome. Likewise, if a given reaction or series of reactions; involving highly unstable intermediates, required a special organization of the enzyme system in the cytoplasm, this organization might be reflected in the arrangement of the genes in the chromosomes. Information upon these subjects is still fragmentary, but nevertheless is highly interesting and significant.

The genes controlling different steps in the same reaction chain are usually scattered indiscriminately amongst the various chromosomes. No general order

is apparent and mimic genes are rarely at all closely linked. A few exceptions have been noted in *Neurospora*, namely a fairly close linkage of two genes concerned in pigment synthesis, and a fairly close linkage within one chromosome arm of three genes concerned in pyrimidine synthesis.

When single reaction steps are considered, it is found in several cases that mutation of each of two or three different genes may result in the same apparent defect. Thus, in the methylation of homocysteine to form methionine (Fig. 44, *me*–1), probably three different genes are concerned. Such reactions are necessarily complex in that, as Emerson (1950) has pointed out, the enzyme or enzyme system concerned must not only have an affinity for the substrate and product but also for a methyl donor, presumably choline in this case, and for a co-enzyme as an energy donor. The condensation of cysteine with homoserine to form cystathionine (Fig. 44) likewise requires the co-operation of the products of three unlinked genes (*me*–3). Whether we should regard these instances as indicative of several genes being concerned in the final specificity of one enzyme is an open question. However, in all these cases, heterocaryons formed between two mutants grow perfectly well on minimal medium without any supplement. Thus, the two normal genes in separate nuclei can co-operate in producing a completely active enzyme system in the cytoplasm.

A different situation is evident in the cases of the three biotinless mutants, described by Roper (1950) in *Aspergillus nidulans*, and the three nicotinicless mutants (*nic*–3) in *Neurospora*, described by Bonner in 1950. Here the three mimic genes are extremely closely linked, so closely as to be pseudoalleles separable only in large genetic experiments; moreover, heterocaryons still require the specific growth substance. These are instances where the reaction requires the organization of the catalysts close together in an assembly line, perhaps because the intermediates are unstable or because the reaction rate is extremely small. If the reaction takes place upon the chromosome the juxtaposition of the genes is readily understood. If it takes place upon an enzyme system in the cytoplasm, the linkage of the genes implies that the system is made as a whole by the group of genes. Any fault in one of them inactivates the whole system, such that it cannot be complemented physiologically by another deficient system with a different fault. We are led to infer that organization or lack of organization amongst the genes reflects the state of organization in the metabolically active cytoplasm.

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CHAPTER 10

III.—Comparative Pathology

Arnold Sorsby

Clinical genetics, for all the wealth of information it has produced, labours under the disadvantage that in dealing with a patient, alleviation of his ailment is the primary consideration. There is, therefore, no possibility of any experimental observations other than of the simplest and definitely innocuous kind. There is little opportunity of studying the progressive stages of an affection histologically or biochemically, there is hardly any opportunity at all of studying a genetic affection before it has become manifest, and study of relatives is frequently difficult. In consequence clinical genetics is largely descriptive, and it has become obvious that unless experimental methods are developed, further advance will be severely restricted.

The counterpart of the experimental animal that the general pathologist uses for his studies is readily available to the clinical geneticist in animals that show genetic disease. Genetically determined affections are frequent in the common laboratory animals, and in pedigree stock of domestic animals owing to the heavy inbreeding and selection to which they have been subjected. However, though there is much information, little of it is systematized, and less still fully studied.

VARIETIES OF GENETIC DISEASE

Lethal and sub-lethal manifestations

With the development of antenatal services and infant welfare schemes infantile mortality has shown a great decline during the present century in all civilized countries, falling from a rate of 128 per 1,000 in 1901–10 to 32 per 1,000 in 1949 in England and Wales, figures which find their parallel elsewhere. There has, however, been no substantial decline in the mortality of infants during the first 24 hours of life. The present-day methods of care of the markedly premature infant enable many such infants to survive but sometimes at the cost of growing-up as defectives. The problem of habitual miscarriage has remained largely unresolved, and though recent work has shown that maternal infections, such as rubella and toxoplasmosis, may cause congenital abnormalities, it has also become established that incompatibility of the genetically determined Rh blood groups in the parents may likewise be a cause of severe defects, or of death of the infant. That habitual miscarriage and congenital anomalies may in fact be determined to a considerable extent by genetic factors with lethal or sub-lethal manifestations is suggested by well established observations in animals.

The classical incidence of a genetically determined lethal factor is derived from the work of Cuénot in 1905 and his successors, who established that the homozygous yellow mouse became absorbed during the blastula stage, and that only heterozygous yellow, or completely non-yellow, are viable. Since then many

other lethal and sub-lethal effects have been recorded. In mice " white spotting " is due to a dominant gene with homozygous lethal effect. The affected animals all die in the course of a few days owing to severe congenital anaemia.

Likewise there is a dominant gene which produces shortening of the tail in the heterozygous mouse, but is lethal in embryonic life in the homozygous state. This gene has also a recessive allelomorph which in the simplex state has no obvious effect, but is lethal at an even earlier embryonic stage in the homozygous state. Another dominant gene also produces a short tail in the heterozygous state, whereas the homozygous are born alive but die within 24 hours; they are tailless, show spina bifida and no anal opening or genital papilla, and the kidneys are rudimentary or absent. The grey lethal mouse is also born alive, but yellow pigment formation is suppressed, extensive skeletal abnormalities develop owing to the absence of secondary absorption processes, growth is retarded, and the mouse dies before the end of the first month. In the rabbit, recessive sub-lethal genes determine congenital hairlessness and a fatal shaking paralysis. A similar palsy has been observed in guinea-pigs, whilst a congenital palsy and a congenital lack of balance causes early death in chickens.

(*a*) (*b*)

FIG. 49.—A rare sub-lethal affection in the dog and its counterpart in man. (*a*) A dachshund homozygous for dappling. It is dirty white in colour, microphthalmic, "wall eyed", and deaf. The eyes are set obliquely. (*b*) A patient with the syndrome of white forelock, heterochromia iridum with or without microphthalmis, deaf-mutism, lateral displacement of medial canthi, and prominent root of the nose—a dominant affection. ((*b*) *After Waardenburg, P. J. (1951). Amer. J. hum. Genet.*, 3, 195). (*See also* Fig. 67.)

A skeletal anomaly similar to human achondroplasia is lethal in the chick in the homozygous state; when they survive to the stage of organ formation these homozygous embryos lack hind limbs and eyelids, and show gross eye abnormalities such as microphthalmos. The findings in the Dachshund are illustrative of the range of reaction of these lethal and sub-lethal genes (Fig. 49). The Dachhund is normally black or tan in colour. " Dappled " Dachshunds show such physiological variations as unusual colouring, discoloration of the iris (" wall eye "), and total or subtotal lack of the tapetum, but they do not breed true : their homozygous offspring show a markedly abnormal coat together with

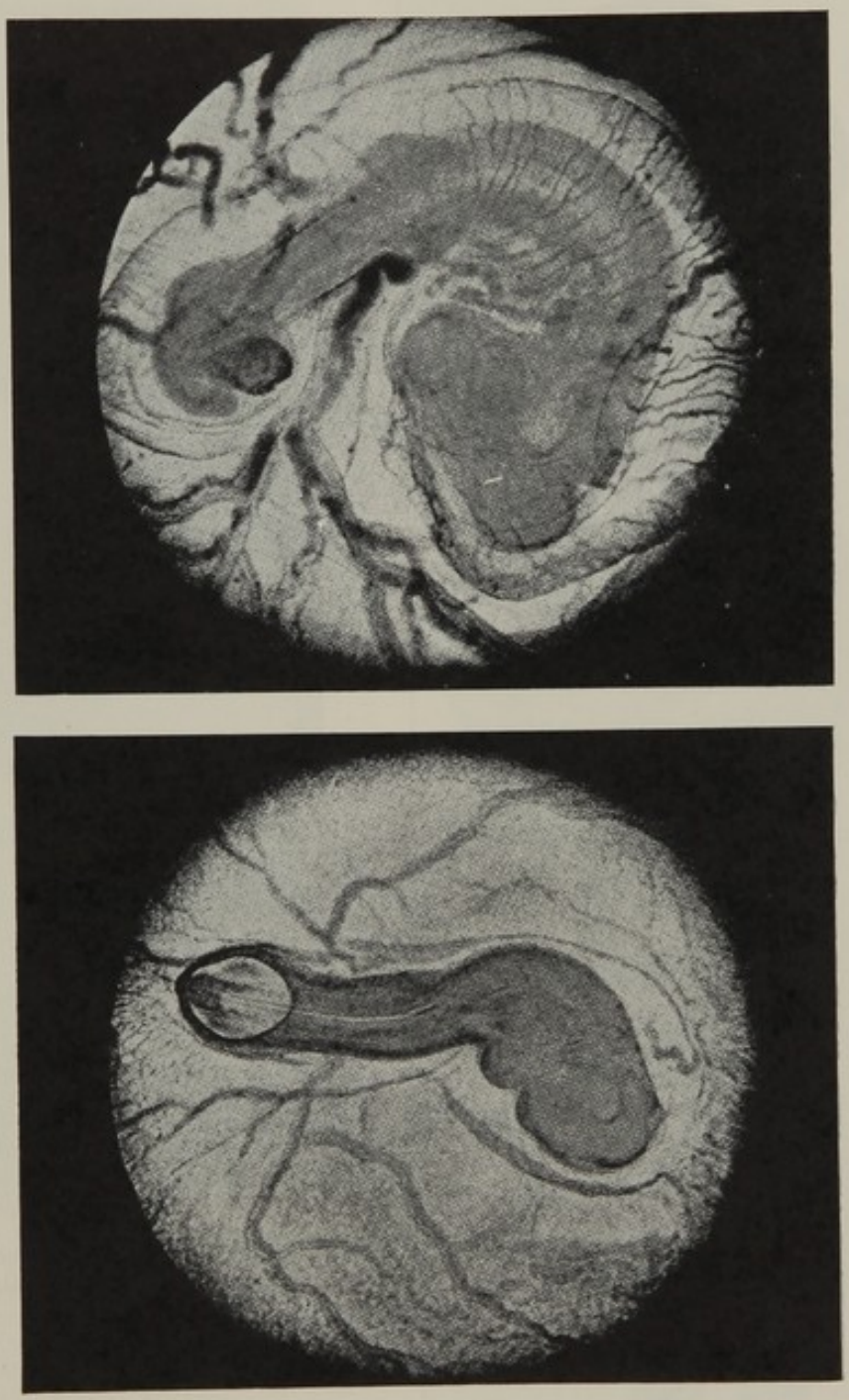
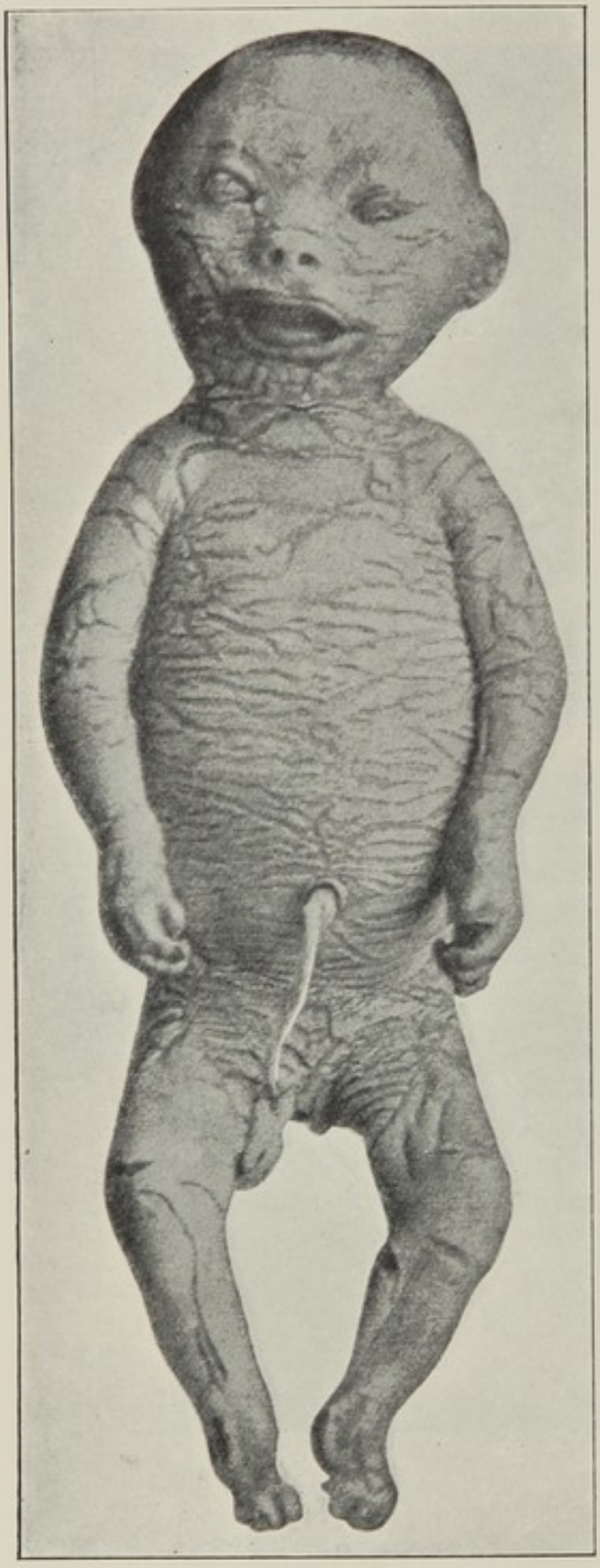


FIG. 50.—Lethal effect in the chick induced by the " creeper " gene in the homozygous state. Above, normal (heterozygous) embryo from creeper parents, 72 hours of incubation. Below, homozygous creeper embryo, 72 hours of incubation. (*After Landauer, W. (1932). J. Genet.*, **25**, 367.)



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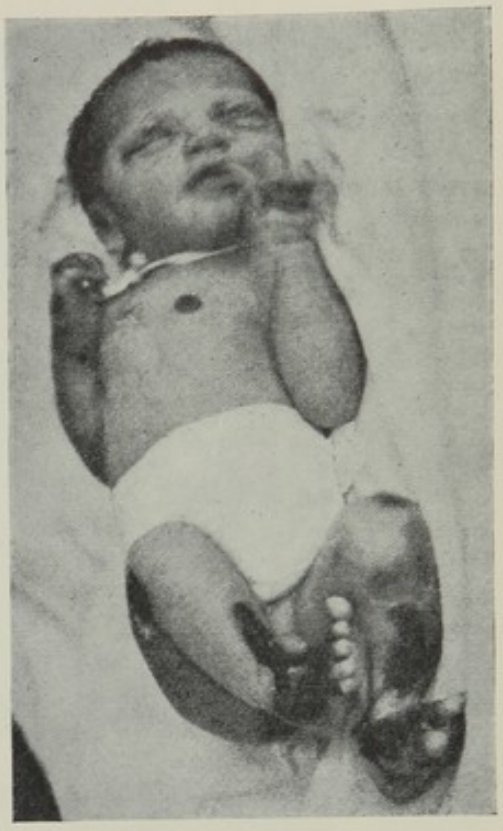
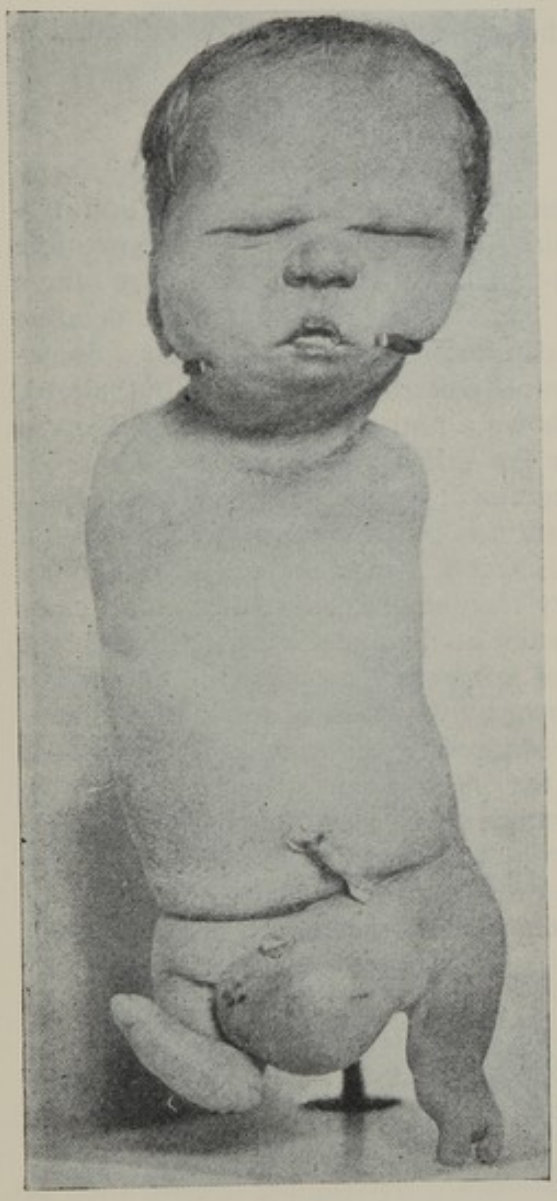


(*b*)

FIG. 51.—Recessive lethal and sub-lethal-genes in man. (*a*) Congenital ichthyosis (*After von Reuss, A. K. (1921). Diseases of the Newborn. London; Bale.*) (*b*) Congenital epidermolysis bullosa. Congenital skin defect present at birth in a child who survived for 8 days. The affection is recessive and sub-lethal. (*After Heinrichsbauer, F. (1928). Arch. f. Gynack.*, **134**, 673.)



(*a*)

(*b*)

FIG. 52.—A rare recessive affection in man and its counterpart in cattle. (*a*) " Amputated " abortion in man. The parents were first cousins. (*b*) " Amputated " calf due to hereditary skeletal abnormalities affecting skull and skeleton of legs. (*After Mohr, O. L. (1939). In IV Cong. Intern. di Patol. Comp. Rome*, **1**, 247.)

deafness and microphthalmia, and possibly other defects. Breeders maintain the dappled strain by mating dapple to full-coat ; they thus obtain both dapples and self coloured without any loss from homozygotes.

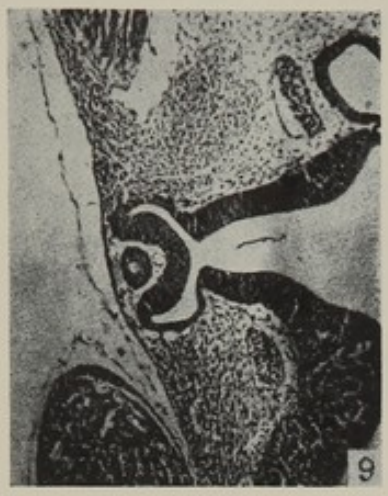
The bearing of these and such like studies on clinical genetics is indicated in Figs. 50, 51 and 52.

Congenital defects

The line of demarcation between congenital defects and the manifestation of a sub-lethal gene is tenuous. Some congenital abnormalities are not compatible with life ; others produce severe but non-lethal disturbances, whilst yet others have minor effects. Animal observations have made possible a more detailed understanding of the nature of genetically determined congenital defects. Sometimes the disturbance shows a relatively simple pattern. Thus in anophthalmos, embryological studies in the mouse have shown a normally developing eye up to the ninth day of gestation. At this stage the primary optic vesicle undergoes abnormal differentiation, and different degrees of anophthalmos arise in consequence (Fig. 53). A more complex situation is presented by multiple defects. As opposed to the concept of the pleiotropic effect of a gene, there is the possibility that the multiple defects may be secondary to a single disturbance at an early stage of development. Where the defects assume no definite pattern in the different animals affected, but show a wide range of apparently unconnected anomalies, their secondary nature has been clearly shown by the classical work of Bonnevie (*see* pages 16–18). Here the defects were produced by the irregularly distributed myelencephalic blebs, themselves caused by the one single disturbance of excessive oozing of cerebrospinal fluid through the foramen anterius. Apparent pleiotropism is also present in the lethal effects due to cartilage abnormality in the rat described by Grüneberg (Figs. 54 *a–d*). To what extent more defined syndromes are secondary effects, or true expressions of pleiotropism, remains to be established.

Abiotrophic defects

Ophthalmology, neurology, and dermatology are particularly rich in examples of abiotrophic disease. Studies on abiotrophic retinal lesions in the mouse, rat, and the dog appear to confirm the clinical postulate that the tissue has, in fact, developed normally until the onset of the genetically determined degeneration in postnatal life. In these animals there is considerable postnatal development of the retina. At birth the tissue is still undifferentiated, and differentiation into distinct layers occurs in the mouse on the eleventh day, in the rat on the twenty-first day after birth, and in the dog later still. Degeneration of the retina develops only after differentiation has taken place. The assumption that this degeneration occurs in fully differentiated retina does not, however, appear to be valid, for, in the mouse at any rate, degeneration sets in before full development of the retina—as distinct from differentiation—has taken place. Whilst the different layers of the retina are differentiated by the eleventh day, postnatal development in the rods continues until 28 days after birth, by which time the apparently abiotrophic process has already run a destructive course in the affected animal.



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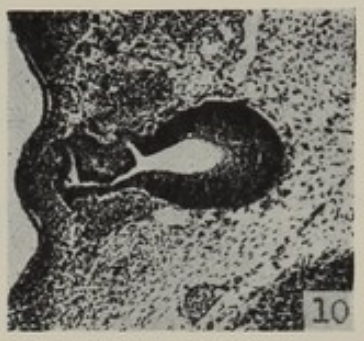

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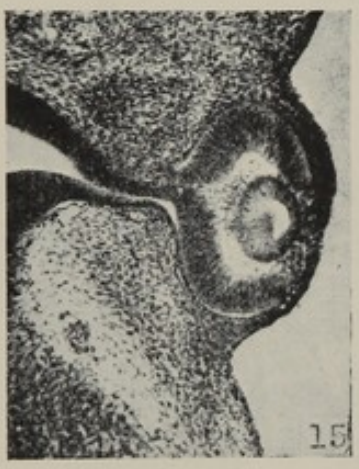

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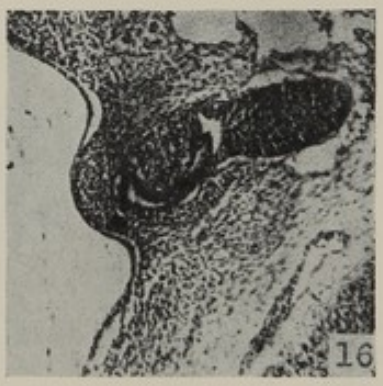

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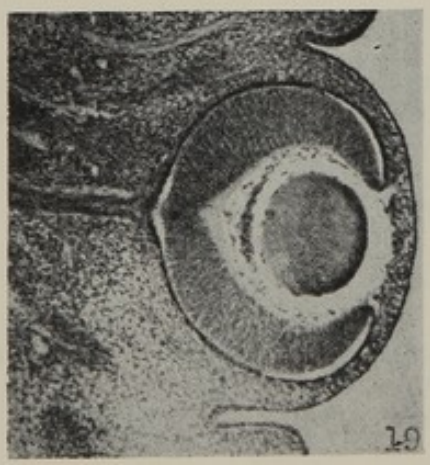


(*e*)

(*f*)

FIG. 53.—Congenital defect: hereditary anophthalmos in the mouse from disturbance in development (× 60). *After Chase, H. B.*, and *Chase, E. B. (1941). J. Morph.*, **68**, 279.)

Control:	At:	Anophthalmic strain:
(*a*) Left eye	10 days 23 hours	(*b*) Left eye
(*c*) Right eye	11 days 20 hours	(*d*) Left eye
(*e*) Right eye	13 days 2 hours	(*f*) Right eye

"PEDIGREE" OF CAUSES OF LETHAL CARTILAGE ANOMALY IN THE RAT

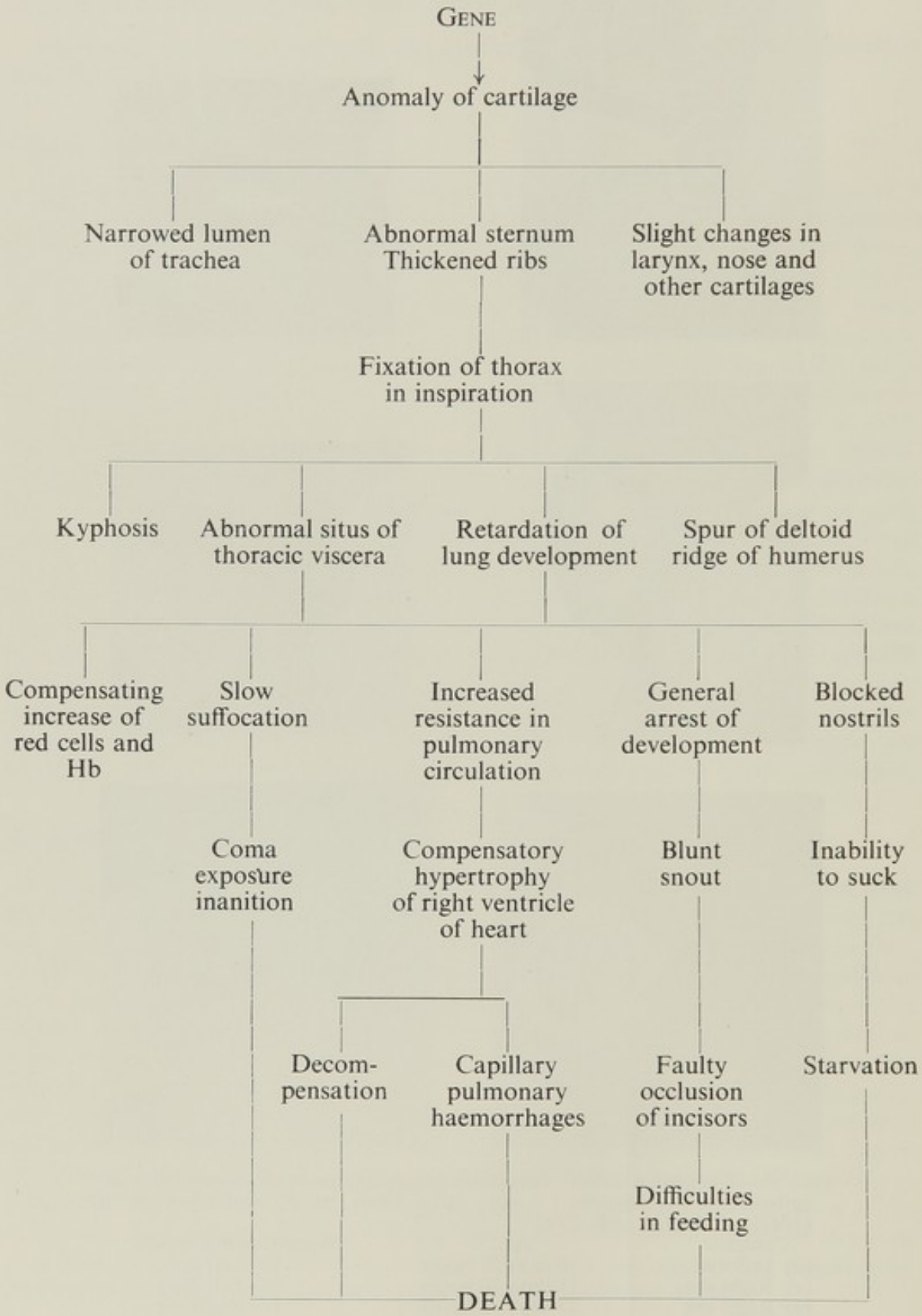


FIG. 54.—Congenital defect with "pleiotropic" lethal effects. ((*a*) and (*d*) *After Grüneberg, H. (1938). Proc. roy. Soc. B.*, **125**, 123.) (*a*) Pedigree.

FIG. 54 (cont.)—(*b*) Sections through the lungs of normal (*a*, *b*, *c*) and abnormal (*a'*, *b'*, *c'*) rats at the age of 2 days (above) at the age of 7 days (middle) and at the age of 12 days (bottom). ((*c*) *After St. Engel*, and *Grüneberg, H.* (*1940*). *J. Genet.*, **39**, 343.)

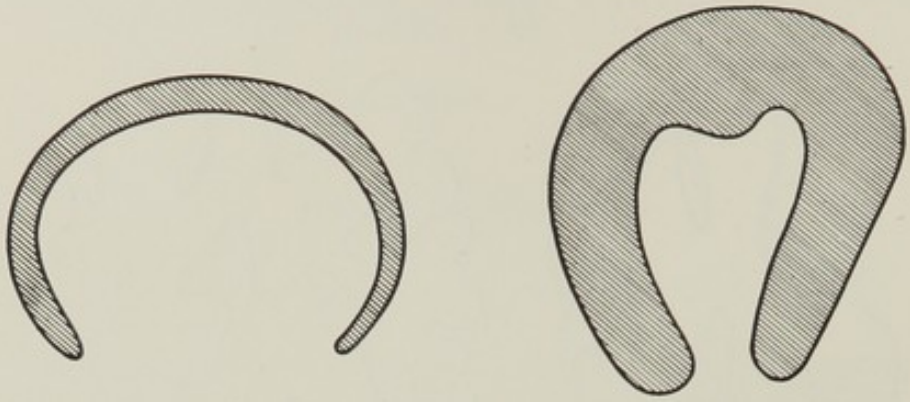


FIG. 54 (cont.)—(*c*) Cross sections through the trachea of a normal rat and a lethal litter-mate, 14 days old. (*After Grüneberg, H. (1947). Animal Genetics and Medicine. London; Hamish Hamilton.*)

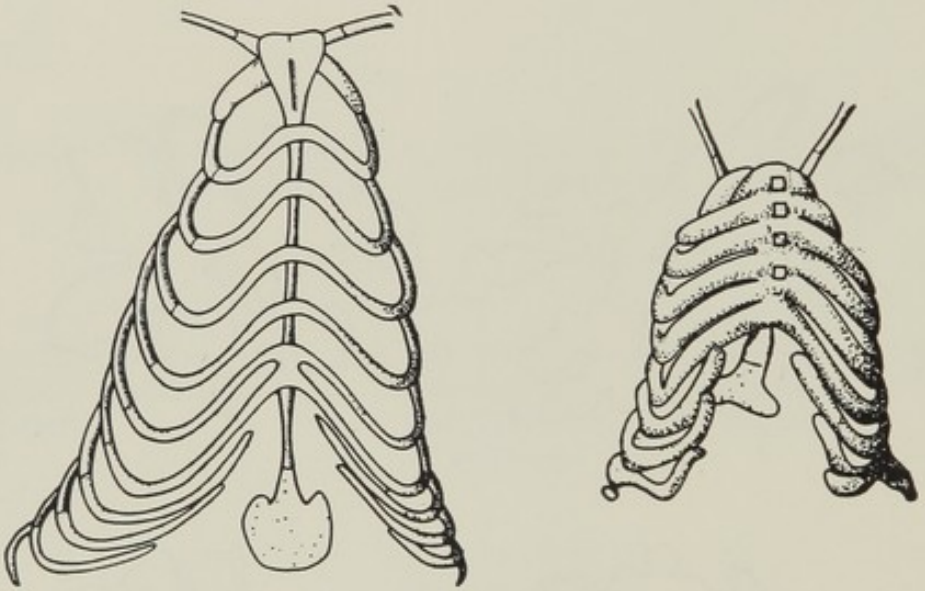


FIG. 54 (cont.)—(*d*) Thoracic basket of a normal rat and a lethal, 22 days old (litter mates).

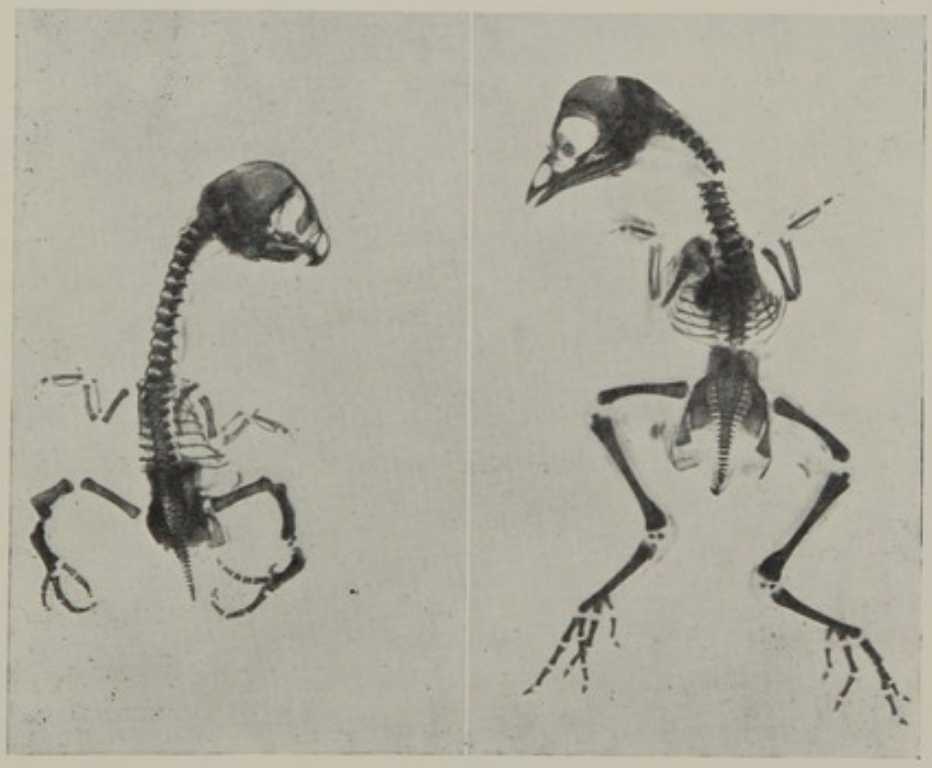
Studies of retinal dystrophy in the Irish setter (Plate II) suggest that the same ophthalmoscopic and histological picture may be conditioned by two sets of recessive genes, thus confirming the clinical assumption that retinitis pigmentosa is a congeries of affections rather than one definite clinical entity.

SOME ANIMAL COUNTERPARTS OF HUMAN DISEASE

A few animal affections closely simulating genetic conditions in man have been studied in some detail. Outstanding amongst these are the following.

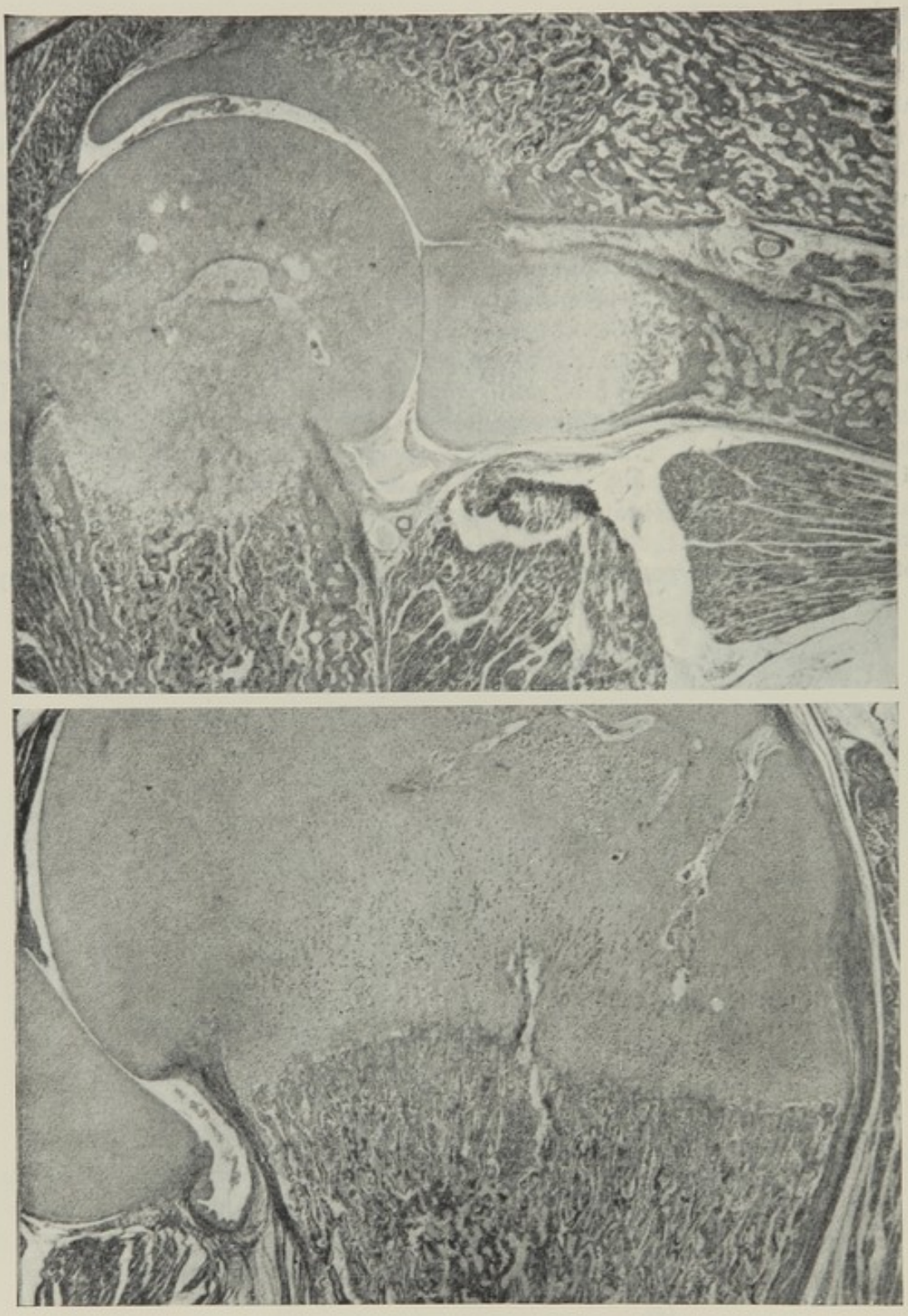
Achondroplasia (chondrodystrophy)

This is widely spread and has been observed in Dexter cattle, in the fowl, rabbit, and in incomplete forms in the dog. In the rabbit the affection is recessive and is lethal in the homozygous state. The trunk is only slightly affected, but the limbs and tail are greatly reduced. The head is broad and rather square ; the base of the nose is depressed and cleft palate is not uncommon. The abdominal muscles are weak, and the skin is stretched tautly over the protuberant abdomen, in striking contrast to the folds it shows on the short neck and legs. Haemorrhagic exudates are present in the abdomen, and the liver is enlarged and congested. The cartilage in the skeleton is abnormal throughout, the changes being similar to those observed in human achondroplasia (Fig. 56). The primary disturbance is yet unknown ; findings in the rabbit suggest that the endocrine system may be at fault. In the Dexter breed of cattle somewhat similar changes are observed, whilst in the fowl the affection has been observed in several breeds : the *courtes pattes* of France, the Scots Dumpies, the Japanese bantams and the Creepers of the United States. As in the rabbit, and in cattle, the affection is recessive and lethal in the homozygous state. Occasionally the homozygote chick survives for a time (Fig. 55), whilst the lethal effect is observed in some 5 per cent of heterozygotes. The heterozygotes are more readily susceptible to rickets induced by



(*a*) (*b*)

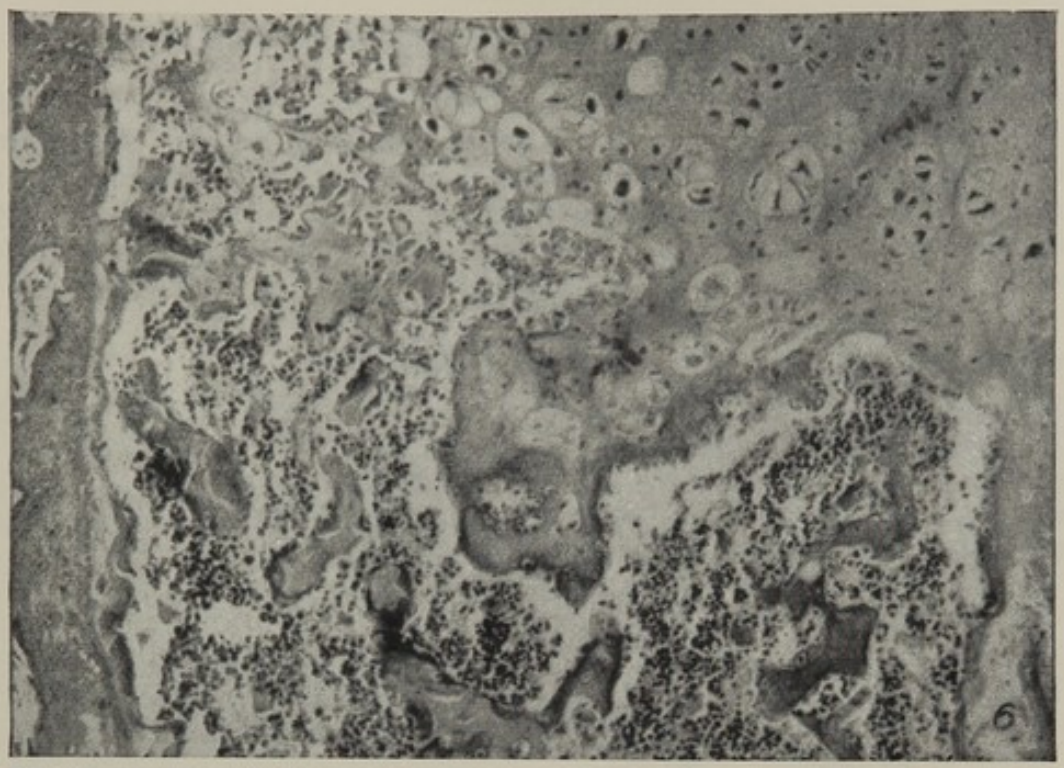
FIG. 55.—Achondroplasia in the chick. (*a*) An extremely chondrodystrophic embryo after 21 days of incubation. Note particularly the short curved beak and the extremely shortened and bent tibiae and tarso-metatarsi. (*b*) A normal embryo the same age. (*After Lamoreux, W. F. (1942). J. Hered.*, **33**, 275.)



(*a*)

(*b*)

FIG. 56.—Achondroplasia in the rabbit. (*a*) Photograph of sagittal section through the elbow of an achondroplastic dwarf. Note the small size of the bone, the much less advanced differentiation of the epiphyseal cartilage, the narrow markedly abnormal zone of ossification and the small narrow cavity. The zone has a curved or " cupped " shape (× 22·8). (*b*) Photograph of a sagittal section of the distal end of the right humerus of the normal litter mate (× 22·8).



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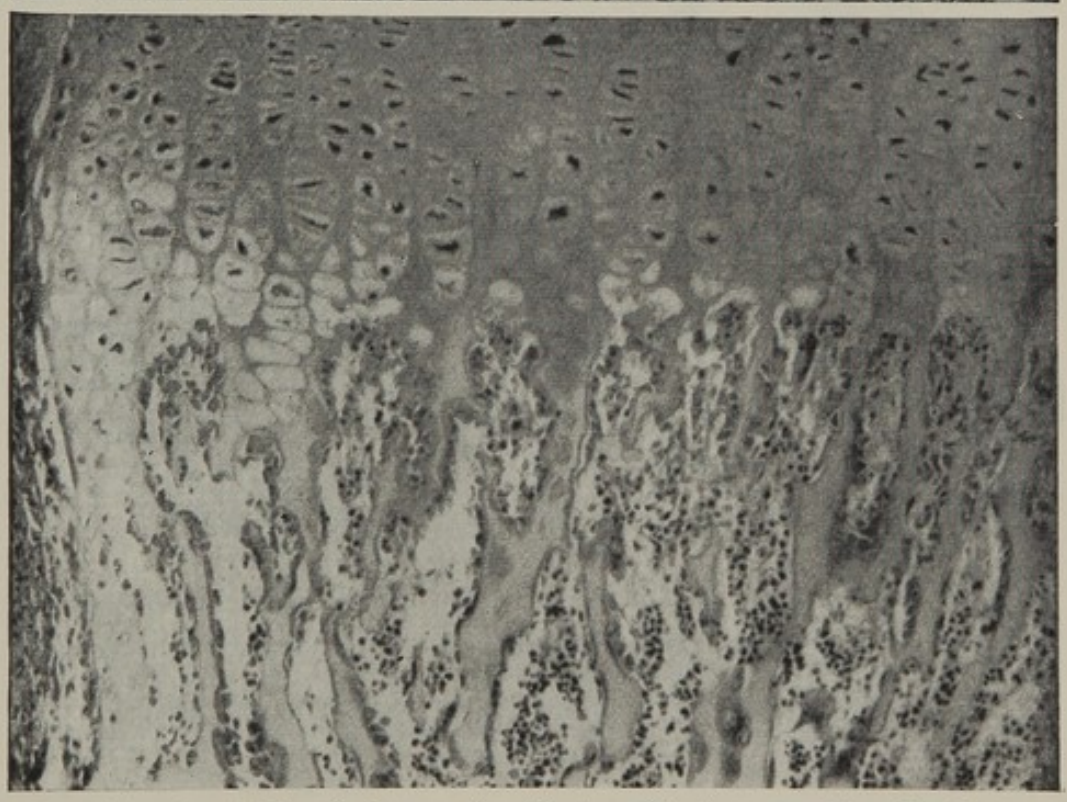


(*d*)

FIG. 56 (cont.).—(*c*) The distal zone of ossification of the humerus of an achondroplastic dwarf. The cartilage cells of the epiphysis are crowded and grouped in a bizarre fashion with little or no regular row arrangements. Short irregular projections and tags of cartilage take the place of the orderly columns of disintegrating cartilage cells and osteogenic tissue characteristic of the normal zone. The direction or position of the line of ossification is slanting, not straight, as in the normal (x 127). Higher magnification of the section of the humerus of the achondroplastic dwarf shown in Fig. 56*a* and of the normal litter mate in Fig. 56*b*. (*d*) The distal zone of ossification of the humerus of a newborn normal rabbit (× 127). (*After Pearce, L. and Brown, W. H. (1945). J. exp. Med.*, **82**, 261.)

vitamin D deficiency than the normal ; they are apparently also more susceptible to toxic substances. In the dog, achondroplasia tends to be more limited and does not apparently carry any pathological consequences. It is rather marked in Pekingese, whilst the Dachshund, Basset, Scottish terrier, Sealyham terrier, Skye terrier, the Boston terrier and the English and French bulldogs, are all examples of partial achondroplasia compatible with normal health.

Hare-lip and cleft palate

The condition observed in the mouse is analogous to that seen in man, the various degrees of severity being duplicated in the mouse. The affection is recessive and embryological studies suggest that failure of fusion is due to retarded growth of the maxillary processes, or possibly to the formation of cysts at the lines of fusion (Fig. 57). Cleft palate is also seen in bulldogs.

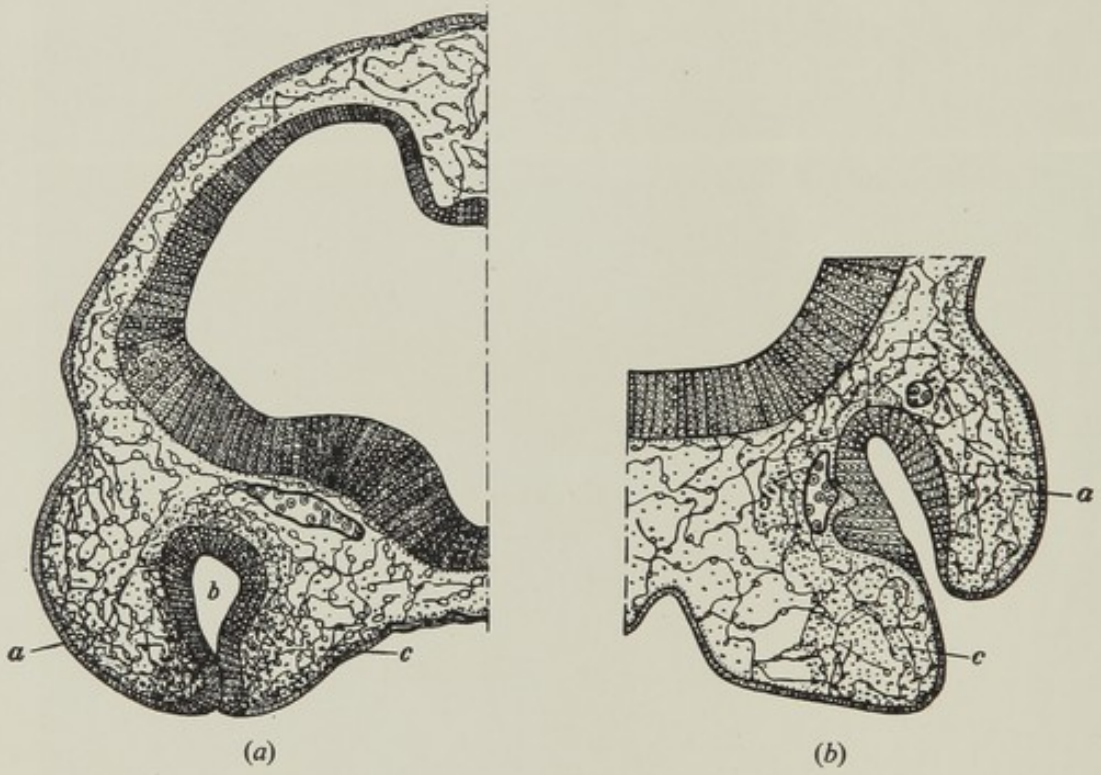


FIG. 57.—Hare-lip in the mouse. (*a*) Normal closure of lateral and mesial nasal processes. (*b*) Formation of hare-lip observed at 11 days of intra-uterine life owing to failure of fusion of nasal processes. *a*=lateral nasal process; *b*=primitive nasal fossa; *c*=mesial nasal process. (*After Reed, S. C. (1933). Anat. Rec.*, **56**, 101.)

Latent diabetes in the rat

A reduced glucose tolerance has been observed in rats. There is no actual excretion of glucose in the urine, but the blood sugar values are characteristic. The immature animal is normal and glucose tolerance decreases with age. Various endocrine abnormalities have been observed, but their full significance is not yet

known. It is assumed that the metabolic disturbance is due to hyperfunction of the anterior pituitary.

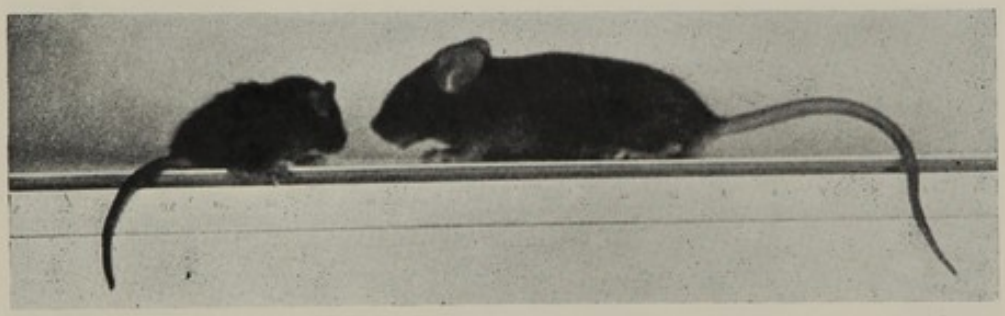
The opposite condition—a high insulin tolerance—has been observed in some strains of mice.

Acholuric jaundice in the rat

Homozygous animals are heavily jaundiced at birth, or soon after. Improvement tends to occur. Unlike human acholuric jaundice, splenectomy does not cure the affection, but as in human acholuric jaundice, the affection is not fully recessive, the heterozygous showing increased fragility of red blood corpuscles.

Pituitary dwarfism in the mouse

In this recessive affection the animals are of normal size at birth. They develop normally for some 16 days when growth ceases, becoming resumed at about the fifth or sixth week. Apart from being dwarfed they retain some infantile features throughout life and are sterile. The pituitary is much reduced in size, the anterior lobe being ill-developed (Fig. 58). Histological abnormalities first make their appearance at about 5–6 days after birth. The thyroid, too, is hypoplastic as is the thymus, and possibly also some parts of the other endocrines. A similar but more severe and semi-lethal disturbance has been observed in the rabbit.



(*a*)

FIG. 58.—Pituitary dwarfism in the mouse. (*a*) Dwarf mouse and normal mouse.

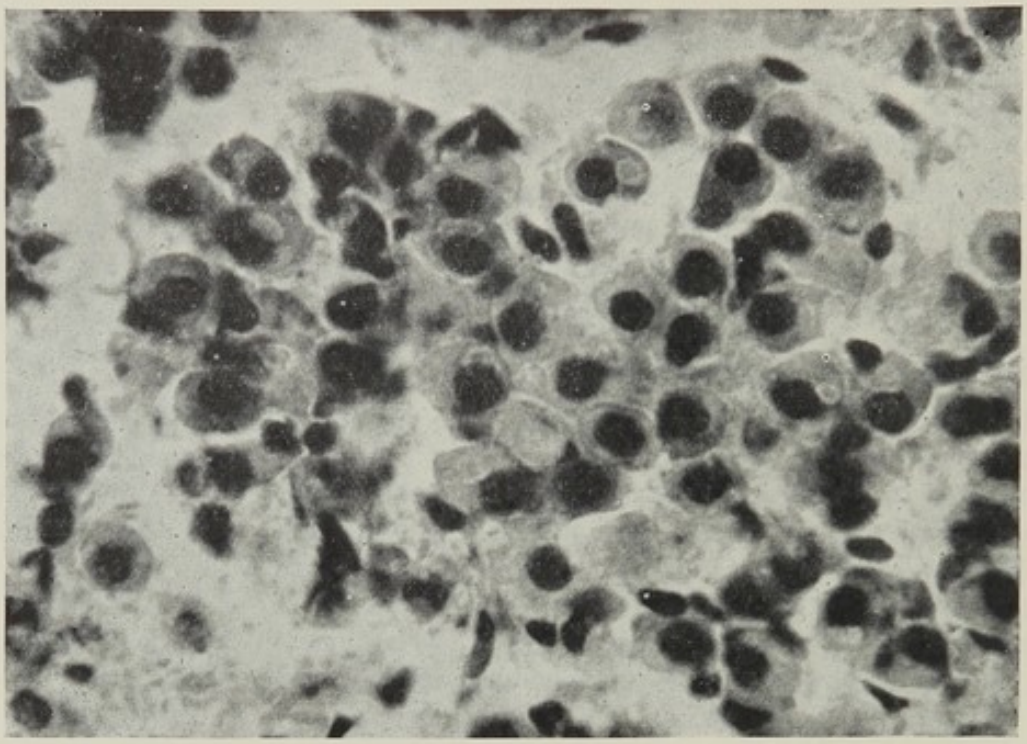
Dwarfism with cataract in the rat

Here, too, the animals are of normal size at birth, dwarfism being due to a growth disturbance which sets in by about the fifth day of life. The association with cataract suggests comparison with the Werner syndrome in man.

Syringomyelia in the rabbit

Histologically and clinically the wide range of manifestations seen in human syringomyelia is duplicated in the rabbit (Fig. 59). If a single limb is affected the viability of the animal is not greatly reduced. Severe cases, as in man, are uncommon. The range of manifestations in the rabbit, where the condition is clearly recessive, helps to explain the apparently sporadic character of human syringomyelia.

(*b*)



(*c*)

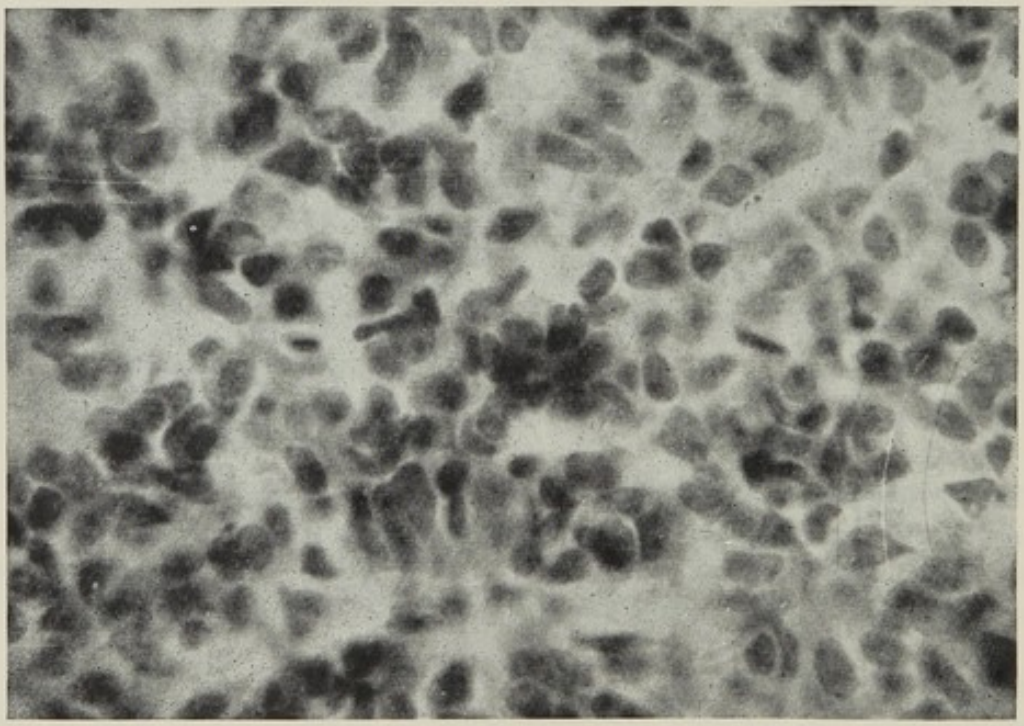


FIG. 58 (cont.).—(*b*) Anterior pituitary of normal mouse (×1400). (*c*) Anterior pituitary of dwarf mouse (×1400). (*After Francis, T. (1944). The Development of the Pituitary at Hereditary Anterior Pituitary Dwarfism in Mice, Vol.* 7. *Copenhagen: Munksgaard. Op. Dom. Biol. hered. hum. Kbh.*

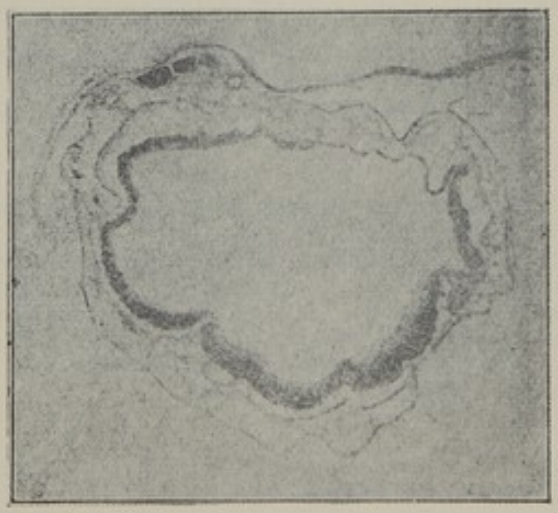
Albinism

Albinism is widespread throughout mammals and birds. In the fowl, autosomal and sex-linked forms have been recognized. In the turkey, the sex-linked form is lethal or sub-lethal.

Retinal dystrophy

The histological studies on retinal dystrophy in the mouse, rat, and dog, with their bearing on the nature of abiotrophy, have already been indicated.

(*a*)



(*b*)

FIG. 59.—Syringomyelia in the rabbit. Sections through the spinal cord of rabbits with various degrees of syringomyelia. (*After Ostertag, B. (1930). Dtsch. Z. Nervenheilk*, **116**, 147.)

MODIFICATION OF MANIFESTATIONS

Experimental genetics has shown the possibility of modifying genetically determined anomalies, just as theoretical genetics generally has emphasized the possibility of modifying gene effects. In the mouse, the pituitary dwarf may be made to develop normally by daily pituitary grafts. In the bent-nose rat, vitamin D, suitably administered, will prevent the anomaly. In the mouse with dominant spotting, life may be prolonged by blood transfusion.

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SECTION II

CLINICAL

CHAPTER 11

INHERITANCE OF MORPHOLOGICAL AND PHYSIOLOGICAL TRAITS

J. M. TANNER

PHYSIQUE

The influence of environment

THE DIFFERENCES in bodily form seen amongst humans vary through all degrees of detail, from the general size and shape of the individual to the curve of the eyelid, the form of the ear lobe or the cast of the particular finger. They are, in the main, hereditarily determined. Prolonged malnutrition during childhood, and, perhaps especially in the case of the head and face, during intra-uterine life, can disturb the smooth pattern of development and produce a build somewhat different from that which the genes would have created in better times, but the malnutrition must be severe for the effect to be at all large or lasting. Severe malnutrition causes a general reduction in size, and a postponement of the growth spurt of adolescence; its effects on shape and more detailed characters are not yet certainly known.

By the same token, during adult life, the muscular and fatty aspects of physique may in some individuals be altered by exercise and gluttony, but these effects too are for most people quantitatively small. Despite a variety of claims, there is little evidence that the effects of exercise on the muscles persist when the exercise

TABLE I

VARIABILITY OF ANTHROPOMETRIC MEASUREMENTS AMONGST OPPOSITE-SEXED NON-IDENTICAL TWINS DUE TO MEASURING ERROR, ENVIRONMENT AND HEREDITY

From a comparison of 96 identical and 142 non-identical pairs of twins aged 3–25 years. (Calculated from data of Table 21 in G. Dahlberg (1926), *Twin births and twins from a hereditary point of view*, Stockholm: Tidens.)

Dimension	Measuring error %	Environment %	Total heredity %	Sex-controlled heredity %	Non-sex-controlled heredity %
Stature	½	8	91	14	77
Leg length (symphysis height)	2	7	91	25	66
Arm length	2	7	90	52	38
Biacromial diameter	2	12	86	51	35
Bi-iliac diameter	1	23	76	40	36
Head breadth	2	12	86	30	56
Head length	1	15	85	35	50
Face breadth	2	9	88	52	36
Face length	8	14	78	42	36
Bigonial diameter	3	13	84	26	58

is stopped, and whether or not an individual grows fat in middle age depends a good deal more on his genetically determined build than upon the amount of food he takes. It seems that the potentiality for becoming fat depends on the genes, which limit severely the possibilities of accomplishment in some, while permitting dangerous licence in others.

That monozygotic or identical twins resemble each other very closely in appearance is well known, and an extension of this observation is seen in Table I, taken from Dahlberg's data. Here the effects of heredity and environment on various anthropometric measurements are given in terms of the percentages of total variability observed between non-identical twins of opposite sex. The children lived mostly in the rural districts round Stockholm, and so presumably were well nourished. Heredity accounts for about 90 per cent of the variability of the body length measurements, and for a trifle less of the body breadths and the head and face dimensions. The subjects were of all ages from 3 to 25 years, and it was thus possible to see whether or not environment accounted for an equal percentage of variability at all ages during growth. With increasing age the environment effect did increase a trifle, but to such a small extent that the increase was probably due to sampling error only. Dahlberg remarks also that males and females do not show any evidence of different plasticity to the environment; however, the actual hereditary variation is slightly larger in females.

TABLE II

CORRELATION COEFFICIENTS FOR FOUR ANTHROPOMETRIC MEASUREMENTS BETWEEN MEMBERS OF PAIRS OF IDENTICAL TWINS REARED TOGETHER (50 pairs), REARED APART (19 pairs), NON-IDENTICAL TWINS (50 pairs), AND SIBLINGS (26 pairs).
(*After Freeman and Holzinger. Stern (1950), Principles of Human Genetics in* San Francisco; *Freeman.*)

Dimension	Identical reared together	Identical reared apart	Non-identical	Sibs
Height	0·932	0·969	0·645	0·600
Weight	0·917	0·886	0·631	0·584
Head breadth	0·908	0·880	0·654	
Head length	0·910	0·917	0·691	

Two measurements of the same person usually have a correlation of 0·99 for height and weight and 0·97 for head breadth and length.

A possible criticism of this study is that the identical twins were reared together and were thus subject to the same home environment. As the effect of environment in Table I is measured by difference between identical pairs minus measurement error, environment here refers to the environment *within* different homes, whereas one normally uses the word to cover environmental differences *between* homes as well. This is without, in the present context, extending the term to include environments other than those commonly met in Western Europe and America. The study by Newman, Freeman and Holzinger of nineteen identical twins reared apart from infancy, however, shows that the similarity in height, weight, head length and head breadth is practically the same for these as for 50 pairs of identicals reared together (Table II). These figures also lead to the

conclusion that about 90 per cent of the variability in height and about 80 per cent of the variability in head dimensions are due to heredity.

Inheritance of physique

About the mechanism of the inheritance of physique we know very little. This is due partly to the difficulty of describing, or classifying, so complex a thing as the human form, and partly to the multifactorial nature of the mechanism and to the probably very involved relationship existing between a given gene and a component of physique. Up to the present the only traits among the more general aspects of build which have been studied are height (presumably as a rough measure of general size), and alternatively weight/height^2 and height/$\sqrt[3]{\text{weight}}$ as measures of linearity of build. Probably a more rewarding approach in the future will be to consider general size, which is adequately described by an equation involving height and weight or simply by the DuBois formula for surface area, followed either by the three non-orthogonal components of endomorphy, mesomorphy and ectomorphy described by Sheldon, or the orthogonal factors of physique—leptosomic, trunk length, limb length, body width and so on—described by Burt. The factor analysis technique is capable of extension to cover the more detailed features of the face, and the genetical analysis of dysplasias might also be handled in this way. The inheritance of androgyny also calls for study, with its possible bearing on the sex-controlled physique differences between males and females (for references *see* Tanner, 1953).

Body form in other mammals and birds can be described in terms very similar to those of the factors in man. In the rabbit, for example, there are factors for general size, general linearity, and growth of particular regions (Tanner and Sawin, 1953). Each set of factors is genetically controlled, and the genetical influences make themselves felt very early in embryonic development. Gregory and Castle (1931) showed that a race of large rabbits had already larger blastocysts 30 hours after fertilization than a race of small ones. In the mouse and rat several genes affecting body size have also an effect upon coat or eye colour through common physiological mechanisms of an unknown nature. The number of genes concerned in the control of size and shape in these species is not known, but it is usually thought that some exist on all or most of the chromosomes.

The most characteristic thing in man about either single anthropometric dimensions or components or factors of physique is that they are distributed in the adult population continuously and unimodally, and, in the case of stature and most other skeletal measurements, in gaussian form. Measurements of breadths and depths depart somewhat from normality in the direction of platykurtosis and positive skewness, but the departure is not very great and seems to depend for the most part on the distribution of the subcutaneous fat, which enters into them, being approximately logarithmic. This distribution makes it immediately apparent that stature, for example, depends either (i) on a single locus with many multiple alleles, or (ii) on many loci each with two alleles, or (iii) on many loci some or all with more than two alleles. The first alternative has been shown to be incorrect; according to it only 4 genotypes can exist in any one sibship, and studies of large sibships have shown that more phenotypes than this occur with differences between them which cannot be due to environment. Between alternatives (ii) and (iii) we cannot at present distinguish, nor do we as yet know at all the number of

genes concerned in the genesis of the various components of build, nor which chromosomes are involved. The approximate normality of the distributions does not necessarily mean that very large numbers of genes are concerned, since distributions not easily distinguishable from the gaussian can be brought about by relatively few genes if some have a greater effect than others, providing no single locus controls more than about a third of the variability. Nevertheless it seems likely by comparison with other species that large numbers of genes are involved at least in the general size and shape components. In Table III is shown, in

TABLE III

INHERITANCE OF LINEARITY OF PHYSIQUE AS MEASURED BY THE RATIO WEIGHT/HEIGHT^2 (GM./CM^2)

Linear (L) ratio $< 2{\cdot}15$, Medium (M) ratio $2{\cdot}15$–$2{\cdot}56$, Thickset (T) ratio $> 2{\cdot}56$. Condensed from tables 1 and 2 of Davenport (1923), *Publ. Carneg. Instn.*, **329**.

Type of mating	Male offspring			Number of matings	Number of male offspring	Male offspring per mating	Sex ratio of offspring
	L	M	T				
L—L	25	8	1	27	34	1·3	1·41
L—M	14	123	46	109	183	1·7	1·21
L—T	10	63	50	65	123	1·9	1·35
M—M	18	117	43	92	178	1·9	1·19
M—T	13	139	101	144	253	1·8	1·27
T—T	33	65	57	70	155	2·2	1·18
	Female offspring				Number of female offspring	Female offspring per mating	
	L	M	T				
L—L	20	4	0	27	24	0·9	
L—M	42	88	21	109	151	1·4	
L—T	24	41	26	65	91	1·4	
M—M	23	81	45	92	149	1·6	
M—T	24	119	56	144	199	1·4	
T—T	15	51	65	70	131	1·9	

condensed form, Davenport's data for linearity of build; besides showing the multiple factor inheritance, the figures also show that linear parents have fewer children than thickset parents; the sex ratios in this data do not differ significantly, though some other studies have led to a significant deficit of males in matings of fat parents. In Fig. 60 some pedigrees are given.

Probably fewer genes are concerned in the genesis of the more detailed traits. Danforth has shown that polydactyly in the cat, which is caused by a single dominant gene, comes about as the result of an excess of digit-forming tissue appearing on the pre-axial side of the limb bud at a third of the time through intrauterine life. The abnormality is not a grossly pathological or biologically unfitting one, and it seems reasonable to suppose that most ordinary local growth patterns are brought about in much this way, and on much this scale. If so, there is nothing

improbable in the idea that some facial and other detailed traits in man depend on single dominant genes, and there is some family evidence, none of it very satisfactory, in favour of this assumption. The Hapsburg lip is the example usually quoted; many members of the Hapsburg dynasty had a narrow, protruding lower jaw with a protruding lower lip, and this was apparently inherited as a single-locus dominant. Family resemblances not infrequently depend on sharply localized

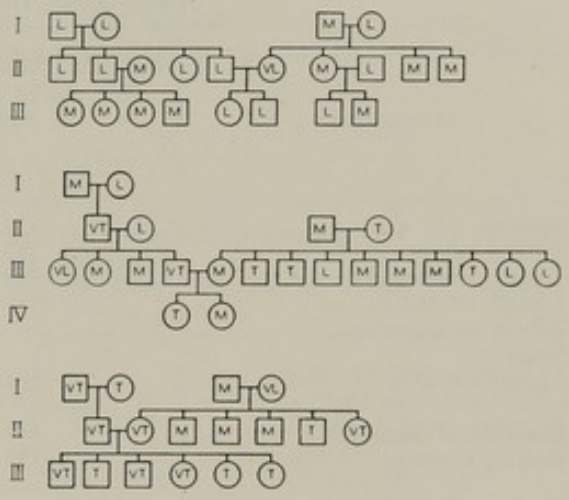

FIG. 60.—Three pedigrees of inheritance of linearity of body build, as measured by weight/height^2. VL very linear, weight/height^2 $<1{\cdot}80$ gm/cm^2, L linear 1·81–2·14, M medium 2·15–2·56, T thickset 2·51–3·05, VT very thickset $>3{\cdot}05$. (*After Davenport (1923), Publ. Carneg. Instn.*, **329**.)

features such as the shape of the tip of the nose, the position of the eyes, the form of the epicanthal folds, the shape of the rolled-over part of the ear, the form of the fingers and so on. Many of these may be determined chiefly or exclusively by genes at single loci. Possibly even larger regional effects may in some cases be due to a single loci; at least chondrodystrophic dwarfism is produced by a single dominant, though it would be hazardous to argue about the normal situation from this. Certain dysplasias, such as stocky muscular legs with slender fragile arms, appear to run in families in a not too complicated way.

In the endeavour to find out whether the genes for such traits as stature are mainly dominant or recessive in type, and whether any of them are sex-linked, correlations and regressions between the various members of families have been much used, despite the paucity and unsatisfactory character of the family data, most of which was collected over 50 years ago. Karl Pearson reported correlations of approximately 0·5 for stature, span, and elbow-to-fingertip (when due allowance is made for unreliability of measurement) in father–son, father–daughter, mother–son, mother–daughter, brother–brother, sister–sister and brother–sister relationships. In these various relationships the correlations are approximately the same in this data. The more recent figures of Howells on correlations between brothers, reproduced in Table IV, show that between different groups of measurements considerable and consistent differences in correlation exist. The long bone figures are about 0·5, and so are the facial heights; all these are manifestations of the leptosomic factor, which would presumably have the highest correlation of all. Head dimensions have somewhat lower correlations, and shoulder and hip width somewhat lower still. Facial breadths and ear dimensions are the lowest. The

grouping squares very well with the factor analysis classification of physique, but the interpretation of the relative size of the coefficients is not easy. In Table V are given the theoretical correlations expected in multiply-determined traits under various conditions. The approximate figure of 0·25 is taken for parent–parent correlations, that is, as the measure of assortative mating, though it is from an

TABLE IV

CORRELATION COEFFICIENTS FOR ANTHROPOMETRIC MEASUREMENTS BETWEEN PAIRS OF BROTHERS, BOTH ADULT

Dimension	Howells (1948) *Amer. J. phys. Anthropol. N.S.*, **6**, 449* 90–97 pairs	Bowles (1932), from Howells 79 pairs	Pearson and Lee (1903) *Biometrika*, **2**, 357 328 pairs
Stature	·473	·57	·511
Sitting height	·393	·46	—
Upper arm length	·455	·60	—
Length of radius	·516	—	—
Elbow to fingertip	—	—	·491
Span	—	—	·549
Length of tibia	·584	—	—
Biacromial diameter	·447	·22	—
Bi-iliac diameter	·358	—	—
Head breadth	·484	·29	—
Minimal frontal diameter	·474	—	—
Head height	·492	—	—
Head length	·384	—	—
Head circumference	·422	·50	—
Bizygomatic diameter	·294	—	—
Bigonial diameter	·303	—	—
Nose breadth	·251	—	—
Face height	·590	—	—
Upper face height	·507	—	—
Nose height	·511	—	—
Ear length	·271	—	—
Ear breadth	·216	—	—
Weight	—	·55	—

* A few of the figures have been corrected from the published ones (Howells, Personal communication).

old study and needs confirmation. The theoretical figures, though interesting, make too many assumptions for them to throw much light on the correlations of Table IV. In particular the figures given for complete dominance assume a frequency of 50 per cent for each allele (though the number of loci is unrestricted). The sibling correlation is reduced to about 0·3, however, if the average frequency of the dominant alleles is 90 per cent, and elevated to nearly 0·5 if the average frequency is 10 per cent. Howells' low correlations for face width, nose breadth and ear shape may mean that these features are controlled in large part by dominant genes with some of the recessives relatively rare in the population, or may indicate a degree of genic interaction.

A somewhat different approach has been used by Fisher and Gray (1937) and by Finney (1939). If x_1 is the father's stature and x_2 the mother's the the multiple regression of offspring's stature, y, can be calculated, between sibships, as

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_1x_2$$

and Fisher and Gray pointed out that the x_1x_2 term represented the effect of dominance in the genes concerned. If it is significantly positive, there is negative dominance, that is the heterozygote more nearly resembles the smaller than the larger of the homozygotes ; and if it is significantly negative, the reverse is the case. In Boas's data, which, being on children, are not entirely satisfactory for the test, they found in stature, head breadth and face breadth a slight tendency to negative dominance, though the significance lay only at about the 25 per cent level.

TABLE V

THEORETICAL FAMILY CORRELATIONS EXPECTED UNDER VARIOUS CONDITIONS OF GENE ACTION AND ASSORTATIVE MATING

(*After Hogben (1932) J. Genet.* **26**, 417, and *Stanton (1946) Ann. Eugen., Camb.* **13**, 18.)

Relationship	Random mating. Parent–parent correlation zero				Assortative mating. Parent–parent correlation 0·25 for 3 generations	
	Heterozygote intermediate		Dominance complete		Heterozygote intermediate	
	Autosomal	Sex-linked	Autosomal	Sex-linked	Autosomal	Sex-linked
Father–son	·50	·00	·33	·00	·63	·19
Mother–daughter	·50	·50	·33	·33	·63	·66
Father–daughter	·50	·71	·33	·58	·63	·77
Mother–son	·50	·71	·33	·58	·63	·77
Brother–brother	·50	·50	·42	·50	·63	·60
Sister–sister	·50	·35	·42	·29	·63	·51
Brother–sister	·50	·75	·42	·67	·63	·83
Sib–sib	·50	·33	·42	·20		

In another connexion the reverse situation, that is, positive dominance, has been suggested by Dahlberg for the genes concerned in body size and particularly stature. During the last hundred years there has been all over the world an increase in body size, which is apparently still continuing. Most anthropologists think this is a true increase in adult dimensions, but a few believe that it is entirely accounted for by the earlier maturation that has certainly taken place ; these workers say that 25-year-olds, as distinct from 20-year-olds, are no bigger now than previously. The alleged increase in size is usually accounted for on the basis of better nutrition, and this view is probably partly, but only partly correct. Against it are the facts that all classes of the community have increased and that the increase has been uninterrupted despite variations in living conditions. Dahlberg has therefore suggested that some part of it is due to the breaking up of genetic isolates and the acquisition by the offspring of dominants for large size from parents each of whom possessed some of them only in the ineffective homozygote (that is, AAbb and aaBB parents produce AaBb offspring, who are therefore larger).

Finney (1939) has pointed out that a simple test can be made for sex-linkage in any quantitative character. If any of the genes for a character lie on the X chromosome, then the value of the quantity (S–D), where S is the mean for sons in a family and D the mean for daughters, is significantly variable from family to family, since in families with inheritance of these genes from the father one sex will receive them with greater frequency than the other. Thus in the analysis of variance of measurements on siblings, the sex-family interaction is significantly greater than the within-sex-and-family mean square. Applying this test to the inheritance of stature Finney obtained equivocal results in that Galton's old data, which he used, appeared to be internally inconsistent; however, Tanner (unpublished), using the more restricted but satisfactory material published by Brues (1950) could find no evidence for sex-linked genes controlling stature, the interaction mean square being only very slightly more than the mean square for within sex and family. For the ratio height/$\sqrt[3]{\text{weight}}$ the interaction is significant at about the 3 per cent level, a result already obtained by Brues herself using a slightly different method. For surface area, the measure of body size, the interaction is larger, being significant at nearly the 1 per cent level. It is evidently by virtue of the weight rather than the height element that the height/$\sqrt[3]{\text{weight}}$ ratio gives a significant result, and it seems likely that genes for gross body size, body fat, or breadth of the skeleton and muscles exist on the X chromosome. Brues also found that the height/$\sqrt[3]{\text{weight}}$ ratio was linked with the character freckling, and since freckling and sex are not linked, the relationship is evidently through an autosomal gene.

GROWTH PATTERNS AND MENARCHE

Differences in physique come about as the result of differences in growth rates of various parts of the body, and it is likely that the action of many of the genes controlling size and shape is on growth-rates either locally in the body or at a

TABLE VI

CORRELATION COEFFICIENTS BETWEEN TIME OF APPEARANCE OF EPIPHYSEAL OSSIFICATION CENTRES IN IDENTICAL TWINS, SIBLINGS, COUSINS AND UNRELATED CHILDREN.
(From Reynolds (1943) *Amer. J. phys. Anthropol. n.s.* **1**, 405.)

Number of pairs of persons	Number of pairs of centres	Relationship	Correlation coefficient for centres
6	178	Identical twins	0·71
22	666	Siblings	0·28
8	256	First cousins	0·12
9	274	Unrelated	−0·01

particular period of time. Some act by affecting the secretions of the endocrine glands, but probably more by their local effect. The mechanism of inheritance of body build will probably be clarified more by the longitudinal study of the growth

of siblings and families than by any other measure applied to the human, and it is encouraging that in two of the longitudinal growth studies in the United States of America the enrolment has begun of children of parents who were themselves members of the growth study as children. The growth curve of the human is a complex and intricate one, but under reasonable environmental circumstances it is followed with astonishing regularity. Reynolds, for example, has reported the time of ossification of 38 epiphyseal centres appearing between birth and $6\frac{1}{2}$ years in identical twins, siblings, cousins and unrelated children. Some of his results are reproduced in Table VI. The agreement in time of appearance of centres is much greater between identical twins than between siblings, and greater between siblings than between unrelated children.

There have been practically no studies of the inheritance of growth rates in man, partly for lack of longitudinal sibling data, and partly for lack of a useful equation for growth in the various dimensions, whose parameters would measure the relevant rates. One event has, however, received a good deal of attention. This is the time of the ménarche or beginning of menstruation. The ménarche has been getting earlier over the last hundred years or more, and this effect is probably partly or wholly environmental, but resemblances within families have persisted despite the general drift. Table VII lists the difference in months for identical twins, non-identical twins, sibs and others. It should be noted, however, that the mother–daughter difference, owing to the secular trend, is probably greater than would be due solely to genetical causes.

TABLE VII

MEAN DIFFERENCE, IN MONTHS, IN TIME OF FIRST MENSTRUATION
(From Stern (1950) after Petri.)

Number of pairs	Relationship	Difference, months
51	Identical twins	2·8
47	Non-identical twins	12·0
145	Sibs	12·9
120	Mother–daughter	18·4
120	Unrelated women	18·6

Palmer (1934) and others have adduced some evidence that genes controlling the *rate* of growth are to a considerable extent independent in action of those controlling final *size* achieved. This is particularly so at adolescence where the time of onset is quite independent of final body size. In cattle (Rollins and colleagues, 1949) and in rabbits (*see* Tanner and Sawin, 1953) rate and size seem also to be considerably independent.

LONGEVITY

Many families have the reputation of producing long-lived individuals, and the studies of Raymond Pearl and others have made it clear that longevity in man is indeed a hereditary characteristic. Many factors enter into the determination of a person's life span, and the hereditary ones are perhaps divisible into two main

groups: resistance to infection, particularly in infancy, and resistance to metabolic decay, in particular cardiovascular disease and cancer, in later life. In the pedigrees investigated by Pearl, one of which is shown in Fig. 61, resistance to infection

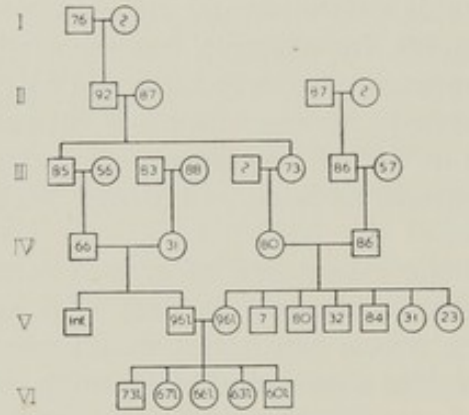

FIG. 61.—Pedigree of a family of long-lived people. Age at death in years, or, if living, present age followed by letter l. *Inf* (VI) signifies died in infancy. (*After Pearl (1931). Hum. Biol.*, **3**, 31.)

probably plays as large a part as resistance to metabolic decay, since the individuals concerned lived before the days of effective chemotherapy or even hygiene. The advent of modern medicine has made longevity more than ever a hereditary matter, and changed somewhat its genetical basis, allowing people with genes for resistance to metabolic decay in old age to express them even if they do not also have genes for effective resistance to bacterial disease such as pneumonia and meningitis.

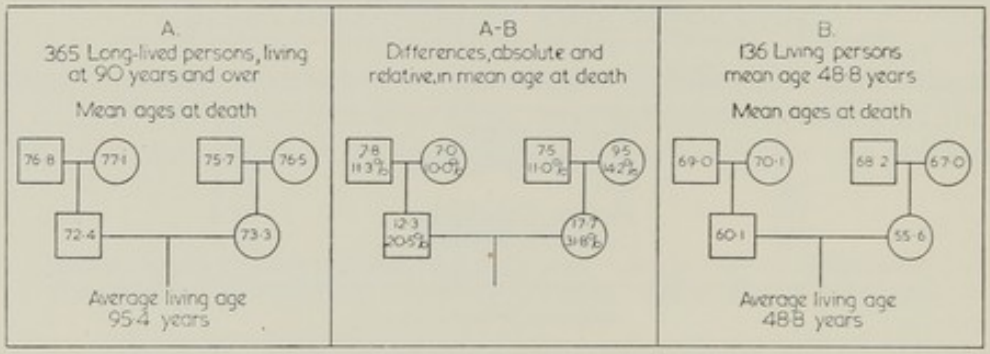

FIG. 62.—Influence of immediate ancestry upon longevity. Mean ages at death of parents and grandparents of 365 long-lived persons, and of 136 persons few of whom will become long-lived. (*After Pearl, R. and Pearl, R. D. (1934). The Ancestry of the Long-lived. Baltimore; Johns Hopkins. University Press.*)

It would hardly be expected that the genetical control of the life-span is a simple matter, and little can be said except that it is multifactorial. Fig. 62, from Pearl, shows the mean ages at death of parents and grandparents of 365 long-lived persons compared to 136 living persons, few of whom will turn out to be long-lived. The differences, given in the central block, show the parental influence stronger than the grandparental, and neither male nor female ancestors clearly more important. Pearl also showed that the expectation of life of the sons of fathers who lived to be 80 years or over is greater at all ages from birth to 80

than is the expectation for sons of fathers dying between 50 and 80. In turn this latter group has a greater expectation of life than the sons of fathers dying before 50. The differences are considerable and highly significant statistically; at age 60 the expectation for the fathers–over–80 group is 40 per cent greater than for the fathers–under–50 group.

Twins have also served as material for studies of longevity. Kallman and Sander in 1948 reported that in 36 pairs of twins, all of whom lived to be over 60 and all of whom were dead at the time of inquiry, the difference in age at death for 18 monozygotic pairs was 37 months, while for 18 dizygotic pairs it was 78 months.

TASTE THRESHOLD FOR PHENYLTHIOCARBAMIDE (P.T.C.)

In 1931 Fox discovered that crystals of a synthetic chemical, phenylthiocarbamide or phenylthiourea, usually known as P.T.C., could be tasted by some people, but not by others. This ability was soon shown to be hereditarily determined, and probably dependent upon a single pair of genes. The ability appeared to be dominant to the lack of it, a single dose of the taster gene producing apparently the same effect as a double dose. Thus phenotypic tasters have the genotype TT or Tt, non-tasters tt. Apart from the blood group antigens P.T.C. was the first clear-cut case of a physiological process in man depending directly upon probably a single gene, and it has been widely used in anthropological work and in studies of linkage.

Further experience with the test has shown that the relation between phenotype and genotype is not quite so clear-cut as was at first imagined, however, and it is not invariably possible to state, from giving a subject P.T.C. to taste, whether he has the taster gene or not. Fortunately this indecision applies to only a small percentage of cases. The reason for it is seen in the upper graph of Fig. 63, redrawn from Barnicot; when serial dilutions of P.T.C. in water, instead of crystals, are given to people to taste, it is a difference in *taste threshold* only that is demonstrated and not an absolute ability or inability. At concentrations of about 1,300 milligrams per litre practically everybody can taste P.T.C., but at about 40 milligrams per litre only those with a taster gene can do so. The distribution of taste threshold is bimodal, and, at least in Europeans, the taster and non-taster curves overlap slightly, and a person with a threshold of about 80 milligrams per litre may belong to either population.

The subject has suffered somewhat from different investigators using different methods, not equally reliable, for obtaining the taste threshold. A recent technique which has much to recommend it consists in making up 14 solutions of P.T.C. in boiled tap water, the first solution containing 1,300 milligrams per litre of P.T.C., the second being the first diluted to half strength, the third the second diluted to half strength, and so on. The subject is given a preliminary test working from the higher dilutions downwards till he tastes a solution. He is then presented with 8 tumblers, 4 filled with the solution he tasted and 4 with the next highest dilution. To be counted as tasting a given dilution, the subject must classify all 8 tumblers correctly. The solutions must all be kept at the same temperature and made up with the same water at the same time. With this technique subjects rarely alter threshold by more than one dilution upon repeated tests.

It has been shown that the sensitivity both of tasters and non-tasters decreases slightly with age (as does that for vibratory sensation and acuity of vision) and so the concentration of P.T.C. best separating the genotypes rises with age. It about doubles for each 20 years of adult age, so that if the taste of 40 milligrams per litre is the criterion at ages 10–19, 80 milligrams is the criterion at 20–49, and

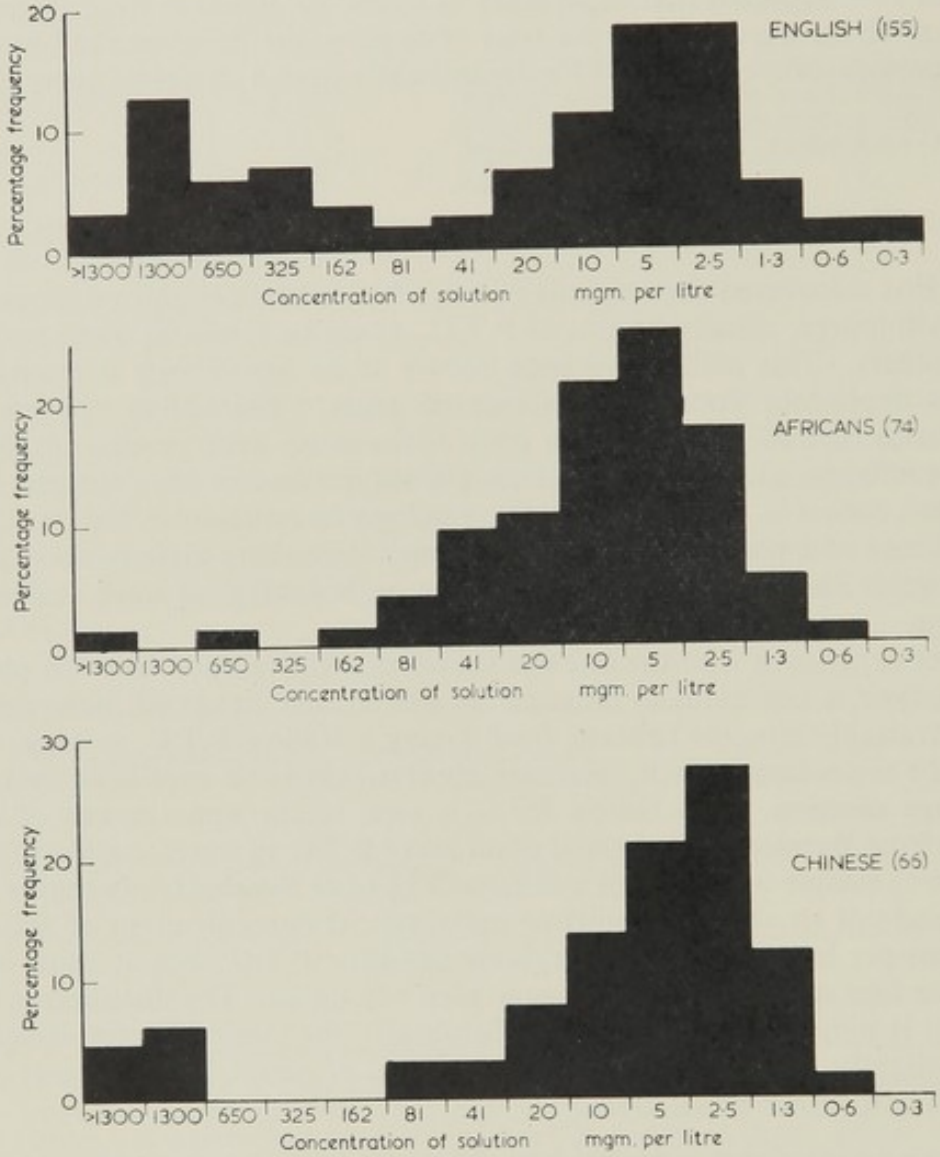

FIG. 63.—P.T.C. taste thresholds in English (males aged 20–41), Africans and Chinese. (*After Barnicott (1950). Ann. Eugen., Camb.*, **15**, 248.)

160 milligrams at 50 years and over. Women also are slightly more sensitive than men, whether tasters or non-tasters, and so the separating criterion should be slightly different for the sexes, but the difference is small and does not amount to a whole step on the serial dilution scale of Fig. 63. Fig. 63 also provides some evidence that the sensitivity may differ in different racial or geographic groups. It looks as though the separating criterion should fall at a concentration of about

160 milligrams per litre for Africans and perhaps Chinese aged 20–39 rather than at the European figure of 40 milligrams per litre. However, more data are needed before this can be regarded as established. The essential point is that in any study using the P.T.C. solutions for determining the presence or absence of the taster gene, not only must an adequate tasting technique such as that described above be used, but also the criterion for separation of tasters and non-tasters must be adapted to the population sampled.

The proportion of non-tasters seems to be about 30 per cent in Europeans and white Americans, though there is some evidence that significant differences exist within the European group, for example between the English and the Danes. Amongst Africans the proportion of non-tasters is very much lower, being of the order of 5 per cent, and amongst Chinese about 10 per cent. No difference in proportion of non-tasters as between men and women has been found in most English data, but there are suggestions that such may exist in some other groups.

The taster gene exists in polymorphic equilibrium with the non-taster, and it seems that this state of affairs has persisted for some time, since amongst chimpanzees similar differences in taste threshold have been shown to exist. The situation is thus somewhat similar to that of the blood group antigens. The significance of the polymorphism is still entirely unknown, however. A considerable number of substances chemically related to P.T.C. share the same bimodal taste threshold, though none has yet been found which separates tasters and non-tasters as well as P.T.C. The chemical group to which the taster gene confers sensitivity seems to be $=N-\overset{\|}{\underset{S}{C}}-$. Some substances with this grouping do occur in nature, but none has been shown to have physiological significance for the human, at least under ordinary circumstances. The heterozygote taster is thought to have the same taste threshold as the homozygote taster, though no critical tests with serial dilutions on genetically identified subjects are available. It seems likely that the sensitivity of the taste-buds to P.T.C. and its relations must be the surface part of the iceberg; more interesting physiological effects of the gene probably lie beneath.

EYE COLOUR

In the early days of genetics it was believed that eye colour was determined simply by a single pair of allelomorphs, blue eyes being recessive to brown; in fact in 1907 eye colour was hailed as the first single-pair trait to be established in the human. This view we now know to be incorrect, though a good first approximation to the truth; eye colour is controlled by genes at at least three and at perhaps not more than six loci.

The colour of the eye depends both on the structure of the iris and on the amount of pigment in it. The anterior or outer epithelial layer, which is complete in the majority of mammals, atrophies to a greater or lesser extent in some groups of men. Brues (1946) designates the appearance of the iris as smooth, striated, eroded, cryptose, ridged or scalloped, according to the degree of atrophy. In the smooth there is no atrophy, and in the scalloped atrophy has gone so far that only an irregular ridge immediately around the pupil still persists ; in a few people even this disappears. Blue eyes are said to occur

in the human only when there is both lack of pigment in the stroma of the iris, and atrophy, more or less complete, of the anterior layer. It is believed that they cannot occur in the absence of this atrophy though it is possible that grey eyes are those with lack of stromal pigment but a less completely atrophied anterior layer.

In other mammals however, for example rabbits, blue eyes certainly occur without anterior layer atrophy, and result from pigment being lacking in the anterior layer and stroma, but present in the posterior layer. Absence of pigment in the posterior layer as well as at the other sites causes the pink albino eye. Brown eyes in man as a rule are associated with a smooth homogeneous anterior layer, but a small number of brown-eyed people exist in whom there is a considerable degree of atrophy. The colour of the iris itself is seldom uniform, the general colour being interfered with by superimposed detail colour, usually in the form of spots or small patches. Both general and detail colour range from blue to dark brown through a series conveniently designated blue, grey, green, yellow, tan and chocolate. Like the hair, the iris gradually becomes darker as the individual ages, except in those with very light eyes to begin with.

All these factors make a genetical analysis of eye colour a matter of very considerable difficulty. It is thought that the original human colour was dark brown, with a smooth anterior layer, and that mutations to blue have occurred and in some instances spread to produce the present West European population. Blue eyes occur only in those have a double dose of the mutated gene; a single dose probably produces some lightening of the brown eye. If both parents are blue-eyed, the children are as a rule also blue-eyed, but a few may be grey-eyed, and in Winge's data 12 out of 644 children of such parents were brown-eyed. It is not clear, however, whether any cases of brown-eyed children coming from blue-eyed parents exist which cannot be explained by errors in recording, disease of the eye, or illegitimacy.

There are differences seen amongst brown eyes however, which are not accounted for by homozygosity or heterozygosity at this locus. At least one other autosomal locus is concerned, perhaps with a multiple allelic series. There is thirdly a gene situated on the unpaired portion of the X chromosome whose usual form in single or double dose makes for a dark eye. In most Western European countries there are more brown-eyed women than brown-eyed men due to the presence of this gene. There may be another locus controlling the rather rare advent of dark brown eyes with nearly completely eroded anterior layers; these do not occur in the families with brown eyes and homogeneous anterior layers, but more often in families of predominantly light-eyed individuals. Lastly some authors believe that the yellow pigment often seen in the eye is not a member of the brown pigmentation series at all, but due to the action of another, separate, pair or series of genes.

SKIN COLOUR

Multifactor inheritance, so characteristic of most normal traits in man, was first described in human genetics in relation to skin colour. This was in 1910 and 1913 by Gertrude and Charles Davenport, who studied Negro-white crosses in the West Indies. They divided the amount of pigmentation into five classes, using a colour-matching scale; nowadays spectrophotometric reflectance curves from various parts of the body would be used (*see* Hooton, 1946), or actual pigment concentrations from biopsied material. The colour difference

between Negroes and whites is mainly or wholly due to differences in melanin concentration in and between the cells of the stratum corneum, stratum granulosum and stratum germinativum. Though exposure to sunlight causes an increase in melanin concentration, this lasts only so long as the exposure is maintained, and the differences in skin pigmentation ordinarily observed are due to hereditary causes.

TABLE VIII

SKIN PIGMENTATION OF FIRST AND SECOND GENERATION NEGRO–WHITE HYBRIDS
(From Stern (1950), after Davenport)

	Colour class				
	0	1	2	3	4
Children of Negro–white (0×4) cross (first generation hybrids)	0	2	22	5	0
Children of marriages between first generation hybrids	3	10	13	5	1

In Table VIII are shown the distribution of colour classes for first and second generation Negro–white hybrids. The original parent classes were 0 and 4. To explain these results the Davenports invoked two independent loci, each represented by two alleles, with the alleles having each a uniformly cumulative effect. It is probable however that the distribution of skin colour is more continuous than such a hypothesis would allow for, and that more than two loci are concerned, with more than two alleles at some or all of them.

HAIR

Colour

The colour of the hair depends mainly on the amount of pigment present but also partly on the structure of the hair. The hair shaft consists of a thin unpigmented outer cuticle made of overlapping scales, a cortex of cells in which both granular melanin and some diffuse non-granular pigment are found, and a medulla of loosely packed pigmented cells interspersed with air spaces. There appear to be two distinct series of pigments present. The first, melanin, occurs to some extent in everybody except albinos, and is responsible for all the white-black series of colours from light blond to jet-black, the colour varying chiefly with the concentration of the pigment. The amount of melanin present is a hereditary trait, probably depending on a multiple allelomorphic series on one of the autosomes, with perhaps other complicating factors as yet unknown. This allelomorphic series is presumably the same as that determining the brownness of the eyes, and controls pigmentation throughout the body, including the skin. Evidently a double dose of the gene for lack of eye pigment (that is for blue eyes) can overcome locally the effects of this pigmenting gene, since some groups of people, notably in Ireland and northern Scotland, have dark hair and skin with

blue eyes, and Gates has described a family of Singhalese in some of whose members the eyes were blue, but whose hair and skin were pigmented as usual.

The second pigment present in some but probably not all people is a red one, which is chemically different from melanin and inherited independently. Its presence is believed to be governed, at least in the main, by a single pair of genes, which Penrose has shown to be located on the same chromosome as the ABO blood group locus, the cross-over value between the two being about 9 per cent. People with bright red hair have a double dose of this gene, and very probably those with reddish-brown hair and freckles represent the heterozygotes. Possibly a small percentage of heterozygotes approach the homozygote in phenotype. Redheads are present in West European populations to the extent of 2–3 per cent, and to the extent of about 1 per cent in southern European countries, and occur occasionally, it seems, amongst all peoples; they have been described in Eskimos, Japanese, African Negroes, and the natives of New Guinea. Red hair in Europeans occurs equally in both sexes and quite independently of eye colour.

There are difficulties in ascertainment of hair colour just as there are of eye colour. The hair darkens with age up to about 40 years, and it is not clear to what extent the presence of the red pigment can be masked by strong concentrations of melanin. The reddish tinge is often seen in the beard, axillary hair or pubic hair when the head hair does not show it. Studies of hair colour are usually carried out nowadays using the reflectance curve of a sample of hair placed in a spectrophotometer, but excellent colour standards also exist, manufactured by makers of hair dyes.

Hair form

The form of the head hair, which probably depends on its protein structure, is also a hereditary characteristic, though one not easily quantified. Between the extremes of completely straight hair and the short hair that grows in tightly coiled spirals and has been called " woolly " or " peppercorn ", there appears to be a continuous range, designated roughly by straight, wavy, curly, and woolly. The definitive hair form may not be established till maturity and may, of course, be masked by such procedures as permanent waving. Its inheritance seems probably to depend on a series of multiple alleles, with straight hair recessive to the others. Matings of straight × straight produce nearly all straight-haired children, with an occasional wavy or curly; straight × curly and straight × wavy produce about equal numbers of straight and of curly or wavy respectively; and wavy × curly produces a mixture of straight, wavy and curly. Woolly hair seems to represent a fourth gene at the same locus, with effects which predominate over the other three. There are considerable numbers of European pedigrees in which closely curled woolly hair appeared, it seems spontaneously, in a family, and in these instances it is inherited as a simple dominant over both the straight and wavy characters. It is uncertain whether this form of woolly hair is identical with that often seen in Negroes.

Hair weight

Hair weight, that is, the difference between fine and coarse hair, is said to be inherited, but has been insufficiently studied for any mode of inheritance to be suggested.

Mid-digital hair

It was shown by Danforth in 1921 that the presence or absence of hair on the dorsum of the middle phalanges of the fingers was an inherited trait, and he suggested that absence of hair at this site was recessive to its presence. This too is in reality a quantitative character, the number of hair follicles present varying from person to person, and also the absence or presence varying from one finger to another. It was suggested by Bernstein and Burks in 1942 that the trait depends on a multiple allele series with perhaps five members producing quantitatively increasing effects, and the data published since that time do not contradict this assumption.

Occipital hair whorl

The hair whorl in the occipital region may turn clockwise or counterclockwise, and Bernstein in 1925 suggested this was a hereditary character dependent on a single pair of genes with that causing a clockwise turn recessive to that causing a counter-clockwise. About 70 per cent of people have counter-clockwise whorls, 25 per cent clockwise and 5 per cent double whorls, which may go both the same way or, more frequently, different ways. Rife in 1933 found that in identical twins the whorls did not invariably go the same way, suggesting either an environmental effect, or, more probably, mirror imaging. Later studies have not shown Bernstein's hypothesis to be necessarily wrong, but there are probably further complicating factors concerned. Kloepfer's (1946) data, for example, give for counter-clockwise × counter-clockwise parents 88 counter-clockwise but also 12 clockwise offspring, and for the other two matings combined approximately equal numbers of clockwise and counter-clockwise. Burks in 1938 provided evidence that the main locus for occipital hair whorl was on the same chromosome as that for absence of third molar teeth; but since both characters may be somewhat complicated genetically, this observation needs to be confirmed and clarified.

Frontal hair-stream direction

Hair-streams in other parts of the body have been considerably studied by anatomists and others, and Kiil (1948) has suggested that the direction of the short downy hairs, or vellus, on the forehead, is genetically determined in a fairly simple manner. There are two main streams on the forehead, one originating at the crown of the head, the other at the root of the nose. Kiil designates as Type I streams which go downwards between the hairline of the head hair and the eyebrows, as Type II streams some parts of which go up and some down, and as Type III streams which go up. Analysis of family material suggests that at least 3 multiple alleles are concerned, with dominance in the order Type III, Type II, Type I. In addition there may be modifying factors, and some dependence on embryonic environment. The hair-streams probably result from differential stimulation of growth areas at the corona and the glabella at a particular time in embryonic life.

Baldness

Elsewhere (page 48), it has been shown that baldness is a hereditary, partially sex-controlled affection. Harris (1946–47) believes that this inheritance only holds

good for the baldness which develops before the age of 40 (called premature baldness), later-developing baldness being supposedly due to other causes. This opinion is based on the single-locus hypothesis fitting well a series of family data on the assumption of a male population incidence of baldness of about 10–15 per cent, in which range the premature baldness figure lies, but not fitting the data supposing the incidence to be of the order of 30–40 per cent, which seems to represent the figure for baldness incidence at all ages. If Harris is right then about 18 per cent of the population, assuming random mating, are heterozygous for the premature baldness gene; but if in reality only one sort of baldness, inherited similarly, exists, somewhere nearer 30 per cent of people are heterozygous.

OTHER TRAITS

Tongue curling

In 1940 Sturtevant pointed out that the ability to curl up the lateral edges of the tongue to make a tube is hereditarily determined. About 65 per cent of people seem able to do this; some others can curl the tongue slightly, and some practically not at all. On the first test the variation appears to be purely or mainly genetic, but there are reports that non-curling sibs of curlers can produce a fair imitation of a curl after a certain amount of practise in front of a mirror. Kloepfer has reported combined figures from Sturtevant's data and his own, and these are reproduced in Table IX. The mode of inheritance is not clear, except that the ability does not seem to depend on a single pair of genes with simple dominance.

TABLE IX

DISTRIBUTION OF TONGUE-CURLING IN OFFSPRING ACCORDING TO PARENTAL MATING

(*From Kloepfer, 1946*)

Parents	Offspring		
	Curler	Non-curler	Total
Curler × curler – – – –	43	9	52
Curler × non-curler – – –	53	30	83
Non-curler × non-curler – –	3	22	25
Totals – –	99	61	160

Handedness

Handedness is probably in the main a hereditary character; that is to say, heredity determines some neurological difference which predisposes the individual to use preferentially his left or right hand. Despite a considerable volume of work on this subject, however, the nature of the neurological difference is not yet understood. Handedness is certainly a graded character, not an absolute one; there are a considerable number of people who are ambidextrous in the sense that they show no striking preference for one hand or the other; indeed, when a test is given allowing complete quantitation of " handedness " the scores are distributed quite unimodally, with no indication of a break between left-handers and right-handers at all. Hand preference is one of the results of the dominance

of one cerebral hemisphere over the other, and preference for use of the right or left eye and the right or left foot comes from the same source. There are many individuals in whom the preferences are mixed, however; a person may be right-eyed, left-handed and right-footed. In these circumstances it is not surprising that the genetics of handedness is confused, and likely to remain so until its physiological basis is better understood.

Finger and palm patterns

The patterns of the papillary ridges on the fingers and palm are genetically determined, and indeed used as one of the prime indications of monozygosity in twins. The mode of their inheritance is not clear, however, beyond the fact of being multifactorial. The finger patterns are classified in whorls, loops, and arches, but intermediate forms are numerous, and it appears that the patterns depend on genes controlling skin thickness and the general shape and structure of the hand as well as on genes concerned with the growth of the ridges themselves.

Electroencephalographic pattern

Under standard conditions of rest and relaxation individuals have a characteristic electroencephalographic pattern which does not vary much from day to day. Studies on monozygotic and dizygotic twins by Lennox, Gibbs and Gibbs (1945) provide evidence that a great deal of the E.E.G. differences between individuals are hereditarily determined, though not in a simple way. They compare the E.E.G. record to the facial features in complexity. Using apparent identity of E.E.G. record as a test of monozygosity, they were able to pick out the two sorts of twins with only 4 per cent wrong and 11 per cent doubtful in 55 monozygous pairs and 5 per cent wrong and none doubtful in dizygous pairs.

Superficial veins of mammary region

The pattern of the superficial veins draining the mammary region of the chest can be visualized by infra-red photography, and appears to fall into one of two distinct classes, transverse or longitudinal. In the former the veins travel across the chest and drain into the axillary region, and in the latter they travel upwards along the chest and drain into the clavicular area. Spuhler (1951) has reported that in American Indians (Ramah Navahos) about 70 per cent have the transverse pattern, and quotes a corresponding figure of about 90 per cent for American whites. There seems to be no sex difference in incidence. Spuhler's figures agree with the hypothesis that the pattern is controlled by a single autosomal pair of genes with full penetrance, the transverse pattern being given by the heterozygote as well as by one of the homozygotes. In the same paper Spuhler discusses the less well-defined inheritance of the peroneus tertius muscle and the number of vallate papillae on the tongue.

Tests of physiological function

There have been very few studies on the genetics of physiological function in the human, despite the obvious importance they would have in elucidating differences in morphology and behaviour. Jost and Sontag (1944) have reported a study from the Fels Research Institute in which heart rate, respiration rate,

pulse pressure, palmar skin resistance standing and lying, 5-minute salivary output and persistence of a skin flush following a standard slow stroke over the biceps were measured. The subjects were children aged 6–12 years, and included some pairs of identical twins. The tests were done under standardized conditions of rest, in the morning at least one hour after breakfast. In each of the measurements the average difference between pairs of twins was lower than that between siblings, which in turn was lower than the difference between unrelated children paired at random. The difference recorded for twins is significantly less than that for sibs in the case of persistence of skin flush, standing palmar skin resistance and pulse pressure, and significantly less than that for unrelated children for these and also for respiration rate.

Blood pressure and heart rate were also studied in twins by Malkova cited in Stern, 1950). Concordance, as defined by similarity in measurements, was present for blood pressure in 63 per cent of 62 monozygotic and in 36 per cent of 84 dizygotic twins. For heart rate, the percentages were 56 per cent and 34 per cent. Evidently many physiological functions are to a considerable degree genetically controlled, and this field, so far ignored by professional physiologists, lies wide open for cultivation. A lead in this direction has recently been given by Fuller's (1951) work on dogs.

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CHAPTER 12

METABOLIC DISORDERS

D. KLEIN

DISTURBANCES OF PROTEIN METABOLISM

DISORDERS OF THE INTERMEDIARY METABOLISM OF AROMATIC AMINO ACIDS

Alkaptonuria

ALKAPTONURIA is a congenital disorder of the intermediary protein metabolism, in particular of phenylalanine and tyrosine. The transformation of these two aromatic amino acids is interrupted at the stage of homogentisic acid (Fig. 64). The incapacity of these intermediates to undergo further changes is probably due to an enzymatic defect. The homogentisic acid is eliminated in the urine where it may be detected either by a darkening of the urine when exposed to air or by the addition of alkali.

Clinical aspects.—The condition is recognized very early in life by darkening of the urine on standing and black-brown colouring of the urine stains on napkins after

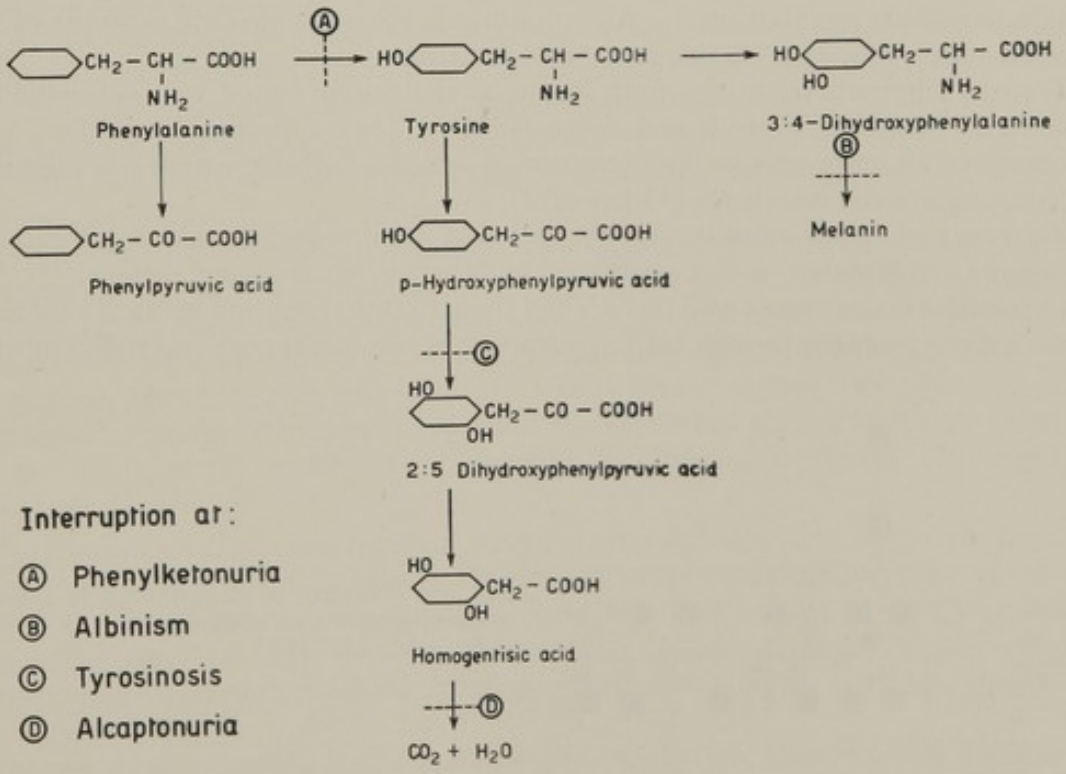


FIG. 64.—Phenylalanine-tyrosine metabolism in man. (*Based on Haldane J. B. S. (1941). New Paths in Genetics. London; Allen and Unwin.*)

washing with soap. There is a greenish-brown coloration of the sebum secretion, primarily in the axilla, and of the cerumen. The cartilage of the nose and ears may show a brownish-blue pigmentation (*ochronosis*). Blue spots may also appear on the sclera, the conjunctiva, the cheeks, the gums, and even, at times, on the nails and the thenar and hypothenar eminences. Anatomically, ochronosis has been observed in the trachea, the vascular intima and the endocardium.

More serious complications—degenerative osteoarthritic lesions—may develop at about the age of 40 years. These primarily affect the vertebral column and the large joints, owing to the deposition of homogentisic acid in the articular cartilage (arthrotropic substance) and lead to diffuse rheumatic-like troubles.

The clinical diagnosis is based on the reducing properties of alkapton (homogentisic acid). The urine reduces Fehling's and Benedict's solutions, but gives negative results with Nylander reagent, the fermentation test and the polariscope, thus distinguishing it from diabetes. Pseudo-positive Wassermann reactions may be present.

Heredity.—Alkaptonuria was the first example of mendelian heredity demonstrated in man. In 1902, Sir Archibald Garrod recognized the familial occurrence of this disease, the high frequency of consanguineous marriages among the parents; he interpreted these phenomena as the expression of a recessive mode of transmission. Alkaptonuria also formed the basis for Garrod's conception of " inborn metabolic errors ", under which term he later also included cystinuria, albinism, porphyrinuria and pentosuria. To explain the altered metabolism in these diseases, Garrod put forward the hypothesis of the absence of an enzyme, determining the " failure of some step or other in the series of chemical changes which constitute metabolism ". Alkaptonuria is the most striking example of the limited action of a gene on one metabolic reaction.

Garrod's hypothesis of a single recessive mendelian factor was subsequently proved by Hogben, Worrall and Zieve (1931). They collected 45 families with 63 cases of alkaptonuria in the literature of which 13 sibships were the offspring of consanguineous marriages (43 per cent).

Garrod had called attention to the fact that alkaptonuria is more common in males than in females—a fact confirmed by Hogben, Worrall and Zieve (1931/32), who found a males excess of 2 to 1. They suggested that routine medical examination is more frequent in men (as for purposes of life insurance) and the condition

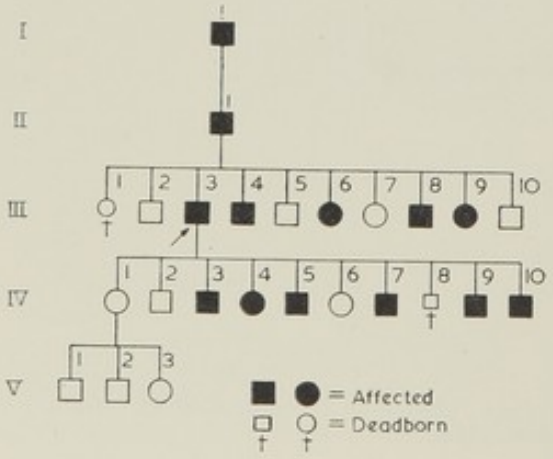


FIG. 65.—Pedigree of alkaptonuria in a Santo Domingo family. (*After Pieter, H. (1925). Pr. méd.*, **23**, 1310.)

is therefore more often discovered in them. It is, however, just as likely that the male excess is an example of sex-limitation in genetically determined affections.

The literature contains 5 cases of alkaptonuria with dominant transmission: Marshall (1887), followed up by Futcher (1898) and Osler (1902); Orsi (1899); Fromherz (1908); Umber (1914); Pieter (1925), of which one, that of Pieter, is beyond doubt, since the transmission covers 4 generations (Fig. 65). The pedigree of a large family with many consanguineous marriages and with 15 cases of alkaptonuria, recorded by Hall, Rawls and Child (1950), as an example of recessive inheritance, is better explained on the assumption of dominance. On rearranging the pedigree, the dominant transmission with three affected sibships of non-consanguineous parents, one of whom was likewise affected, becomes more evident.

The frequency of the anomaly has been estimated by Hogben and his colleagues as being $1:10^{6}$–10^{7}.

Phenylketonuria (phenylpyruvic oligophrenia)

Clinical aspects.—First described by Fölling in 1934, this metabolic disorder consists in a failure of the transformation of phenylalanine into tyrosine (*see* Fig. 64), probably due to an enzymatic deficiency. The disturbance is present from birth and is characterized by the elimination of phenylpyruvic acid, a substance which is never found in the urine of normal individuals. The ferric chloride test for phenylpyruvic acid (addition of a few drops of a 5 per cent solution to the previously acidified urine) produces a deep green colour.

There exists a close biochemical relationship with alkaptonuria, since both derive from a disorder of the aromatic amino acids (*see* Fig. 64). However, unlike alkaptonuria, in which there are no psychic or neurological repercussions, those affected by phenylketonuria always show mental retardation and definite neurological, pigmentary and constitutional peculiarities.

In about 60 per cent of cases, the mental level is that of idiocy; some 30 per cent are imbeciles, while the rest attain a somewhat higher mental grade. Epileptiform seizures are frequent.

Neurologically, one frequently finds hyperkinesias and synkinesias and other extrapyramidal signs manifesting themselves by a pithecoid attitude, muscular rigidity (rigid walk with propulsion—cog-wheel phenomenon), hyper-reflexia, choreo-athetotic movements of the fingers and other digital mannerisms (Fig. 66*a*). In general, blond, blue-eyed individuals predominate among the patients. The skin shows a tendency to hyperidrosis and is, in addition, very sensitive to exposure to the sun's rays, which easily provoke an intense erythema. Eczematous affections are frequent.

Pathogenesis.—The relationship between phenylketonuria and the psycho-neurological syndrome is obscure. On the basis of encephalographic examinations Jervis (1937) assumed a frontal lobe atrophy, and suggested that the extra-pyramidal signs of these patients represent a functional predominance of the extrapyramidal system resulting from an insufficiency of the regulatory effect of the cortex.

Of the three anatomical examinations recorded, two, those of Penrose and of Coquet and his colleagues, did not reveal any specific pathological alterations,

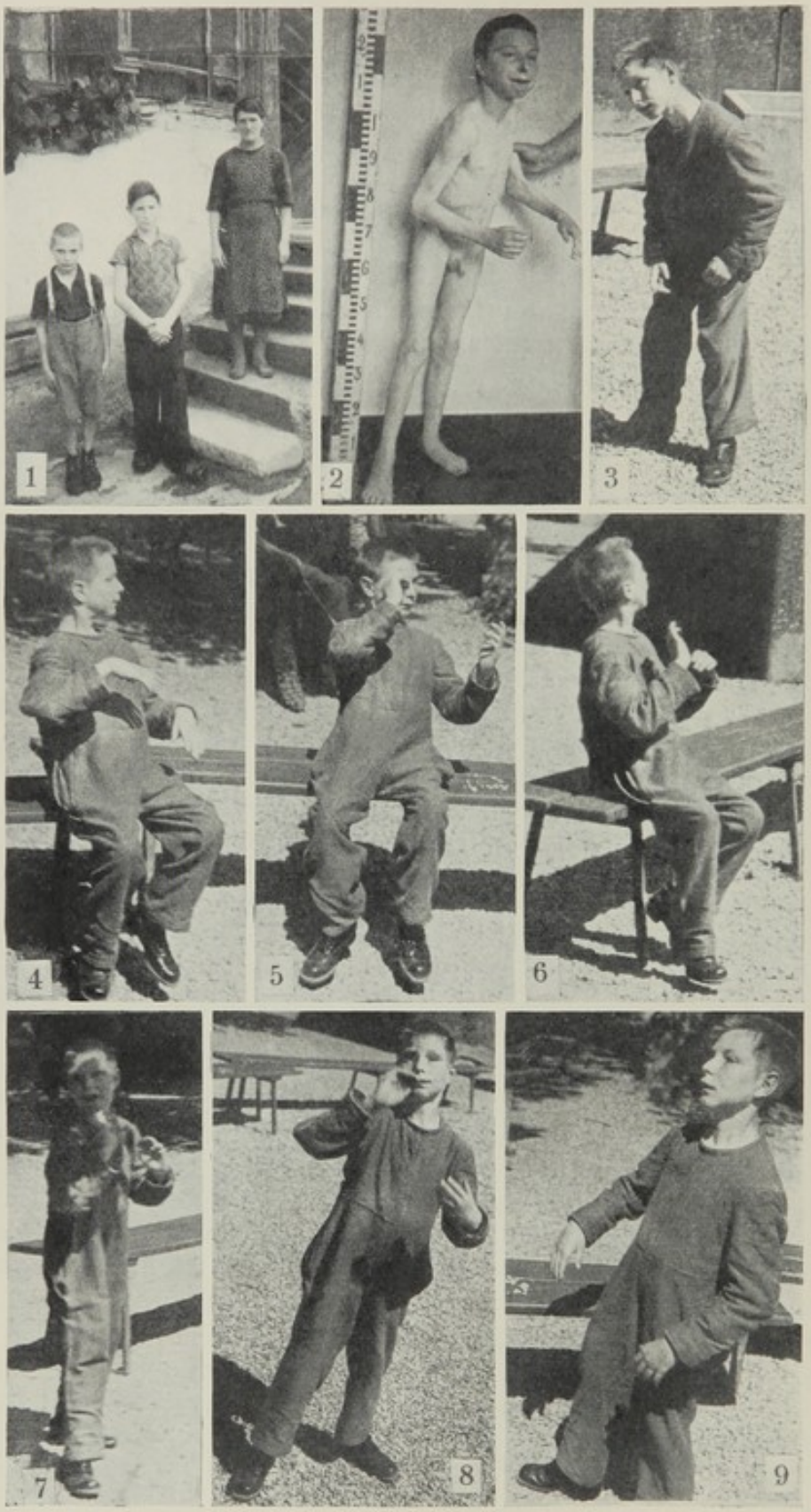
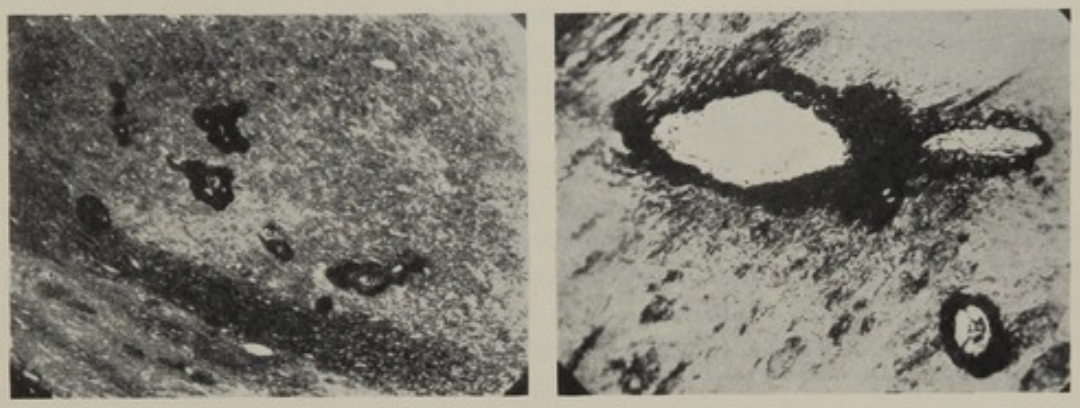
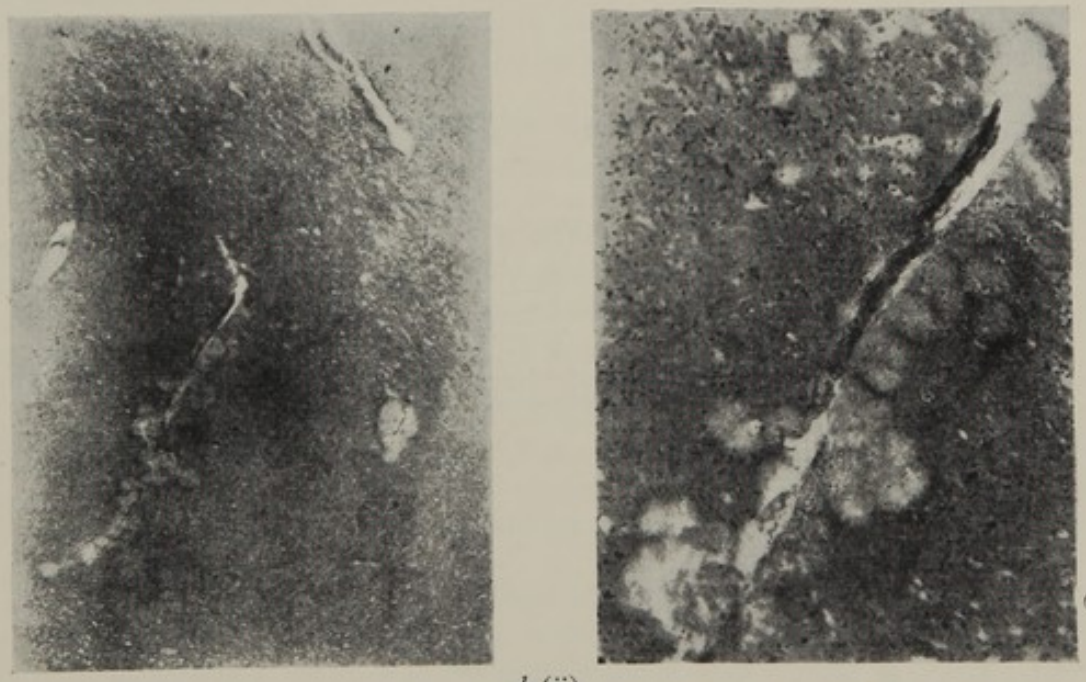


FIG. 66*a*.—Phenylpyruvic idiocy with dwarfism in a 20-year-old patient. The parents were consanguineous and Swiss gypsies. (1) Mother and 2 deaf mute brothers; (2) the patient at the age of 20 years showing infantilism (height 4 feet 3 inches); (3) typical pithecoid attitude; (4–6) different phases of hyperkinetic movements of the fingers; (7–9) different phases of rhythmic hyperkinesia of the hands and body. (*After Klein, D. (1946). Mschr. Psychiat. Neurol*, **111**, 275.)

but the third, that of Klein (1946) and Sander (1951), showed well-marked pathological changes, which could be correlated with the clinical picture (Fig. 66*b*). Macroscopically, there was a hemiatrophy of the left hemisphere. The main lesions were found in the left extrapyramidal centres (lentiform nucleus, subthalamic nucleus, substantia nigra, red nucleus, dentate nucleus) consisting of diffusely scattered perivascular areas presenting a flaky structure (particularly stained by Spielmeyer's myelin sheath stain) and vascular alterations resembling an *état criblé*. The marked idiocy of this patient could not be sufficiently explained by the morphological modifications of the brain and were probably secondary to



b (*i*)



b (*ii*)

FIG. 66*b*.—Post-mortem examination of the preceding case by G. Sander (1951) at Professor Minkowski's Institute. (*By courtesy of Professor Minkowski.*) (*i*) Putamen (Spielmeyer's myelin sheath stain; magnified 33 and 86 times respectively). Dilated perivascular spaces of Virchow-Robin, around which are diffusely scattered areas, particularly stained and presenting a flaky structure. (*ii*) Thalamus opticus (Van Gieson stain; magnified 27 and 81 times respectively). Flaky areas around one vessel.

the metabolic disturbances. The dwarfism in this case was apparently related to the severe hypophyseal lesions that were present.

Heredity.—The high frequency of familial cases and of consanguineous marriages among the parents of the patients (5 per cent, Jervis (1939); 14 per cent, Folling, Mohr and Rund (1944); 10 per cent, Munro (1947)) suggests simple recessive inheritance (Fig. 66*c*). (There is the exception of two families quoted by Jervis (1937) in which the mother was also affected.) Simple recessive inheritance is borne out by Munro's statistical analysis, based on 46 families with 85 cases among 261 sibs, which showed an incidence of 25·7 per cent affected. The proportion of phenylketonurics among feeble-minded patients in different countries is now less than 1 per cent. The frequency of this disease in the population as a whole is estimated to be about 1:25,000 for the United Kingdom (Munro,1947) and for the United States of America (Jervis, 1937).

Tyrosinosis

In 1932, Medes described a new anomaly of tyrosine metabolism, tyrosinosis. A patient aged 49 years, who clinically presented a myasthenia gravis, had a daily urinary elimination of 1·6 grammes of p-hydroxyphenylpyruvic acid, a reducing, non-glucidic substance. The family history of the patient was negative. It is probable that the heredity of this affection is recessive. The disease must be

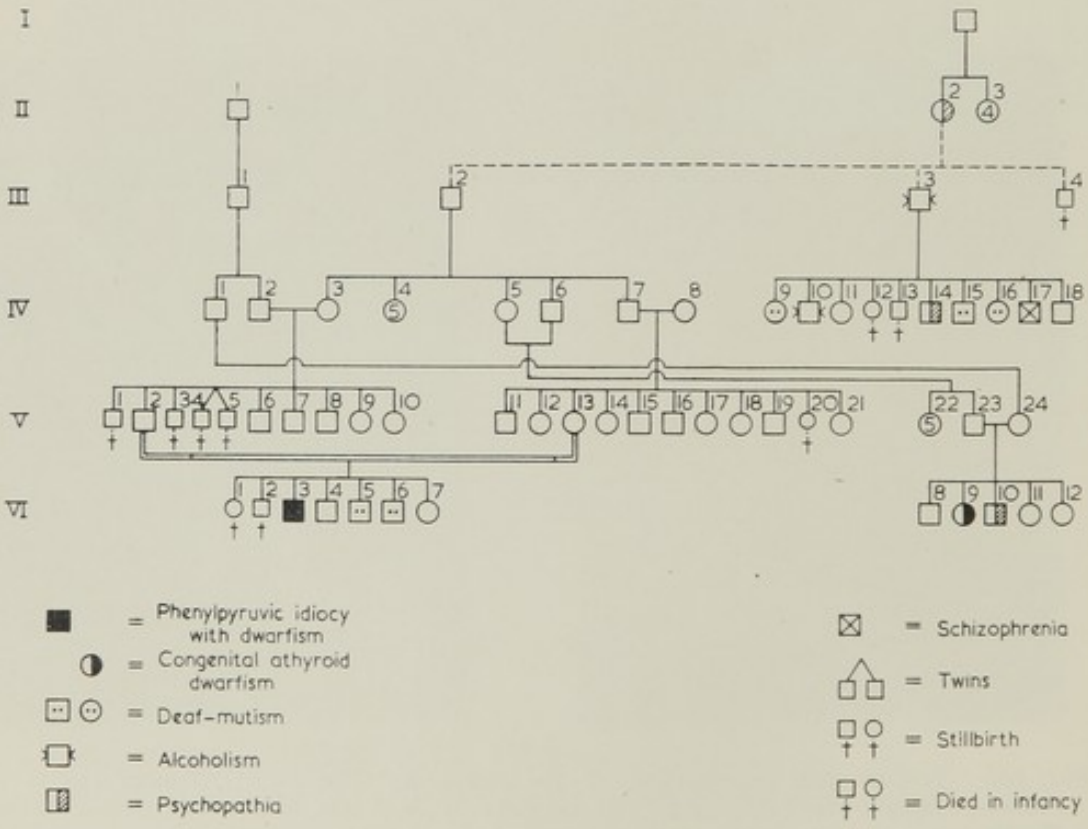


FIG. 66*c*.—Pedigree of a case of phenylpyruvic idiocy with dwarfism in a Swiss gipsy family. Parental consanguinity. (*After Klein, D. (1946). Mschr. Psychiat. Neurol.*, **111**, 273.)

extremely rare since 26,000 reducing urines did not reveal a second case (Blatherwick). Tyrosinosis is determined by the failure of the oxidation of p-hydroxyphenylpyruvic acid, a normal intermediary product of tyrosine metabolism, probably due to an enzymatic defect.

Albinism

Clinical aspects.—Generalized albinism is characterized by an absence of pigment, especially in the skin, hair and eyes. Diminution of vision is not due merely to the dazzling resulting from the absence of ocular pigment, but mainly to hypoplasia or aplasia of the fovea centralis.

According to Bloch and others, melanin is formed in the basal layers of the epidermis. These cells, called melanoblasts, contain an oxydizing enzyme, dopa-oxydase, which transforms the uncoloured chromogene (a substance very close to tyrosine and dioxyphenalalanine, " dopa ") into melanin. The process of pigmentation begins during the last months of embryonic life, when the first pigment granules appear, and finishes after birth. Embryologically, the melanoblasts are derived from the neural crest.

Generalized albinism is assumed to be due to the absence of a principal chromogenic factor (conditional factor C), resulting in a complete inhibition of the process of pigmentation. Partial albinism is said to be brought about by a functional insufficiency of the oxydizing enzyme, and is traceable to a deficiency of other pigmentary factors (factors of distribution, of intensity, and so on (Cuénot)). It is supposed that these factors determine the degree of production of this enzyme and its mode of action on the chromogene.

Associated anomalies.—Albinism, both generalized and partial, is often combined with other anomalies—in particular with deaf-mutism, oligophrenia, epilepsy, and polydactyly.

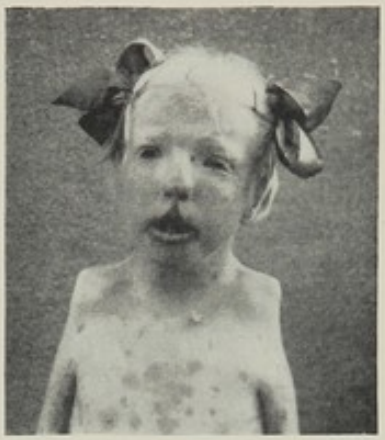
Albinism complicated by labyrinthine deafness is a well-known occurrence among animals (Sichel, Darwin and others). Albinism of the fur and deafness are often found in conjunction with a blue iris (observed primarily in cats and dogs) owing to the absence of pigment in the stroma of the iris. Ruth Bamber's extensive study of the relationship between the pigmentation of the fur, the stroma of the iris and the hearing capacity showed them to be closely related and due to a single causal factor.

In human pathology, this triad is extremely rare (Hammerschlag, Van Gilse). An unusual case showing this clinical complex, and in addition many other congenital malformations, is illustrated in Figs. 67 *a–e*. This polymorphic syndrome involving ectodermal and mesodermal organs illustrates that in human pathology anomalies of pigmentation may indicate severe morphological disorders (*see also* Fig. 52).

Heredity.—There exist in the literature at least 700 pedigrees and almost all furnish proof that generalized albinism is transmitted as a recessive trait (Fig. 68). The frequency of this anomaly in the population is estimated at 1 : 10,000–20,000. The highest incidence has been found among the San Blas Indians of Panama (7:1,000; Harris, 1926).

The recessive nature of albinism is confirmed by the great frequency of consanguinity, estimated as high as 20–30 per cent. There are several recorded instances of monozygotic twins, both presenting the affection (Fig. 69).

a



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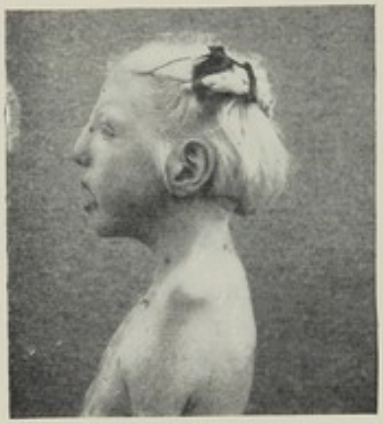

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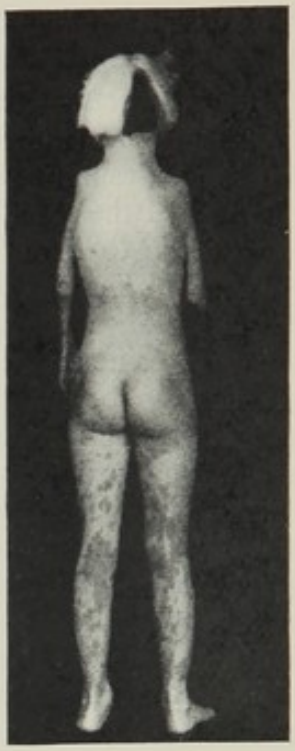

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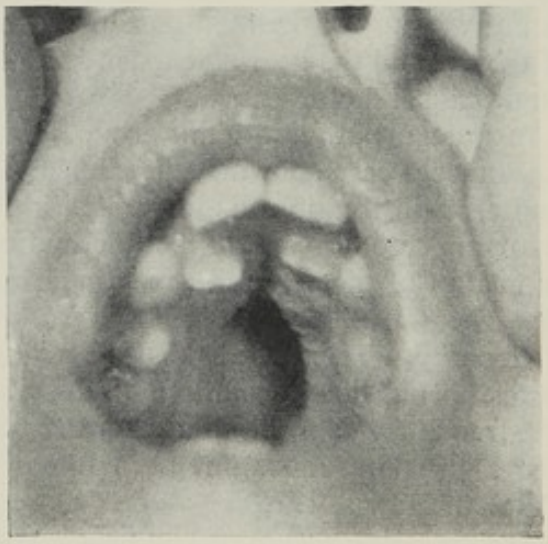

e

FIG. 67.—Partial albinism with multiple defects in a girl aged 10 years. (*a*) General view showing the following anomalies: partial albinism with blue irides and deaf mutism; blepharophimosis, widening of the root of nose and hypertrichosis of the eyebrows; deformity of the skull (absence of the naso-frontal angle and retrognathia); amyoplasia and rigidity of the joints of the upper limbs (the right is fixed in a flexed position and the left in an extended position); and webbed axillary folds and syndactyly of the fingers. (*b*) Peculiar facial expression resulting from the blepharophimosis (operated on), primitively formed nose with widening of the root and brownish circle around the mouth. Note the hypertrichosis of the eyebrows converging at the bridge of the nose. (*c*) Bird-like form of the skull owing to absence of the naso-frontal angle and retrognathia. (*d*) Depigmentation of the skin above the lumber region. Reddish triangle of hair in the occipital region. (*e*) Faulty implantation of the teeth, the superior incisors being in two rows; ogival palate. (*After Klein, D. (1950). Helv. paediat. acta*, **5**, 38.)

In albinism limited to the eye (*ocular albinism*) as in generalized albinism, there is hypoplasia of the macula; nystagmus is always present. This variety is transmitted as a sex-linked recessive (Vogt).

In partial albinism or " leucism " (Fig. 67), there are usually depigmented spots on the forehead, the nape of the neck and near the linea alba. At times, leucism is manifested only by a white lock of hair. The inheritance of this anomaly follows the dominant rules.

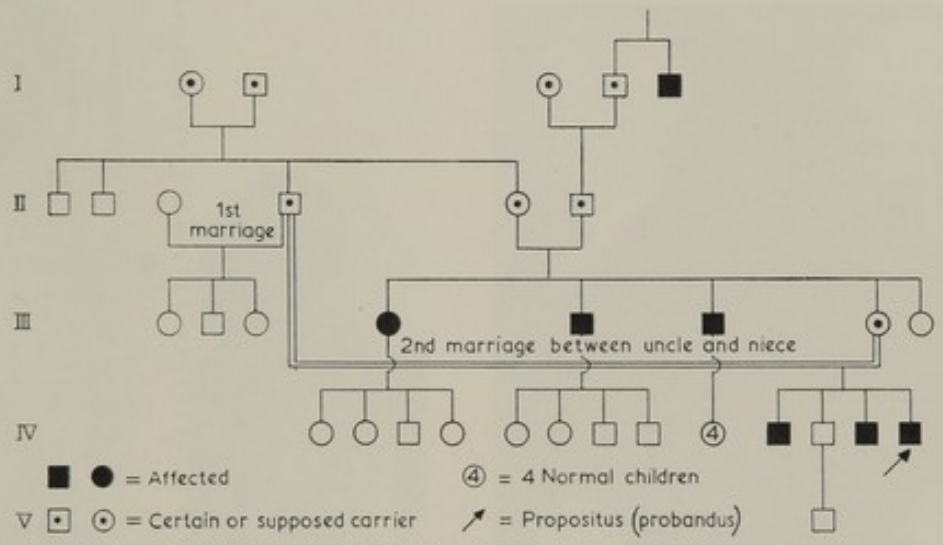

FIG. 68.—Generalized albinism. Manifestation of recessive albinism in two successive generations (" pseudo-dominance ") as a result of backcross. (*After Franceschetti, A. and Klein, D. (1948). Lehrbuch d. Augenheilkunde*, p. 76. Basel; Karger.)

Cystine diathesis (cystinuria)

Clinical aspects.—Cystine, and its higher forms (cysteine, homocysteine, methionine), are sulphur-containing amino acids. Cystine is found in many proteins, particularly in the keratines, serum albumin and insulin. Cystine and cysteine play an important role in the cellular oxidation-reduction processes.

In cystinuria, cystine is eliminated in the urine as a crystallized sediment, in a characteristic hexagonal form, instead of being metabolized to sulphates, sulphonic ethers and neutral sulphur. In addition, cystinuria may be accompanied by the elimination of other, non-sulphurous amino acids (lysine, arginine, ornithine) and of diamines (cadaverine, putrescine).

Since the ingestion of cystine does not increase the amount of this substance in the urine of a cystinuric, whereas the amount does increase after the administration of cysteine and methionine, the pathological factor must be sought at an earlier stage of metabolism and, in particular, at that of the transformation of methionine or cysteine.

Cystine diathesis shows great clinical variability. (1) Cystinuria in the adult may pass unnoticed or may result in the formation of urinary calculi. It is this form of cystine lithiasis which often necessitates a surgical intervention that was described by Wollaston in 1810.

(2) In the child, this affection is usually serious. It appears in the form of renal rickets with inhibition of growth (Fig. 70), signs of bone dystrophy, and

degenerative renal lesions (tubular nephrosis, glomerulo-nephritis and interstitial nephrosclerosis). Finally, the excess of cystine together with the renal insufficiency lead to the retention of cystine in the form of crystalline deposits in the internal organs, primarily the reticulo-endothelial system. The general condition of these children deteriorates progressively and they finally succumb to uraemia.

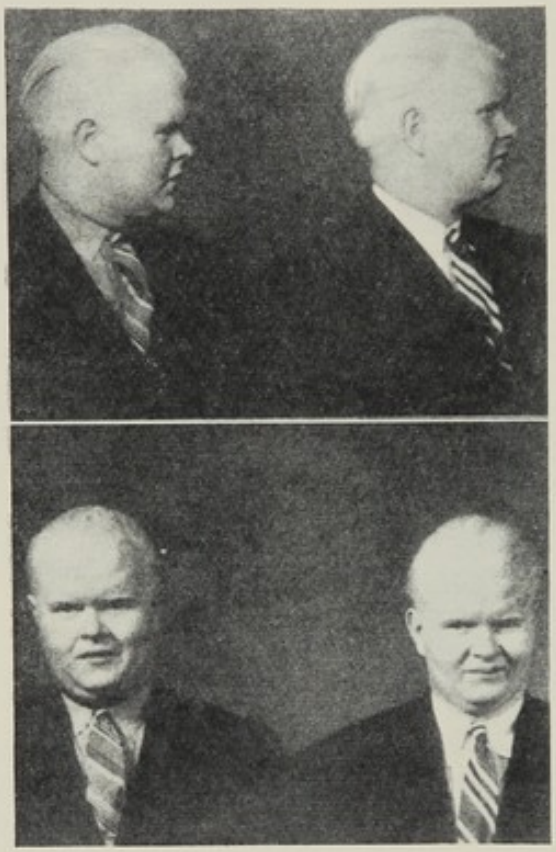

FIG. 69.—Generalized albinism in monozygotic twins. (*Rife, D. C., Schoenfeld, M.D., and Hunstead, M. (1946). J. Hered.*, **37**, 3.)

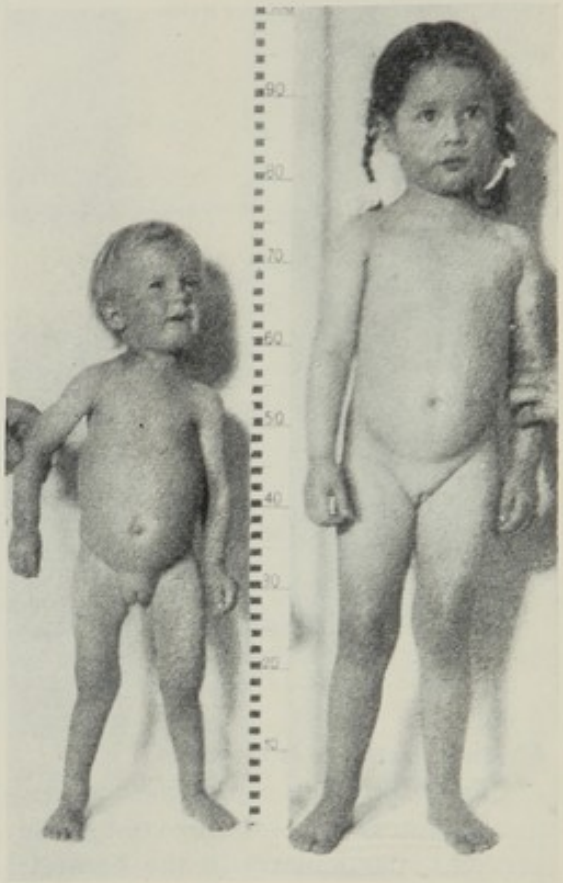

FIG. 70.—Cystine storage disease with dwarfism in a 4-year-old girl (at the right, a normal girl of the same age). (*Case published by Fanconi, G. (1945). Helv. paediat. acta*, **1**, 183. Fig. 9. *Waser, P. (1945). Helv. paediat. acta*, **1**, 206.) (*By courtesy of Professor Fanconi.*)

It is likely that the disease of Fanconi-Debré-de Toni (dwarfing of stature with renal rickets, hypophosphataemia, albuminuria, aminoaciduria and glycosuria), appearing in young infants, is not an autonomous affection, but a syndrome related to a serious cystine diathesis.

Laboratory examinations frequently fail to reveal cystine crystals in the urine, though they may be found in the conjunctiva, the cornea, the iris, and the vitreous body by means of the slit-lamp, or in the bone marrow by sternal puncture.

Heredity.—Dominant inheritance has been recorded by Abderhalden and Kaufmann (Fig. 71); by Hottinger (irregular dominance); by Cohn and by van Creveld. A recessive one, with a high frequency of familial cases is shown in

115 familial cases among 200 cases in the literature (Renander, 1941) and parental consanguinity was noted in some (Thin and Robson, Pache, Schleicher and Ostertag, Fanconi, de Toni). The observations of Abderhalden and Kaufmann (Fig. 71) and Hottinger and of Roulet are important in that they demonstrate the relationship between a grave cystine storage disease in one generation and a slight cystinuria in the preceding generation. These two forms occurring in the same family prove to be phenotypic variations of the same fundamental process.

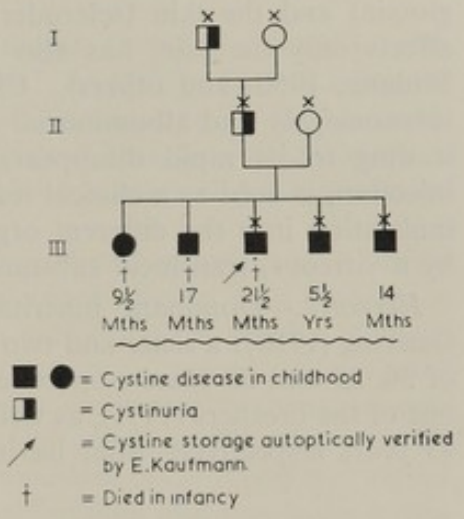

FIG. 71.—Pedigree of cystine disease in childhood. (*After Abderhalden, E., and Kaufmann, E. (1903). Z. phys. Chem.*, **38**, 557.)

The genotypic determination of cystine disease is also demonstrated by its concordant manifestation in identical twins (Kretschmer, 1916; Schleicher and Ostertag, 1935). The case of Schleicher and Ostertag is of further interest because of the coexistence of the condition with optic atrophy, which was concordantly present in the twins as well as in their father; in this family other defects (epilepsy, psychopathy, suicide, diabetes) were frequent. The combination of cystinuria and retinitis pigmentosa was reported by Brooks, Heasman and Lovell (1949), and by Linder, Bull and Grayce (1949) in a case of Fanconi syndrome. Cystinuria in 2 sisters was described by Frankenthal (1936), one of the sisters being also affected by macular degeneration. In the case of Umber (1914), both parents and relatives of the mother had diabetes.

The high incidence of affected sibs in certain families (as in Ullrich's observation, 7 affected sibs in a family of 8) suggests the possibility of a dominant mode of inheritance. This hypothesis of an irregular dominance in certain cases could be corroborated by a more rigorous application of biochemical tests among the relatives of the patients, which might eventually disclose a latent cystinuria among parents and other members of the family. Thus, the frequency of cystinuria in the general population, formerly estimated at about 1: 15,000–35,000 individuals, was raised to 1: 585 (Lewis, 1932) and to 1: 380 (Patch, 1934) when finer tests were used in more than 10,000 individuals in each of these investigations.

It would appear that the gene is very variable in its penetrance and its expressivity. It may have dystrophic repercussions, particularly on the growth of the skeletal system, according to the stage of development at which the factor intervenes and its intensity and quality.

Amyloidosis

Generally, deposits of amyloid are the consequence of a chronic, suppurative infection (osteomyelitis, chronic tuberculosis, bronchiectasis, syphilis, malaria, Hodgkin's disease, and so on).

Primary generalized amyloidosis (atypical amyloidosis, Lubarsch-Pick) is a disturbance of protein metabolism characterized by deposits of a pathological albuminoid in the vascular walls and the pericapillary tissues of different organs: liver, spleen, kidneys, adrenal, intestine, testicle and, at times, the tongue (macroglossia) and the skin (scleroderma, amyloid tumours). An amyloidosis, which affects only the skin, has also been described (Miescher, 1945; Bizzozero and Midana, 1950; and others). Clinically, amyloidosis manifests itself by hepatosplenomegaly and albuminuria. The property of amyloid to absorb congo red, leading to its rapid disappearance from the circulation after an intravenous injection, is used as a clinical test (Bennhold's test). Anatomically, one notes an infiltration into the different organs, in particular the liver, spleen and kidneys, by a vitreous, translucid substance which is coloured brown by iodine solutions.

Heredity.—Dominant inheritance is suggested by the family described by Ostertag (1950): a sister and two brothers died of atypical amyloidosis at the ages of 36, 35 and 39 years respectively (*see* Fig. 72; III/4, 5 and 6). The daughter of one of the brothers (IV/1), as well as their mother (II/4), died at the ages of 18 and 43 years respectively, after having presented similar clinical symptoms.

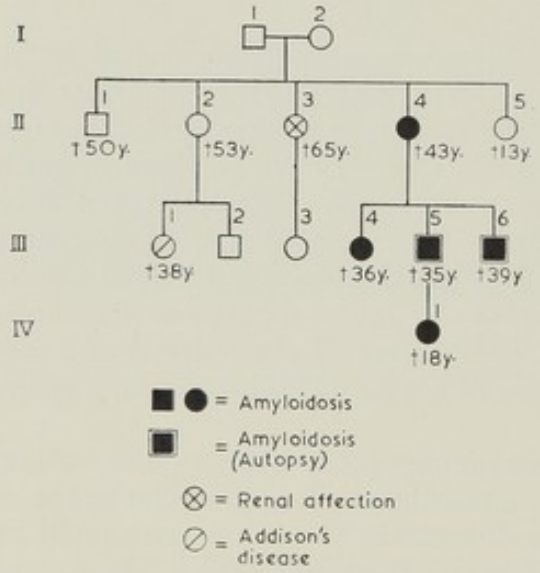

FIG. 72.—Pedigree of familial amyloidosis. (*After Ostertag, B. (1950). Z. mensch. Vererb. Konstitlhre*, **30**, 105.)

DISTURBANCE OF PURINE METABOLISM

Gout (gouty arthritis)

Clinical aspects.—Gout is a disturbance of purine metabolism. Recurrent acute articular affections are accompanied by the precipitation of urates, the formation of degenerative joint lesions and tophi in the advanced stage.

The first attack of gout usually appears between the ages of 26 and 30 years. The attack takes the form of painful articular crises of which the initial localization is often the metacarpo-phalangeal joint of the big toe (podagra). During these

crises, the uric acid in the blood is increased. At the end of the crises, the uric acid concentration diminishes in the blood, and augments in the urine. In chronic gout, there is pronounced, often deforming, osteoarthropathy. The synovial sheaths of the tendons (especially Achilles' tendon) and the aponeuroses may also be involved. The tophi, located primarily on the border of the helix and in the articular and peri-articular regions, are pathognomonic of gout. Nephrosclerosis with arterial hypertension, and various ocular and otological complications may occur.

Heredity.—Gout generally follows the dominant form of heredity with penetrance and expressivity that are often irregular. As early as 1819, Scudamore noted 331 hereditary cases out of 522. Garrod, Lichtwitz, and Le Gendre were each able to follow the male ascendancy in a case of gout back for 300 to 400 years.

Gout is an example of sex-controlled heredity with a marked predilection for men (90–95 per cent).

Since 1915, many biochemical analyses of the unaffected members of a family afflicted with gout have shown that the uric acid concentration may be high in close relatives of the patients, without clinical manifestation of the disease. Garrod (1931) has stressed that a dominant transmission of gout is quite regular if one takes into account the hyperuricaemia—a view confirmed by the systematic biochemical and genetic investigations of Smyth, Cotterman and Freyberg (1948) (Fig. 73). They showed that the concentration of uric acid in the blood was higher in the male than in the female members of affected families, and that in each case of gout, at least one parent was hyperuricaemic, as were also about 50 per cent of the sibship. Only 10 per cent of those with hyperuricaemia showed clinical manifestations of gout. There were as many cases of transmission of the condition by women as by men. They held that the greater manifestation in males is due not only to the higher physiological concentration of uric acid in men, but also to the stronger penetrance of the pathogenic gene in men. They give the average frequency of gout in the population as 88: 100,000 and the frequency of heterozygote carriers as 0·88 per cent.

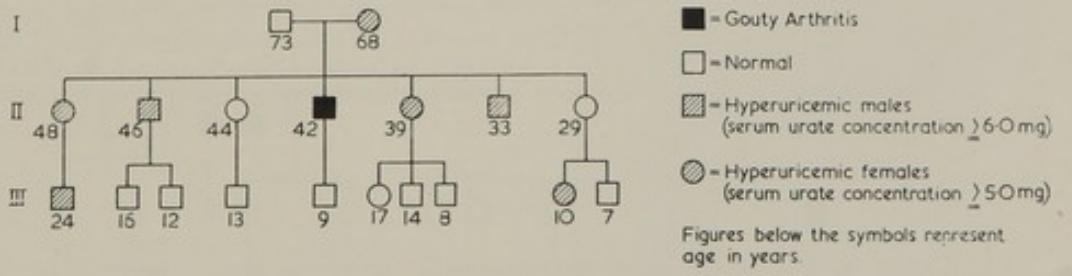

FIG. 73.—Pedigree of gouty arthritis. (*After Smith, C. J., Cottermann, C. W., and Freyberg, R. H. (1948). J. clin. Invest.*, **19**, 645.)

LITHIASIC DIATHESES

Were our knowledge of the heredity of lithiasis more advanced, we might be able to determine whether the formation of various kinds of concretions is due to a general hereditary tendency towards stone formation or—as seems more probable

at present—whether the different deposits of urates, phosphates or oxalates are the result of specific hereditary factors.

Renal calculi arise from a disturbance in the crystalloid and colloid equilibrium of the urine. Malformations of the kidney (hypoplasia, horse-shoe kidneys) favour the formation of calculi, as perhaps do geographical factors, for lithiasis is most common in tropical and subtropical countries. Both sexes are subject to the disorder. Affected persons often show a neuro-vegetative lability.

The hereditary influence in lithiasis is clearly revealed only in cystinuria (*see* page 183 and Fig. 71). In the other lithiasic diatheses, the role of heredity is less certain: Romanow (1935) observed renal calculi in dizygotic twin sisters and in their father. Mingers (1945) has recorded the presence of renal lithiasis in a pair of female twins.

Uric acid lithiasis

Essential uric acid lithiasis is to be distinguished from the secondary lithiasis of gout, although the association of the two affections has been described. It is rare for a young lithiasic to be later affected with gout whereas, on the other hand, uric acid calculi almost always appear with tophi in the case of gout. Crises of renal colic alternating with attacks of gout have been observed.

There are no genetic studies of this type of lithiasis.

Phosphaturia

A pair of twins, probably identical, with a concordant calcariuria and phosphaturia, have been observed (von Domarus, 1917).

Oxaluria

Dominant transmission of a sex-influenced character is shown by an extensive pedigree (Fig. 74) which includes four generations, comprising 15 individuals (Gram, 1932). Except for two doubtful cases, the affection manifested itself

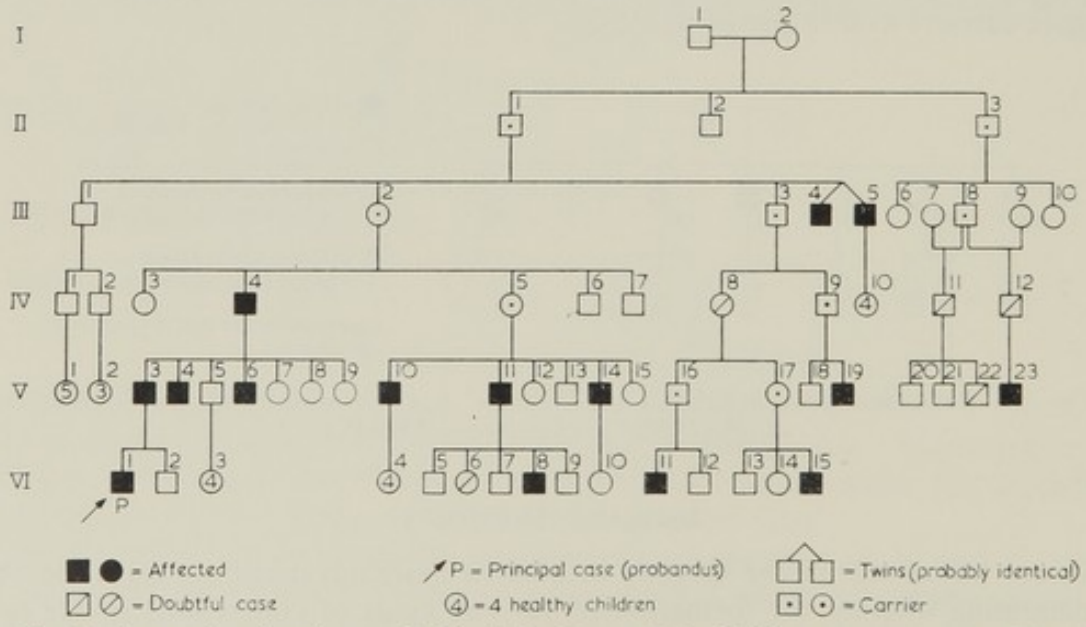

FIG. 74.—Pedigree of oxalic urinary calculi. (*After Gram, H. C. (1932). Acta med. scand.*, **78**, 268.)

only in males whereas the transmission took place through both sexes. This pedigree also shows concordant manifestation in a set of twins, probably identical.

Discordant manifestation of urolithiasis (calcium oxalate) has been described by Ostertag and Spaich (1936) in the case of monozygotic twins aged 54 years. In this case, there was also a discordance in the appearance of a heterochromia present only in the twin exempt from oxaluria.

DISTURBANCE OF CARBOHYDRATE METABOLISM

Glycogen storage disease (von Gierke)

Clinical aspects.—This is characterized by an enormous accumulation of glycogen, primarily in the liver, the kidneys (glycogenic hepato-nephromegaly) and the heart (cardiomegaly). These glycogen accumulations are remarkable for their stability and cannot be used for the intermediary sugar and lipid metabolism. The inability of the organism to mobilize the glycogen is probably due to the inhibited action of a diastase enzyme (amylase) in the hepatic cells.

The abnormal fixation of glycogen in the parenchymal cells of different organs

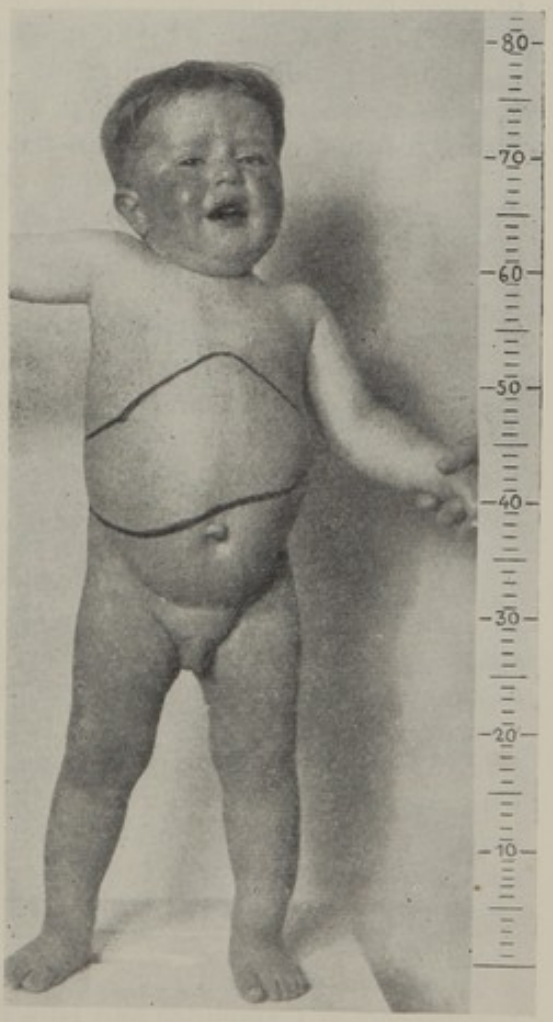

FIG. 75.—Glycogen storage disease in a 3¾-year-old boy with consanguineous parents. (*Published by Fanconi, G., and Bickel, H. (1949). Helv. paediat acta*, **4**, 359. Case 1, Fig. 5.) (*By courtesy of Professor Fanconi.*) Dwarfing of stature, fat red cheeks, protruding abdomen with umbilical hernia, compensatory lordosis.

results in a sugar deficit manifested by (1) a hypoglycaemia with hypersensitivity to insulin, a resistance to adrenaline and an abnormal blood sugar curve; and (2) disturbances of lipid regulation through compensatory mobilization of the fats characterized by hypercholesterolaemia and ketonuria.

The glycogen disturbance appears at an early age and shows the following clinical symptoms: a characteristically large and protruding abdomen, infantilism with retarded static, skeletal and, sometimes, also psychic, development. The patients' moon-shaped face with a doll-like expression suggests a hypophyseal obesity (Fig. 75). Their carriage is that of a pregnant woman. The prognosis for children affected with the hepatomegalic form is fairly good although they are particularly susceptible to infections. On the other hand, the cardiomegalic form frequently ends in sudden death by heart failure. Diabetes is sometimes present.

Histological examination shows voluminous polygonal parenchymal cells, resembling vegetable cells, with a vacuolar cytoplasm containing large quantities of glycogen in the form of droplets, which is often accompanied by an overloading with fat.

Heredity.—Hanhart (1946), in a systematic genetic study in Switzerland, found a total of 24 cases of glycogenosis, of whom 11 were men and 13 women. Eight of these patients (one-third) died of their affection. The recessive character of this disease was shown by its familial occurrence (3 out of 5; 2 out of 4; and 2 out of 2 children, respectively). In one case reported by Ziegler, a woman married successively two brothers and in each marriage had an affected daughter. Hanhart found consanguinity of the parents in 3 of 18 families. Consanguinity of the parents was also present in one case of van Creveld and one of Goeters. The frequency of this condition in the population of Switzerland is estimated to be 1 : 280,000.

Idiopathic spontaneous hypoglycaemia

The hereditary occurrence of idiopathic hypoglycaemia was recognized by Weitz (1936) and Hartmann and Jaudon (1937). Anderson and his colleagues (1950) described fully two affected sibships. In the first sibship, there were three affected brothers, aged 5, 3 and 2 years respectively. They were all mentally retarded and showed mild ataxia and convergent strabismus. The hypoglycaemic syndrome consisted of tremor, clonic spasms, sweating, irritability and occasional convulsions. During these crises, the blood sugar fell to between 10 and 35 milligrams per cent. In the second sibship, hypoglycaemia was present in a brother and sister aged 7 and 2 years respectively, as well as in a cousin (the 3-year-old daughter of a maternal uncle). Only the brother was mentally retarded. His hypoglycaemia, already manifest during the first year of life, was practically constant except for rare remissions. On the other hand, the cousin was subject to intermittent crises with generalized convulsions. In the two children, a diet and subtotal pancreatectomy had no notable effect upon the hypoglycaemic crises, but treatment with adrenocorticotropic hormone (ACTH) was most effective. The cousin's condition was improved by a diet rich in protein, normal in fat and poor in carbohydrate.

These two pedigrees suggest a recessive inheritance, a fact confirmed by the experiments of Cammidge and Howard (1937) on mice.

The Melituras

Renal diabetes (glycosuria)

Clinical aspects.—Renal diabetes is a benign congenital anomaly caused by a lowering of the level of the renal threshold. Clinically, it must be clearly distinguished from pancreatic diabetes since it is extra-insular in origin. It manifests itself by (1) glycosuria without hyperglycaemia and with a normal blood-sugar curve; (2) no tendency toward a progressive evolution or complications; (3) insulin-resistance; (4) practically no subjective symptoms (occasionally fatigue and acetonuria, but no coma); and (5) its frequent occurrence as a familial and hereditary disorder.

Heredity.—Many observations demonstrate the dominant transmission of renal diabetes in contrast to diabetes mellitus which is usually recessive. Von Mentzingen (1935) described a pair of identical twins both affected by renal diabetes and by schizophrenia. The father was also a renal diabetic.

Although the two diseases are clinically distinct entities, familial relationships have been noted between renal diabetes and diabetes mellitus. An intra-familial variability has been observed between these two conditions: there may be an alternation of these affections within the same generation (Johnsson, 1922; Hatlehol, 1924), or renal diabetes may appear in one generation, while diabetes mellitus appears in the preceding and succeeding generation, or *vice versa* (Holst, 1926). Falta (1937) described the combination of renal diabetes and Graves' disease.

Galactosuria

Clinical aspects.—Idiopathic galactosuria (galactosaemia) is a rare metabolic anomaly appearing in infants. It is the result of an inability to convert galactose, a component of milk-sugar, into glycogen, probably owing to an hepatic enzymatic dysfunction. The galactosuria disappears as soon as milk-sugar is removed from the diet. Dextrose and fructose tolerance remain normal. Only 16 cases of essential galactosuria have been described up until 1950 (Bell and his colleagues).

Unlike fructosuria and pentosuria, galactosuria is often accompanied by severe clinical symptoms, such as failure to gain weight or to grow, hepatomegaly, jaundice, diarrhoea, vomiting, albuminuria, and zonular cataract.

The counterpart of the cataract produced experimentally in the rat by galactose feeding has been observed clinically by Bruck and Rapoport (1945), and Greenman and Rathbun (1948) and others. In the latter case there was almost complete regression of the cataract after the elimination of galactose from the diet. The hepatomegaly is caused primarily by a fatty infiltration followed by secondary degenerative alterations in cirrhotic form. Correct diagnosis of galactosuria is important, since the elimination of lactose from the diet may produce a regression of the clinical manifestations which, otherwise, have a serious prognosis.

Heredity.—Familial observations have been reported by Göppert (1917), Boer (1932), Bell and his colleagues (1950), Townsend, Mason and Strong (1951), Donnell and Lann (1951). Fanconi (1933) described a 9-year-old boy demonstrating an extreme intolerance for galactose associated with a zonular cataract and von Recklinghausen's neurofibromatosis. The child also presented a muscular hypotonia. There were no signs of a hepatic lesion. His intelligence and physical development were normal. Two sisters were affected with zonular cataracts and

another sister and the mother presented a neurofibromatosis. The grandfathers of the parents were brothers.

Fructosuria (laevulosuria)

Clinical aspects.—In essential fructosuria there is a defective conversion of fructose into glycogen. The amount of fructose excreted in the urine is always directly proportional to that which is ingested (about 13 per cent). The anomaly is important because of the possibility of its being confused with diabetes mellitus. Fructose is a reducing and laevorotatory sugar, which necessitates special tests for its detection.

The anomaly is harmless and only occasionally shows a few non-characteristic symptoms, such as fatigue and neuralgia. About 55 cases had been described up to 1942 (*see* Lasker, 1941; Sachs, Sternfield and Kraus, 1942).

Heredity.—Lasker (1941) analysed 40 cases collected from the literature and added 7 new cases. The latter occurred in 5 families of which 4 were consanguineous. The familial manifestation and the high frequency of consanguineous marriages speak in favour of a simple recessive transmission. The incidence of the affection is estimated as 1: 130,000. There is no racial predilection. In one case (Soisalo, 1933), a mother and daughter were affected.

The family history of such patients rather frequently mentions cases of diabetes mellitus, which suggests a genetic relationship between the two affections.

The pentosurias

Pentosuria is a congenital anomaly in which individuals excrete the pentose type of sugar. The anomaly is without clinical importance except that it might be erroneously diagnosed as diabetes mellitus since the pentoses reduce copper solutions.

There are two forms of essential pentosuria, (1) the excretion of l-xyloketose, and (2) the excretion of dl-arabinose.

Lasker and Enklewitz (1936) made an extensive clinical and genetic study of xyloketosuria based on 37 personally observed cases in 20 families. Their investigations provided evidence of recessive heredity. They support their findings by the frequency of familial incidence with absence of the anomaly in the parents. In the one exception, in which the patient's mother was also affected, it was a case of pseudo-dominance since the parents were first cousins.

The proportion of affected to non-affected in 10 families (on the reduced sibship method) was 8 : 30 (= 27 per cent $\pm$ 7·2) which corresponds to the expected ratio for recessivity. There was a preponderance of males (119 males; 51 females) which may, in part, be due to external reasons such as detection by life insurance examinations. Those affected with l-xyloketosuria were almost exclusively of Jewish origin whereas there does not seem to be a racial predilection for arabinosuria.

The frequency of pentosuria among the general population is estimated as 1: 50,000 (Blatherwick, cited by Lasker and his colleagues).

The two familial cases of dl-arabinose described by Cammidge and Howard (1926) (a father and son and an uncle and nephew) indicate a dominant heredity. Dominance is also shown in the pentosuric family observed by Jones and Nissler

(1925; 3 affected generations) and by Macumber (1949; a father and 2 of 3 sons affected). Unfortunately the type of pentose was not examined in the latter publication.

It has not as yet been established whether the occasional occurrence of diabetes mellitus in families affected by pentosuria, to which af Klercker (1904) and Garrod (1908) already called attention, are due to a fortuitous coincidence or correspond to a genetic relationship.

Diabetes mellitus

This is discussed on page 529.

DISTURBANCES OF LIPOID METABOLISM

The dyslipoidoses are a group of diseases characterized by pathological accumulations of lipoid substances in different organs, which may include the central nervous system and the eyes.

Gaucher's disease

The study of the lipoidoses began with the description in 1882 by the French dermatologist, Gaucher, of a " primitive epithelioma of the spleen", in which the splenic pulp had been entirely replaced by morphologically characteristic cells. This condition was first considered to be an isolated neoplastic hypertrophy of the spleen. It was later recognized as a systematized affection, characterized by a disorder of the intracellular metabolism of the reticulo-endothelial system (spleen, liver, lymph nodes, bone marrow) with storage of cerebrosides (kerasin) in the reticular cells and histiocytes.

Clinical aspects.—Two clinical forms can be distinguished: (1) a chronic benign form which begins during the second infancy and evolves extremely slowly; and (2) an acute, malignant form which begins in the infant and progresses rapidly.

In the *chronic form* (Fig. 76), there is a pronounced splenomegaly, a less considerable hepatomegaly, a bronze pigmentation of the skin—principally in those areas exposed to light—and a brownish thickening of the bulbar conjunctiva at the angles of the eyes (pinguecula). Sometimes, lesions of the skeletal system—especially the pelvis, vertebral column, the distal portion of the femurs—are marked features. Occasionally a secondary hypochromic anaemia, leucopenia and thrombopenia are prominent. A biopsy (sternal puncture, tibial bone marrow) reveals voluminous cells with eccentric nuclei and a reticular or fibrillar protoplasm containing vacuoles and infiltrated by kerasin.

The *acute, rapidly evolving form* is evident at about the fifth or sixth month of life and is characterized by a voluminous spleen and by the predominance of neurological signs resembling the symptoms of Tay-Sachs amaurotic idiocy: physical and mental retardment, apathy, somnolence, ataxia, hyper-reflexia, opisthotonus, hypertonia of the extremities, immobility and deviation of the eyes and spasmodic crises. This syndrome of " progressive cerebral decortication " ends in cachexia and death.

Heredity.—About 250 cases of Gaucher's disease have been published. Approximately one-third of these are of a familial nature (Groen, 1948). Cases over

2 generations have been observed by Rettig (1909: father and daughter); Bychowski (1911: father and 3 children); Fleischhacker and Klima (1936: 2 boys and their maternal aunt); Groen and Garrer (1948: 2 families with 2 generations affected, 1 family with 2 sibships affected in which the fathers were brothers). Anderson (1933) reported a family in which 5 sisters and probably their grandmother and 2 paternal great aunts were affected.

A recessive mode of inheritance, with 5 cases in 5 separate but closely related sibships in a Negro family, with the parents of 4 of the affected children being second cousins, was observed by Herndon and Bender (1950).

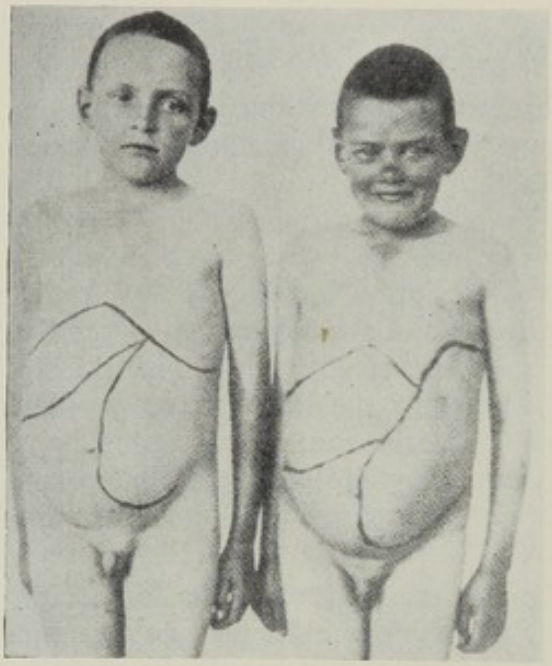

FIG. 76.—Gaucher's disease in two brothers aged 10 and 16 years respectively. (Post-mortem examination of the younger, on left.) (*After Ruppaner, E. (1940). Schweiz. med. Wschr.*, **70,** 584.) (*By courtesy of Dr. W. Ryffel, Kreisspital Oberengadin, Samedan.*)

The condition, therefore, seems to be transmitted generally, as a dominant characteristic, an hypothesis corroborated by the facts that the frequency of the disorder is sometimes very high within a sibship (for example, 6 affected sibs in the family of Brill and his colleagues, 1913; 5 out of 7 in the case of Woringer-Oberling, 1934) and that the proportion of those affected is about 40 per cent (Groen). Groen holds that there is anticipation and aggravation of the affection in the second generation.

There is no sex predilection (Atkinson—50 men to 53 women; Groen—64 men to 64 women). There seems to be a high frequency of stillbirths and abortions in these families.

Sternal puncture may sometimes determine the diagnosis in the latent or sub-clinical forms and thus permit exact statements as to the mode of transmission.

There seems to exist a form of *familial amaurotic idiocy with deposits of "Gaucherian" substance* (Bamatter and Sierro, 1949; Wildi, 1950). In the case published, the clinical, ophthalmoscopic and anatomico-pathological picture was pathognomonic of Tay-Sachs' disease, but a histochemical analysis showed a very high percentage of cerebrosides (kerasin). This case of "cerebral Gaucher's

disease " suggests some relationship between Gaucher's disease and amaurotic idiocy.

Niemann-Pick disease

Clinical aspects.—Niemann-Pick disease closely resembles the infantile form of Gaucher's disease, but runs a more rapid course to a fatal issue before the end of the second year.

Unlike Gaucher's disease the affection is not limited solely to the reticulo-endothelial system (liver, spleen, lymph nodes, bone marrow; Fig. 77), but invades ubiquitously both the parenchymal and mesenchymal elements of the organs (muscles, central nervous system, endocrine glands). The characteristic substance of Niemann-Pick disease is a lipid complex formed primarily of phosphatides (sphingomyelin). The typical histological elements are the Pick foam cells filled with lipoid droplets. The affection is rare (43 published cases by 1949, Didion) and shows a certain predilection for the female sex and for the Jewish race.

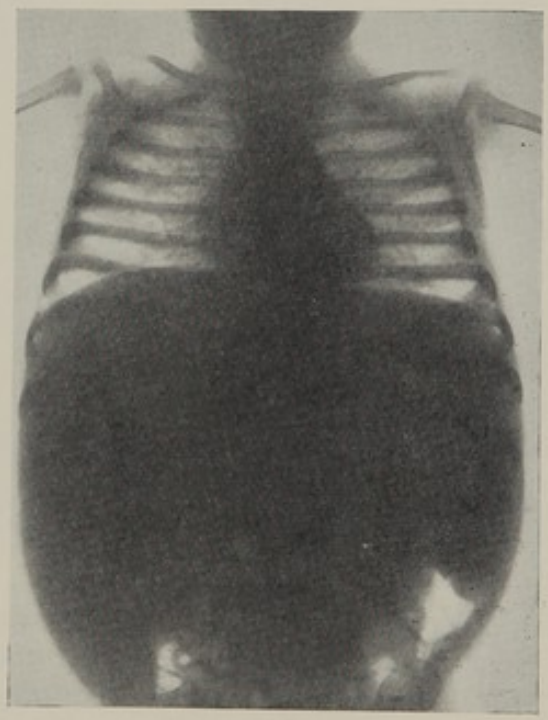

FIG. 77.—Roentgenogram of a boy aged 1 year affected with Niemann-Pick disease. (*By courtesy of Dr. U. Pfändler.*) Note the enormous hepatomegaly and splenomegaly, and the thickening of the pulmonary fibrous framework owing to deposits of lipids responsible for the opacification, and micro-nodular and trabecular aspect.

Clinically, there are feeding difficulties, considerable hepato-splenomegaly, brownish-yellow skin coloration and enlargement of the lymph nodes. The blood frequently reveals hypercholesterolaemia and modifications of the blood concentrations of different lipoid substances.

The neuro-ocular signs simulate those of Tay-Sachs infantile amaurotic idiocy; mental deficiency, spastic paraplegia, opisthotonus, convulsions and, in about one-third of the cases, a cherry-red spot surrounded by a whitish zone in the macular region. The relationship between these two affections is uncertain. Most neuropathologists hold that there is a close relationship and possibly even identity, between both of these diseases—a view based on the presence of visceral

organ changes in Tay-Sachs disease showing foam cells charged with lipoids, the resemblance of the cerebral changes in the two affections and the chemical analogy of the stored substance (sphingomyelin). Furthermore, the symptoms and signs of both affections are present in more than one-third of the cases (*see* Scheidegger, 1941) and the occurrence of these two rare diseases in the same family has been described (van Bogaert, 1934).

A chronic and relatively mild form of Niemann-Pick disease occurs in adults.

Heredity.—The hereditary character of this desease is confirmed by its familial occurrence, and its concordant appearance in identical twins (Freudenberg's case, Fig. 78). Recessive transmission is generally assumed although consanguinity does not seem to have been recorded. As in Tay-Sachs disease, irregular dominance is not unlikely, though there can be no proof of a direct transmission because of the lethal character of the affection.

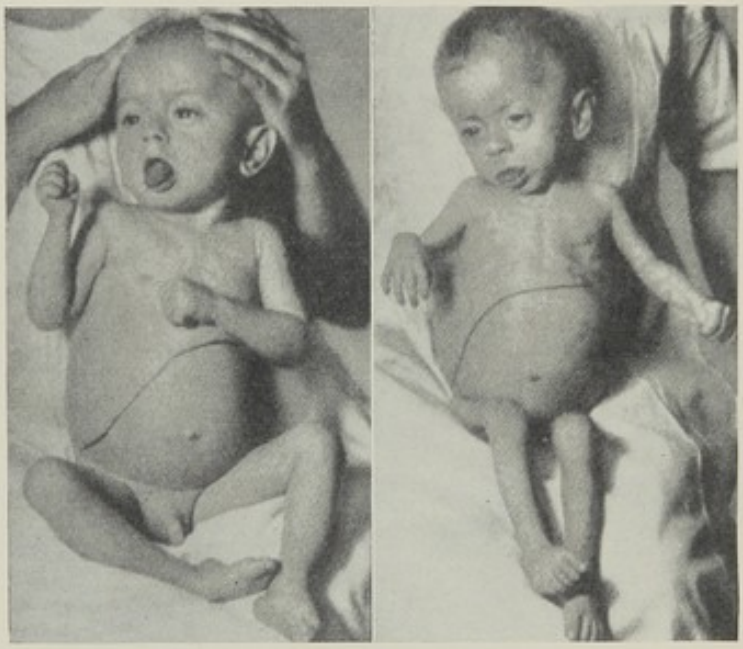

FIG. 78.—Niemann-Pick disease in monozygotic twins aged 1 year 4 months. (*By courtesy of Professor E. Freudenberg.*)

The possibility of dominant inheritance is supported by intensive genetic and biochemical studies in a family presenting 4 cases of the adult form of Niemann-Pick disease (Pfändler, 1946; Fig. 79). Pfändler found pathological changes in the concentrations of the different blood lipids in a number of individuals who appeared normal clinically. These quantitative changes, present not only in the direct descendants but also in collateral branches of the affected individuals, suggest that there is a latent metabolic disorder of the lipoid metabolism in these persons and that the affection shows a regular dominant inheritance with low penetrance.

Familial amaurotic idiocy

Clinical aspects.—The characteristic of this affection is the abnormal storing of lipoids (mainly phosphatides) in ganglion cells of the central nervous system, which are transformed into foam cells.

There exist two main types: (1) the infantile type (Tay-Sachs); and (2) the juvenile type (Batten and Mayou, Vogt and Spielmeyer). Theoretically the late infantile type (Bielschowsky) is important since it represents the connecting link between the infantile and juvenile form. Moreover, an adult form (Kufs, Meyer, Marinesco, van Bogaert and Borremans) can be distinguished.

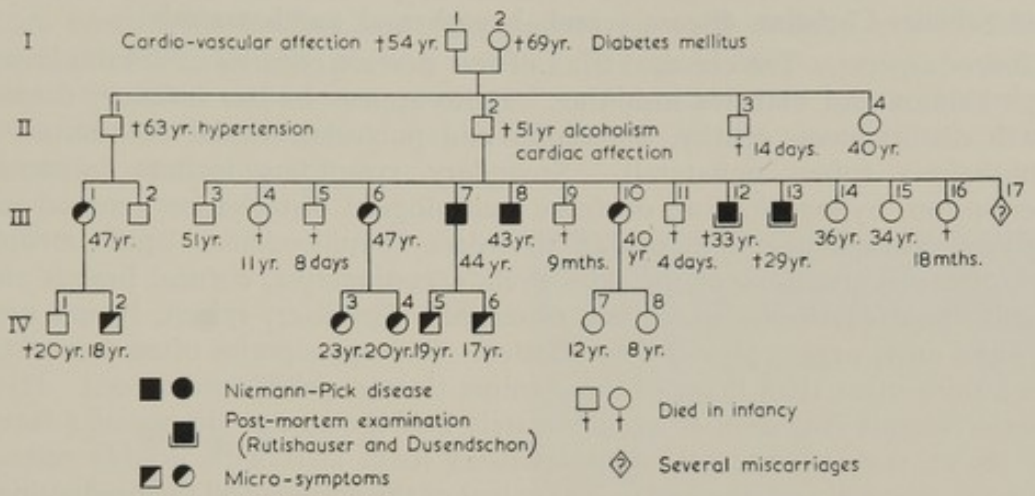

FIG. 79.—Pedigree of Niemann-Pick disease of adult type. (*After Pfändler, U. (1946). Schweiz. med. Wschr.*, **76**, 1128.)

The infantile type (*Tay-Sachs*) usually appears in the first six months of life and generally leads to death between the second and third year. The characteristic symptoms are amaurosis, dementia, and paralysis. The fundus of the eye presents a typical appearance: a cherry-red spot in the macula surrounded by a greyish-white halo; simple atrophy of the optic nerve is present.

The juvenile type starts later and has a slower course. It begins at the time of the second dentition (sixth to seventh year) and leads to death between the fifteenth and seventeenth years). Epileptiform seizures and extra-pyramidal signs form part of the clinical picture. The ophthalmoscopic aspect is much less characteristic than in the infantile type (macular dystrophy or retinal pigmentary degeneration).

Whether the two affections are variations of the same morbid entity or are independent diseases is still uncertain. The occurrence of both types within the same family has been shown only by Higier (1896, 1906).

The identity of the two affections is suggested by the following facts. (1) In both forms the same cellular changes are found with quantitative differences only. (2) The existence of intermediate (late infantile) forms, which sometimes resemble the infantile, and at other times the juvenile type, and must thus be considered as a connecting link. (3) In the juvenile form one may occasionally find modifications of the fundus oculi resembling the infantile type, while, in some infantile cases the cherry-red spot may be lacking.

A possible racial predilection—the infantile type being more common in Jewish families and the juvenile in gentile families—is no conclusive evidence in favour of the two affections being different diseases.

Heredity.—Juvenile amaurotic idiocy is transmitted as a simple recessive (Sjögren, 1931). The mode of inheritance of the infantile form is still uncertain.

The high percentage of consanguineous parentage (according to Slome, 23–30 per cent in Jews, 55·6–66·7 per cent in gentiles) suggests a recessive mode of transmission. However, some other pedigrees, such as those by Falkenheim and Rochliny; Goldfeder; Kingdon, Russell and Stewart; van Bogaert and Bertrand, show the affection in two or three generations and suggest an irregular dominance.

Hand-Schüller-Christian disease (cranio-hypophyseal xanthomatosis)

Clinical aspects.—The classical triad of this desease consists of cranial lacunae, exophthalmos and diabetes insipidus. These appear in late infancy; there are growth disturbances, apathy, polydipsia and polyuria, cranial deformities and exophthalmia (often unilateral). Secondary symptoms include intracranial hypertension, hypogenitalism, deafness, neurological disturbances (cranial nerve paralyses, paraplegia) and ocular disorders (papilloedema, optic atrophy). Xanthomatous eruptions of the skin, eyelids, conjunctiva, corneal limbus and a corneal lipoid dystrophy have been observed. The liver, spleen, lymph nodes, lungs and other organs may also be affected. Roentgenograms often demonstrate bone lesions other than those of the cranium (femur, pelvis, and so on). Hypercholesterolaemia is present in approximately half the cases. Biopsy of a lacunar area shows the characteristic xanthomatous foam cells with double refractile lipoids (cholesterol and its esters). The extent of the process and the predominance of one or another localization may produce great variability in the clinical picture.

Autopsy reveals more or less voluminous cavities with yellowish masses formed by granulomatous tissue with xanthomatous cells.

Chemical aspects.—Hand-Schüller-Christian disease is one of the group of essential or primary xanthomatoses. It falls within the " normocholesterolaemic " or " high normocholesterolaemic " types which include the group of disseminated xanthomatoses.

Three views have been advanced as to the origin of the disease: (1) it is general disturbance of the intermediary cholesterol metabolism, in which a deposition of lipoid fat mixture, particularly cholesterol and its esters, takes place; (2) the xanthomatous cells are the expression of an intracellular lipoid disorder (" metaplastic reticular cholesterosis"); and (3) it is of a primary granulomatous nature, similar to the eosinophilic bone granuloma; the formation of foam cells with cholesterol deposits is considered to be only a parallel or secondary phenomenon specifically bound with this affection.

Heredity.—Though there are about 200 observations in the literature, familial occurrence is very rare. Decken reported atypical Hand-Schüller-Christian disease (without exophthalmos and diabetes insipidus) in fraternal twins, and cites only two other familial cases from literature.

The essential primary xanthomatoses with hypercholesterolaemia

Clinical aspects.—According to Thannhauser and Magendantz, the following forms belong to this group: (1) tuberous xanthomatosis of the skin; (2) xanthomatosis of the tendons and tendon sheaths; (3) cardiovascular xanthomatosis; (4) xanthomatosis of the bile-ducts producing a biliary cirrhosis; and (5) xanthomatosis of the spleen, liver and lymph nodes.

Tuberous xanthomatosis is characterized by the appearance of yellow-brownish nodules or tumours, primarily on the extensor surfaces (elbows, knees, heels, gluteal region) and often involving the eyelids (*xanthelasmas*) (Fig. 81).

All possible combinations and transitions may exist between these forms. The association of tuberous xanthomas, with or without tendinous involvement, and cardiovascular affection merits particular clinical interest since it may lead to sudden death from xanthomatous deposits on the endocardium, in particular on the aortic valves, and the coronary vessels. The lipoid infiltration of the vascular walls of the lower extremities may signal its presence by an intermittent claudication. Muller has emphasized that heart disease in families should direct attention to xanthomatosis (Fig. 83).

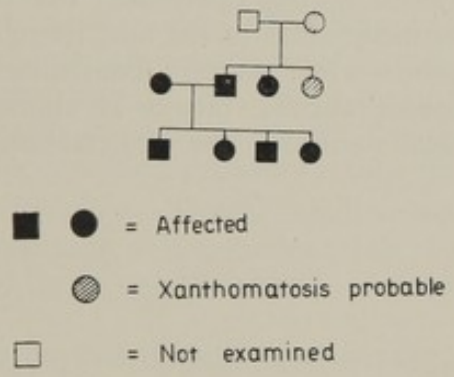

FIG. 80.—Pedigree of xanthoma tuberosum et planum and tendon xanthoma. (*After Thannhauser S. J. (1950). Lipoidoses*, p. 214. Oxford; University Press.)

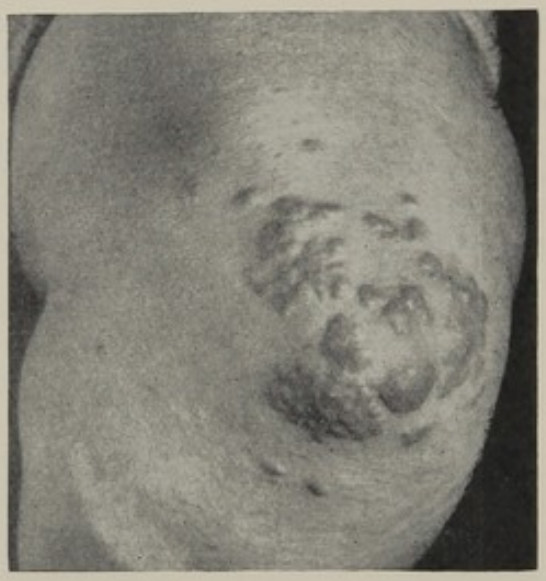

FIG. 81.—Xanthoma tuberosum of elbow. (*By courtesy of Dr. J. Franklin.*)

Heredity.—Tuberous xanthomatosis of the hypercholesterolaemic type can be distinguished from a normo-cholesterolaemic, disseminated xanthomatosis by its familial and hereditary character (Figs. 80 and 83). As early as 1893, Török showed its dominant transmission (3 generations with 10 affected individuals)—a finding repeatedly confirmed.

Irregular dominance is not uncommon, and has led many authors to carry out systematic analyses of blood lipids in these families. The frequently high values of blood cholesterol among the relatives of patients suggests simple dominance with low penetrance. Fliegelmann, Wilkinson and Hand (1948) studied a family of about 270 individuals and hold that hypercholesterolaemia without cutaneous lesions represents the heterozygous and tuberous xanthomatosis the homozygous state of the affection.

Cerebral cholesterinosis

Schneider (1936) and van Bogaert, Scherer and Epstein (1937) described this disease independently. The observation of van Bogaert concerns a man, 36 years of

age, in whom a slowly evolving neurological syndrome appeared at the age of 12 or 13 years. The affection was characterized by cerebello-pyramidal signs, resembling an amyotrophic lateral sclerosis, and myoclonia of the soft palate. There were also mental debility, a radial cataract, bilateral palpebral xanthelasma and tendinous xanthomatosis. The blood cholesterol was normal. Autopsy showed enormous deposits of fat and cholesterol crystals, primarily in the white matter of the cerebellar hemispheres and the cerebral peduncles. A paternal cousin of the patient was similarly affected, with a zonular cataract, but without xanthomatous tumous of the tendons.

In Schneider's case there was also a bilateral cataract, but no tendinous tumours or xanthelasma and no familial manifestation.

Lipoidosis of the skin and mucous membranes (lipid proteinosis)

Clinical aspects.—This affection was described in 1908 by Siebenmann and defined as a clinical entity by Urbach and Wiethe (1926, 1929).

It is characterized by nodular or hyperkeratotic lesions distributed over the face, scalp, neck and extremities. The mucous membranes of the lips, frenulum linguae, palate, pharynx and larynx show yellow-white patches consisting of lipoid deposits. In the child, the affection causes a raucous voice or an aphonia, and may necessitate a tracheotomy for laryngeal stenosis. The cicatrization of

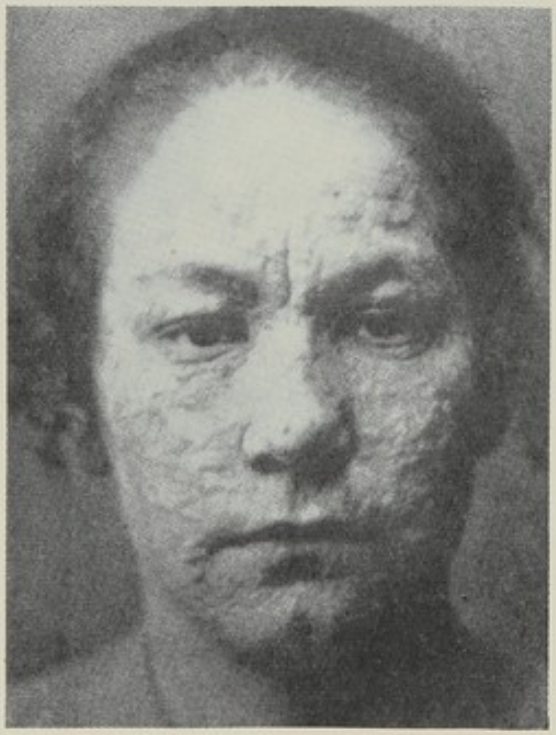

FIG. 82.—Lipoidosis cutis et mucosae. (*Case of E. Urbach. From K. Wiener (1947). Skin Manifestations of Internal Disorders.* St. Louis; Mosby.) Characteristic pock-marked appearance of the face.

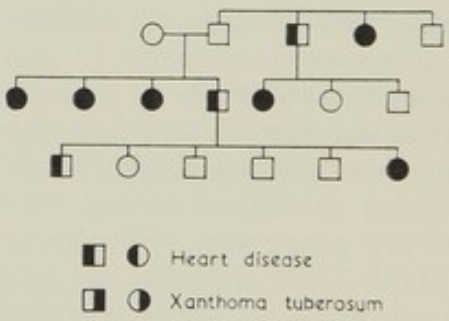

FIG. 83.—Pedigree of heart disease and xanthoma tuberosum. (*After Muller, C. (1939). Arch. intern. Med.*, **64**, 675.)

the varioliform eruptions can produce a " pock-marked " face (Fig. 82). The blood and the skin may show an increase of the phosphatide lipoides. The disease is often accompanied by latent diabetes.

Histologically, lipoid deposits surround the capillaries and infiltrate the neighbouring connective tissue.

Heredity.—The frequent familial occurrence and the high rate of consanguinity of the parents indicate a recessive type of heredity. About 30 observations have been published (*see* Cockayne, 1933; Ormsby and Montgomery, 1948; Wiener, 1947).

The family examined by Nager and Miescher in 1925, consisted of 17 children of consanguineous parents; 2 sets of twins died of asphyxia some days after birth, probably due to laryngeal stenosis (they had never been able to utter a cry), and 4 of the remaining 13 suffered from a generalized keratosis-like dermatosis involving also the mucous membranes (oral cavity, pharynx, larynx).

Essential hyperlipaemia

Clinical aspects.—The characteristic signs of this disorder, usually observed in children, are an abnormal increase of neutral fat in the blood (milky or creamy appearance of the serum), hepatosplenomegaly, xanthomatous skin lesions and attacks of abdominal pain. Ophthalmoscopically, there is often lipaemia retinalis. The condition probably results from a defective mechanism of fat absorption.

Heredity.—Several familial cases are on record. In two records there was a suggestion of dominance (Holt, Aylward and Timbres, 1939; Bruton and Kanter, 1951); in one the parents were consanguineous (Grasso and Negri, 1951).

Gargoylism (lipochondrodystrophy, dysostosis multiplex)

Clinical aspects.—Gargoylism is a rather rare congenital disease—there are about 120 published cases on record characterized by a disproportionate dwarfism, hepatosplenomegaly, corneal opacities and mental deficiency (Fig. 84). The

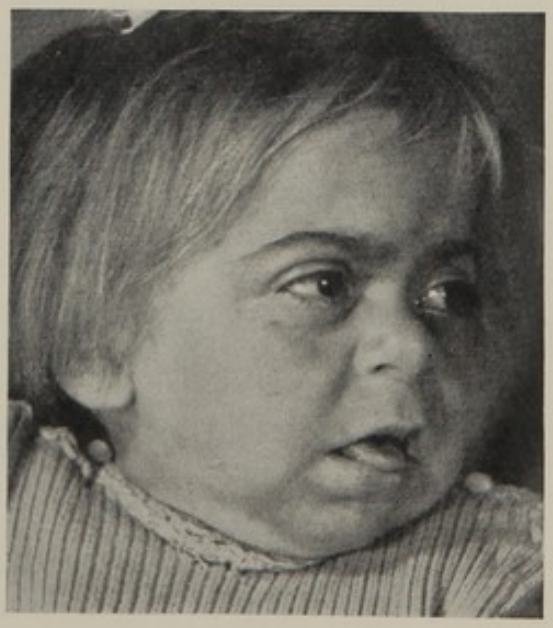

FIG. 84.—Typical gargoyle face. (*By courtesy of Dr. H. Wettler, Universitäts-Augenklinik, Zurich; Professor M. Amsler.*) Girl aged 3 years with hepatomegaly, cloudy corneae, characteristic bone changes, mental deficiency, internal hydrocephalus. Height 2 feet 10 inches.

infants usually appear normal at birth. Only towards the end of the first year does the disease become manifest. There is a striking similarity of the physiognomies of affected children: " They look like members of the same family ". In a typical case, one finds a large and deformed head with widely spaced eyes, saddle-shaped nose, wide nostrils, a large mouth with thick lips and tongue, widely spaced teeth, a high palate, and low-set, large ears. In addition, there is a short neck, a deformed thorax, a prominent abdomen frequently presenting an umbilical hernia, lumbar kyphosis and limitation of joint movements. Occasionally, there is hypertrichosis, optic nerve atrophy and deafness. Roentgenograms reveal osteochondrodystrophic changes: a slowing and irregularity of cartilage growth and disorders of enchondral ossification.

The bilateral corneal opacities found in about 75 per cent of the cases consist of a diffuse milky cloudiness, the result of lipoid infiltration. In one case it did not develop till after middle life.

The patients generally die before the age of 20 years, usually of heart failure.

In certain organs, primarily the liver and spleen, are found vacuolated cells with deposits of substances which have not as yet been chemically identified. There is also a generalized degeneration of the ganglion cells resembling that of juvenile amaurotic idiocy.

Heredity.—The familial occurrence and the consanguinity often found in these cases (*see* Halperin and Curtis, Böcker) speak for a recessive factor with a sublethal character and a polyphenous effect. A sex-linked form may perhaps exist (Njå, Lundström) devoid of corneal opacities. The occurrence of skeletal deformities in the ascendency of patients suggests partial manifestations in heterozygotes. Concordant manifestation (without corneal opacities) has been observed by Nonne in monozygotic twins and discordant manifestation by Cordes and Hogan (1942), and Gasteiger and Liebenam (1937).

A relationship between Hurler's and Morquio's diseases is suggested by their appearance within the same family (Böcker, 1942).

An intermediate form between gargoylism and juvenile amaurotic idiocy has been described by Jervis (1942), and an atypical form of gargoylism combined with xanthomatosis (" familial dermo-chondro-corneal dystrophy ") by François (1949) in a sibship.

DISTURBANCES OF PIGMENT METABOLISM

The porphyrias

Clinical aspects.—The porphyrins belong to a group of pigments composed of a tetra-pyrrol nucleus. They contain no iron, and are important for the synthesis of haemoglobin and the respiratory ferments.

In pathological concentrations, they can produce serious troubles. Porphyrinuria may be secondary to an intoxication or to various diseases (*symptomatic forms* or " primary ") as the result of a congenital or hereditary anomaly of porphyrin metabolism.

Clinically and genetically, the " primary " forms may be subdivided into: (1) congenital porphyria; and (2) acute porphyria in adults.

Congenital porphyria is apparent in early infancy or even at birth (Garrod) and manifests itself primarily by cutaneous symptoms due to the photosensitizing action of the porphyrins. Exposure to light provokes the formation of necrosing cutaneous eruptions (hydroa vacciniforme) with widely distributed and deforming scars, mainly about the face, ears and hands (Fig. 85). One also notes a brown pigmentation around the skin lesions, hypertrichosis and alopecia. A deep red urine and brown-red colour of the dental enamel are characteristic. Porphyrin deposits in the bones may produce a brown pigmentation which becomes visible on transillumination of the hands. (Porphyria occurs normally in the Pennsylvania squirrel (*Sciurus niger*) whose bones are coloured bright red by a substance identified as uro-porphyrin I (Turner).) At a later stage, hepato-splenomegaly may develop. The eye may participate in the photosensitization and lead to the formation of ectropion, corneal opacities, cataract and scleromalacia.

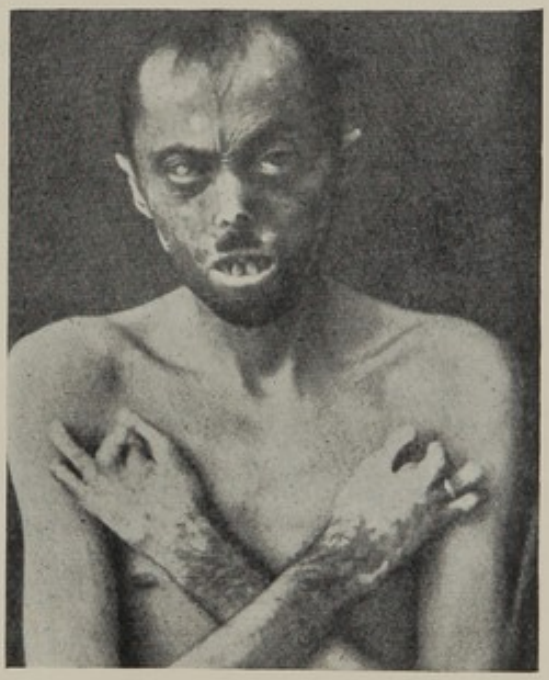

FIG. 85.—Congenital porphyria. (*Case of Günther and Petry. From Thannhauser, S. J. (1929). Stoffwechsel u. Stoffwechselkrankheiten*, p. 540. Munich; Bergmann.) (*By courtesy of Professor Thannhauser.*)

Acute porphyria generally appears between the third and fifth decade, but has been observed in a patient 8 years of age (Ford). It is characterized by the following symptoms: (1) abdominal—acute crises of colic with nausea, vomiting and constipation; (2) nervous—neuralgias, polyneuritis, paraesthesias, peripheral type paraplegias, crises of diplopia with amaurosis, and convulsions; and (3) psychic—motor agitation, anxiety, insomnia, states of confusion and delirious hallucinations.

The abdominal and neurological forms are frequently associated. Death occurs in coma resulting from ascending paralysis affecting the bulbar region.

(*Chronic porphyrinuria* is a form intermediate between the acute and the congenital (Günther). It shows cutaneous lesions and photosensitivity, and may appear in late infancy or in the adult. A latent form with occasional and mild attacks has also been described.)

Heredity.—Acute porphyria is transmitted in a dominant manner, as was demonstrated by Waldenström in his study of 19 families.

In contrast, congenital porphyria is usually a recessive affection with a high frequency of consanguinity in the affected families (45 per cent according to Cockayne, 1933) and some male predominance. Dominant inheritance is also known (Radaëli, Jacobi, Berckel).

Monovular twins showing reddish milk and permanent teeth observed by Heider were probably cases of congenital porphyria.

According to Günther, neuropathic and neurovegetative stigmas should be considered as the morbid territory for predisposition to porphyria. Marcozzi and particularly Lüthy have called attention to the association of porphyria with oxycephaly; Waldenström with migraine; Louis with bronchiectasis, syndactyly or aplasia of one mammary gland; Belloni with hypoplastic and cystic kidneys, and Hijmans van der Bergh with aplasia of the gall bladder.

Idiopathic familial methaemoglobinaemia (hereditary methaemoglobin cyanosis)

Clinical aspects.—This rare congenital anomaly is characterized by the presence of an increased proportion of methaemoglobin in the blood, probably due to a specific erythrocytic enzyme deficiency of the oxydation-reduction system (Gibson, 1948). Affected individuals show a strikingly cyanotic aspect (a blue-grey or slate-coloured skin) without, however, suffering from notable functional troubles.

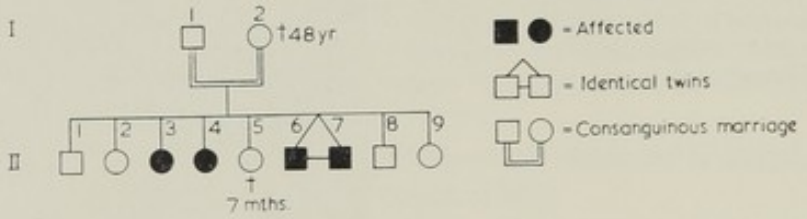

FIG. 86*a*.—Pedigree of familial idiopathic methaemoglobinaemia. (*After Gibson, Q. H., and Harrison, D. C. (1947). Lancet*, **2**, 941.)

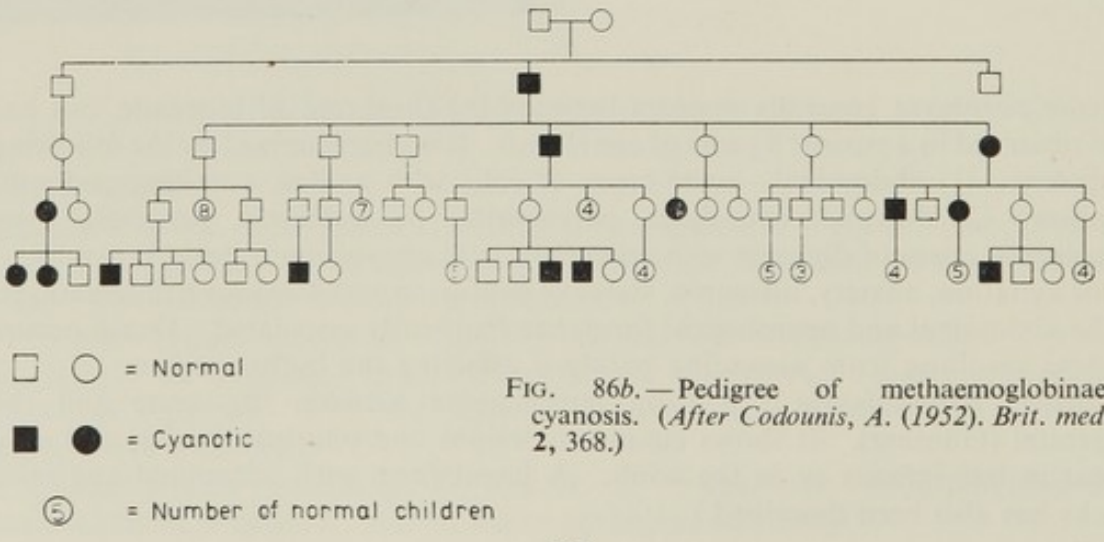

FIG. 86*b*.—Pedigree of methaemoglobinaemic cyanosis. (*After Codounis, A. (1952). Brit. med. J.*, **2**, 368.)

Treatment with methylene blue and ascorbic acid has been effective in some cases by temporarily replacing the oxydation-reduction system of the blood.

Heredity.—Some pedigrees (Hitzenberger, 1933) (Gibson and Harrison, 1947) (Fig. 86*a*) suggest recessive inheritance. Others, such as those by Hörlein and Weber (1948), Lutembacher (1949), and Codounis *et al.* (1952) (Fig. 86*b*) are clearly dominant.

DISTURBANCE OF IRON METABOLISM

Haemochromatosis (pigmentary cirrhosis, bronze diabetes)

Clinical aspects.—The diagnosis of haemochromatosis is based on the classical triad of (1) hepato-splenomegaly, caused by a hypertrophic cirrhosis; (2) a slate-blue-grey colour of the skin and often of the mucosae; and (3) a generally severe diabetes in advanced cases.

With this triad are frequently associated endocrine disorders (sexual hypotrophy, decrease of body hair) and cardiac affection (Fig. 87*a*) (*syndrome endocrino-hepato-myocardique* of the French school). In the majority of cases, the disease appears between the ages of 35 and 50 years.

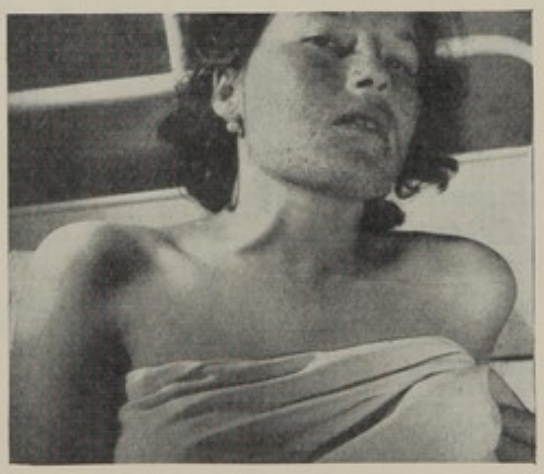

FIG. 87*a*.—Familial juvenile haemochromatosis. Photograph of a woman aged 23 years, VI/9 in Fig. 87*b*, taken two weeks before death from severe cardiac disease. Note the tense engorged jugular vein. (*By courtesy of Drs. T. Nussbaumer and H. C. Plattner; Clinique thérapeutique, Professor G. Bickel, Geneva.*)

Pathologically, there is an enormous accumulation of haemosiderin (iron-containing pigment) and, to a lesser extent, of haemofuscin (iron-free pigment) in different organs (liver, pancreas, other endocrine glands, reticulo-endothelial system, heart, striated muscle, kidneys).

Heredity.—The disease shows a high predominance among males. Sheldon (1934), basing his statistics on 304 cases from the literature and on 7 personal cases, found 296 men to 15 women, or a proportion of 20: 1. At least 15 sibships have been recorded and Laferre and his colleagues have reported uniovular twins, both hospitalized at the same age (29) for haemochromatosis. Likewise Lawrence (1950) described uniovular twins, both of whom succumbed at about 37 years of age. At autopsy, a diffuse haemochromatosis of all organs was found with one twin showing the unusual absence of haemofuscin. In contrast there is an observation of a pair of uniovular twin sisters, only one of whom was affected (de Morsier and Monnier, 1939).

Nussbaumer, Plattner and Rywlin (1952) have described a family in which 3 girls and 1 boy were affected with a juvenile type of haemochromatosis characterized by endocrine disturbances and a rapidly progressive hepato-myocardial failure (*see* Figs. 87*a* and *b*). Of these, 3 died between the age of 23 and 27 years (VI/5, 8, 9; Fig. 87*b*). One case was verified anatomically (Fig. 87*a*; VI/9, Fig. 87*b*). Recessive inheritance is suggested by consanguinity of the parents (cousins of the second to third degree).

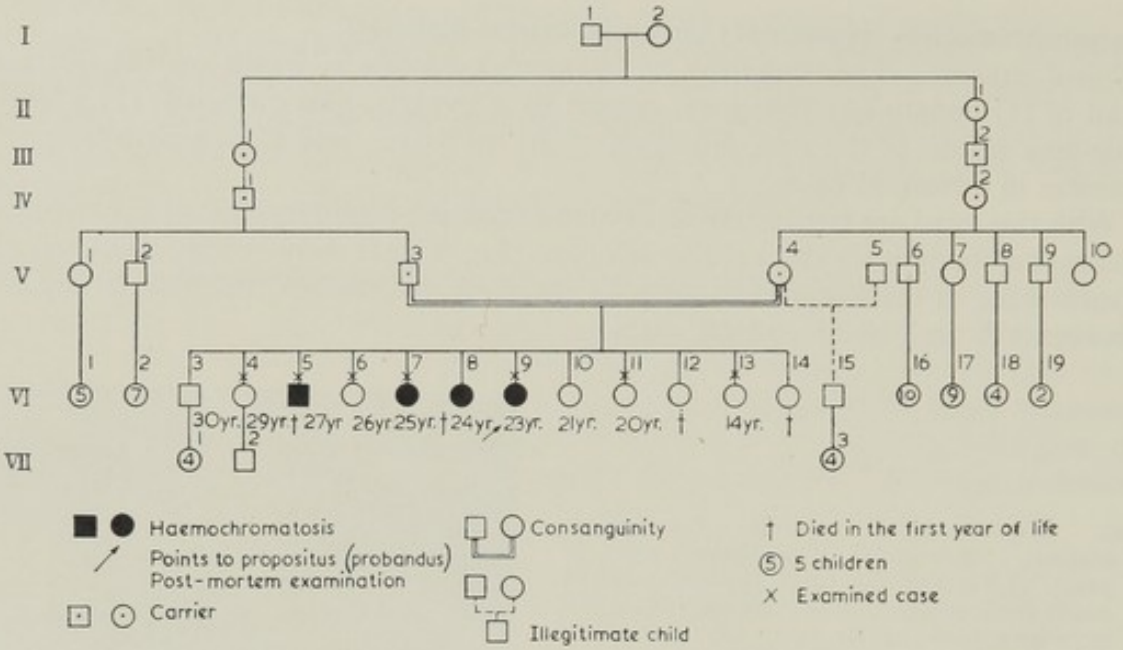

FIG. 87*b*.—Pedigree. (*After Nussbaumer, T., Plattner, H. C., and Rywlin, A. (1952). J. Génét. hum.* (Geneva), **1**, 139.)

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CHAPTER 13

DISEASES OF THE SKIN

OLIVER L. S. SCOTT

THE SKIN, which is the largest organ in the body, is usually the most easily inspected both by the individual and others concerned, so that attention is paid to even minor abnormalities which in deeper organs would cause no symptoms and pass unnoticed. This partly accounts for the many cutaneous diseases that have been described in such detail, and inherited diseases are no exception. The great work of Cockayne (1933) describes several hundred inherited skin disorders. Probably there are as many in other organs, but, being invisible and sufficiently refined tests of function being unknown, they remain unrecognized.

Genes by their nature may affect more than one germinal layer, and in a disorder such as multiple neorofibromatosis both ectoderm and mesoderm are involved. It is convenient, however, to describe skin diseases according to the cells particularly affected, provided that no strict classification is assumed.

DISORDERS OF ECTODERMAL CELLS

Ichthyosis

This group of diseases is characterized by degrees of hard, dry, rough skin more or less suggestive of fish skin. There are various types, but many more designations, like sauroderma, ichthyosis foetalis, ichthyosis congenita, ichthyosis serpentina and so on, merely describe different stages or aspects of the same condition.

Clinical aspects

Ichthyosis congenita, an extremely rare condition, is present at birth, and it affects the sexes equally. Various degrees of severity exist; the so-called harlequin foetus, a form of ichthyosis foetalis (Fig. 50*a*), is incompatible with life. Huge horny plates cover the entire skin surface with deep fissuring between them and make feeding and respiration impossible. The infant is born dead, or dies shortly after birth. Severe deformity exists at the site of these plates, and the ears, face, hands, feet and groin are particularly distorted. Not all cases are generalized and milder degrees exist and are compatible with life. Large or small blisters are often present. The so-called ichthyosis congenita which is compatible with life seems to be merely a variation in degree of ichthyosis foetalis. It is notable that the flexures are commonly affected, in contrast with ichthyosis vulgaris. A similarly inherited disorder is found in calves.

Congenital ichthyosiform erythrodermia, a variety of ichthyosis congenita, was first described by Brocq in 1902. It is present at birth, and the infant has a typical universally red, shiny skin, with sometimes flexural fissuring and bulla formation. The hands, feet and flexures are affected and the nails may be absent

(Fig. 88). Subsequently scaling and hyperkeratosis occur, so that the child becomes a more or less generalized ichthyotic. In adult life the element of erythrodermia has usually disappeared. The appearance of the flexures, bulla formation and erythrodermia serve to differentiate it from other forms of ichthyosis.

FIG. 88.—Congenital ichthyosiform erythrodermia. (*By courtesy of Dr. D. J. Conway.*)

Ichthyosis vulgaris is the commonest type of ichthyosis. All degrees exist, from the follicular type in which pinhead papules cover the hair follicles, to generalized xerodermia and warty plaques of the so-called hystrix type. In the more severe types the sweat glands and sebaceous glands are rudimentary or absent. The extensor aspects of the limbs and trunk are most commonly involved, and the flexures, axillae, face, palms and soles are typically spared.

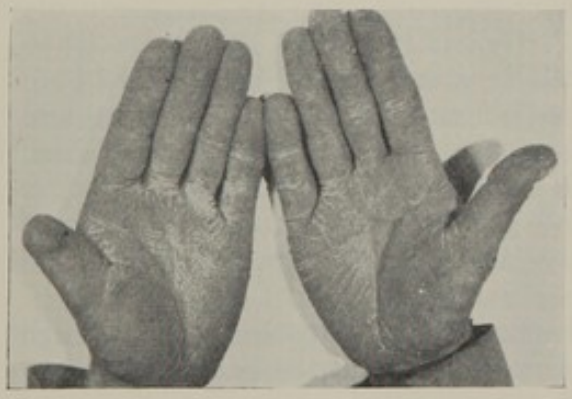


FIG. 89.—Tylosis palmaris. (*By courtesy of St. John's Hospital and the Institute of Dermatology, London.*)

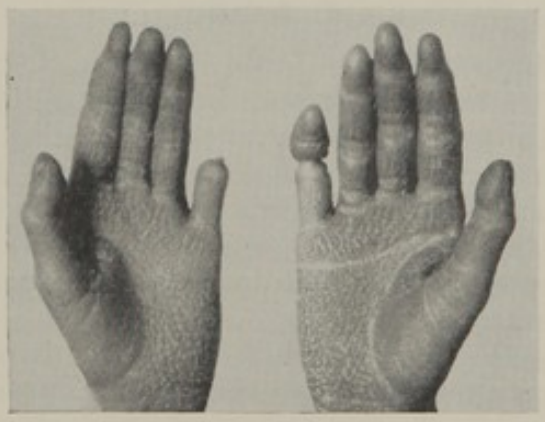


FIG. 90.—Tylosis palmaris et plantaris: palmar lesions showing ainhum-like constrictions leading to gangrene. (*By courtesy of Dr. J. E. M. Wigley.*)

Tylosis palmaris et plantaris is common. It may be present at birth, or the onset may be delayed for 5 or 6 years. It consists of symmetrical thickening, sometimes to the extent of as much as one centimetre, of the skin of the palms, soles and flexor aspects of the digits associated with hyperidrosis of the affected areas (Fig. 89). The margins of the areas are usually pink in colour and sharply demarcated. Histology shows that all the layers of the epidermis are thickened, but this is

particularly well marked in the horny layer which is enormously thickened and appears to be incapable of being worn away by wear and tear as is usual. The sweat glands are increased in number and their dilated ducts can easily be seen on the surface. At first the thickened skin is transparent, but later it becomes brown or black due to decomposition and accumulation of dirt. The openings of the sweat ducts appear as tiny pits on the surface. Periodically the hyperkeratotic mass is shed, or it may be removed artificially by keratolytics, and a tender, erythematous area is left upon which the next horny covering is formed. There may be great tenderness of the soles in particular, and gangrene has been reported as a result of constriction of the digital vessels (Fig. 90).

Mal de Meleda is a rare congenital condition which is found on a Dalmatian island. There is hyperkeratosis of the palms and soles and also of the backs of the hands and feet, elbows, knees, forearms and legs. Hyperidrosis is common. The hyperkeratotic areas are yellowish in colour, with waxy translucency, and the sweat ducts open as black dots in the affected patches.

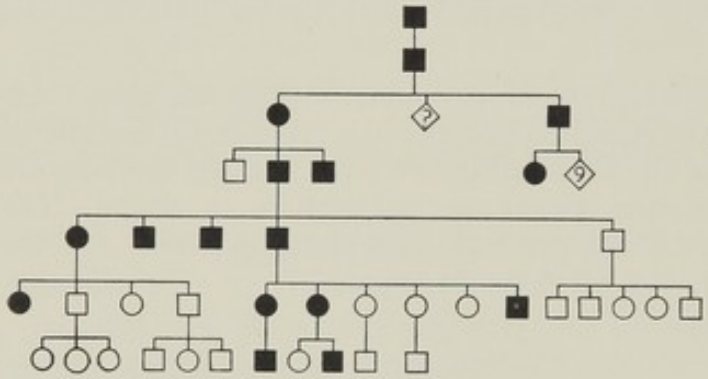


FIG. 91.—Dominant pedigree of tylosis palmaris et plantaris. (*After Macaulay, D. (1951). Brit. med. J.*, **1**, 335.)

Heredity

Ichthyosis congenita.—Siemens and Cockayne give adequate evidence of both the foetal and congenital forms being inherited as an autosomal recessive, and it seems that on clinical grounds the division is unnecessary and that the same single recessive gene is responsible for both the severe and mild cases.

Congenital ichthyosiform erythrodermia.—The affection is due to a single recessive gene, but dominant pedigrees have also been described by Brocq and others.

Ichthyosis vulgaris.—Inheritance is probably a single autosomal gene of high penetrance and expression. Occasional interrupted conduction occurs, however, and Cockayne considered that the defect, whether inherited by direct or interrupted descent, is due to the same gene or genes. As he points out, however, those pedigrees with interrupted descent may be produced by the presence of a modifying gene, by the presence of two genes (one common and one rare) or by an entirely different gene.

Ichthyosis vulgaris may also be inherited as a sex-linked recessive which is indistinguishable clinically from the dominant variety. In this connexion the pedigrees of Csorz and of Ramorino are interesting. The former described 13 cases in 6 generations and the latter 11 cases in 5 generations. Csorz's pedigree shows only males affected until the sixth generation when, owing to a consanguineous marriage, homozygous affected females appeared.

Tylosis appears to be due to a single dominant gene of high penetrance (Fig. 91). Men and women are equally affected and no race is immune. A large number of pedigrees has been collected. Vorner quotes 17 cases in 4 generations, and Hahn 27 cases in 5 generations. A remarkable pedigree traced for 7 generations has been described by Macaulay (1951). There were 17 members affected, of whom there were 10 males and 7 females. Transmission was regular and was apparently due to a single dominant gene. Huei-Lan Chung (1937) reported two Chinese families with similar inheritance; one was traced back for 5 and the other for 7 generations. Two families have also been reported in which the abnormality was apparently due to an irregular dominant gene sex-limited to females. Associated abnormalities are very rare.

Mal de Meleda is possibly inherited as a dominant, although Crocker considered it to be recessive.

Ichthyosis hystrix gravior.—The fantastic pedigree of the Lambert family, showing at least 6 generations to be affected due to a dominant mutation in the Y chromosome, is of historical interest only. The skin was replaced, except for the face, palms, soles and groins by thick hide with wart-like excrescences and bristles, and the subjects were known as porcupine men. Descriptions are given by Machin (1732), Pettigrew (1833) and Pickells (1851), who saw members of the family, and by Cockayne (1933). The line is now extinct.

Congenital anidrotic ectodermal defect

Clinical aspects.—This is a rare condition characterized mainly by agenesis of the epidermis and its appendages. The hair is fine and sparse (Fig. 92); the teeth are absent or deficient with peg-shaped incisors and mis-shapen molars; the sweat, sebaceous, mammary and even lacrimal glands are absent or rudimentary; the mucous glands of the nose are often absent, leading to chronic rhinitis; the bridge of the nose is depressed and lower jaw under-developed; the nails may be dystrophic; milium bodies are seen on the face; and bilateral cataract has been reported. The individuals are usually of normal intelligence but of poor physique. The tooth abnormalities and the dry, anidrotic skin are the main causes of symptoms.

These associated abnormalities, of teeth and sweat glands in particular, have led to the adoption of the current designation. This is an unsatisfactory descriptive term. As Gruneberg points out, the assertion that two or more structural anomalies are related by common origin is at best a repetition of the facts. It is probable that the chemical action of the responsible gene correlates all these structures at about the fifth to sixth week of embryonic life when they normally commence their early and rapid development. These structures are partly mesodermal in origin and further evidence is thus provided of the multiple effects of the gene, whether chemical or mechanical. The primary gene action, however, has not yet been discovered, but it is possibly some noxious influence upon the developing mucosal and epidermal cells at the fifth to sixth week leading functionally and mechanically to the clinical picture described. It would probably be better, however, to remove the adjective ectodermal from the above title and to speak merely of congenital anidrotic defect.

Heredity.—Cockayne believed that there were two types of inheritance concerned, sex-linked recessive and dominant, which resulted in similar clinical pictures, although milder cases were also present in the dominant type. Thadani (1934) described 6 generations with only males affected although the female heterozygotes were not always completely normal. Roberts (1929) described 10 cases, all males, in five generations; here again the female heterozygotes showed minor visible defects. Schwartz (1935) described a family in which four brothers were affected; the mother and one of her sisters lacked permanent canines; the condition was therefore incompletely recessive in the females.

Severely affected females are exceptionally uncommon but have been reported; minor defects in women are not so rare. It seems possible, as Gates suggests, that the condition shows recessive sex-linkage with a variable expression and occasional manifestation in women.

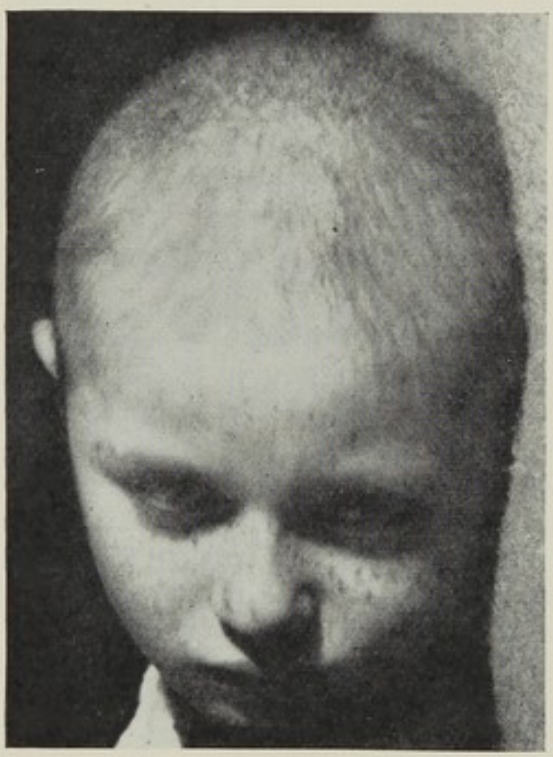


FIG. 92.—Congenital anidrotic ectodermal defect. (*By courtesy of Dr. R. T. Brain.*)

Benign familial pemphigus

Clinical aspects.—This rare bullous disease was first described by Gougerot in 1933 and later by Hailey and Hailey. The eruption occurs most commonly on the neck, in the axillae and in the groin, and is usually preceded by some irritation or burning sensation. The exciting factors are pressure, friction and heat, which explains the localization of the lesions. The eruption is worse in hot weather and is free from serious complications. Patients suffer from it off and on for many years. Histology shows intra-epidermal cleft formation, leading to the appearance of vesicles and bullae. This cleft may be seen microscopically after apparently normal skin of affected patients has been vigorously rubbed a few times. There is dyskeratosis and acantholysis, and rounded acantholytic cells line the cleft and

may lie free within it, either singly or in clumps; the basal cell layer is intact. The acantholytic cells differ from those seen in true pemphigus by the fact that their nuclei are not degenerating, at any rate not in early stages; the nuclei may even be seen undergoing mitosis, which is the reverse of what occurs in pemphigus. It is not justifiable to associate the condition with Darier's disease as has been suggested.

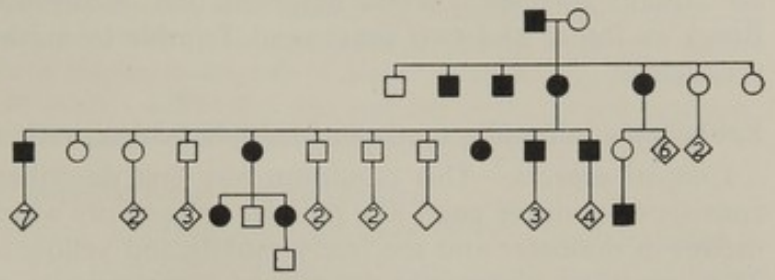


FIG. 93.—Benign familial pemphigus: pedigree showing irregular dominance. (*After Haber, H., and Russell, B. (1950). Proc. R. Soc. Med.*, **43**, 558.)

Heredity.—Isolated cases occur, but more often there is a family history showing inheritance to be due to a single dominant gene. Becker and Obermeyer (1940) described a pedigree which contained 27 cases in 3 generations; in all these cases the axillae and neck were affected. The pedigree described by Haber and Russell (Fig. 93) showed 13 cases in 4 generations to be affected. A typical case is that of a ballet dancer, aged 50 years, who for 30 years had suffered in the summer from crops of vesicles, which later broke down and became encrusted, in the groin and on the neck. He noticed that the groin lesions were always associated with dancing in tights and the neck lesions with wearing closely fitting collars. It seems clear that a dominant gene is responsible in some way for an abnormal reaction on the part of the prickle-cell layer in response to friction, pressure and heat, but the exact mechanism is unknown and invisible.

Darier's disease: keratosis follicularis

Clinical aspects.—This disease is a form of dyskeratosis and usually begins in childhood. It is characterized by the appearance of numerous discrete follicular papules. These are tiny and flesh-coloured at first, but as they enlarge they gradually assume a grey or brown colour and become crusted. The head and neck, back, chest, abdomen and groin are frequently affected. The backs of the hands and the dorsal surfaces of the feet are more sparsely involved. On close inspection the palms and soles are seen to be extensively involved by minute lesions which show up well on palm-printing and finger-printing—a fact well-known to experts in criminal investigation. As the disease progresses the papules tend to coalesce and to form small nodules or tumours. Ulceration may occur and secondary infection results. This is most often seen in the groin and the axillae, where a moist exuding and vegetating area may be formed which has a very offensive odour. Darier's disease is held by some to be due to deficiency of vitamin A, but administration of the vitamin seldom produces improvement. Histologically there is hyperkeratosis, follicular plugging, acanthosis and cleft formation in the prickle-cell layer. In the neighbourhood of the clefts or lacunae are found the *corps ronds* described by Darier, which are dyskeratotic prickle cells, and the small parakeratotic cells which help to diagnose the condition. Benign familial pemphigus may show a somewhat similar appearance to Darier's disease.

Heredity.—Isolated cases are commoner, but the disease has often occurred in several members of a family. The pedigrees reported are small, however, and seldom extend to more than three generations. This may well be caused by social selection in marriage, for the disease is an unpleasant one. It is apparently due to a single dominant gene. No case has been described of the normal offspring of an affected parent transmitting the disease to the next generation. Males and females are equally affected. White described the occurrence in father and daughter; Boeck in father and two sons; and Trimble in mother, three children and one grandchild.

Epithelioma adenoides cysticum (multiple benign cystic adenomas)

Clinical aspects.—This condition was first described by Brooke in 1892, and consists of multiple pearl-like papules or tumours which range from 1 to 10 millimetres in diameter and are freely mobile and yellow to pink in colour (Fig. 94). They are most commonly distributed symmetrically about the eyes and on the

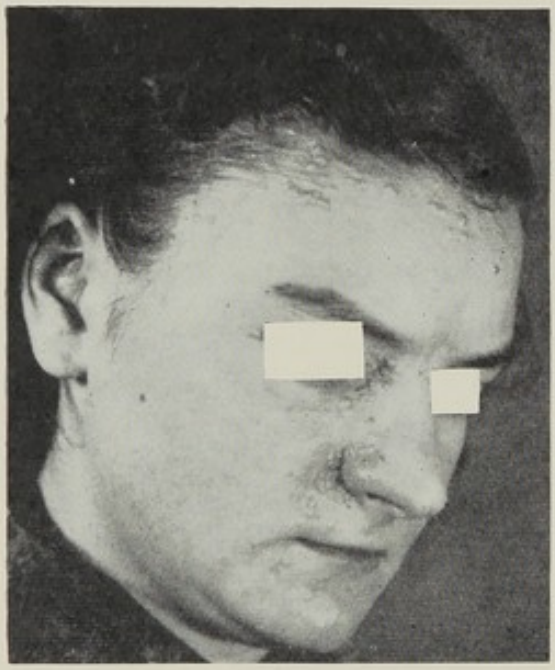


FIG. 94.—Epithelioma adenoides cysticum. (*By courtesy of St. John's Hospital and the Institute of Dermatology, London.*)

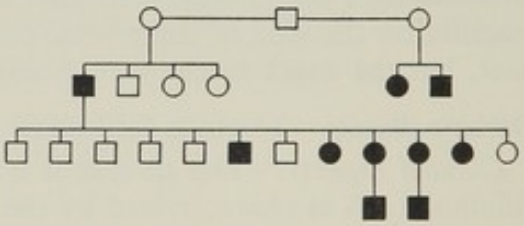


FIG. 95.—Pedigree of epithelioma adenoides cysticum showing regular dominance and transmission by both sexes. (*After Goldman, H. G. (1940). J. Amer. med. Ass.*, **115**, 2253.)

nose, temples, forehead, and chin; less frequently on the trunk, in the axillae and groins and on the arms. The upper lip is usually spared. Milium bodies are often present and occasionally telangiectasia. The condition is probably a hamartoma of hair follicle cells, which in turn arise from the primary germinal layer. Histologically, there is basal cell proliferation in palisade arrangement, often connected with hair follicles; multiple cysts are present which contain keratin. Pautrier and Archambault showed that these appearances are far from uniform, however, and clinically similar lesions in the same patient may show different histology. Basal-cell carcinoma is a rare complication of these tumours.

Heredity.—It is probable that this disease is caused by a single dominant autosomal gene. Cockayne considered it to be dominant with a definite though partial limitation to the female sex. This was found in both sibships and isolated cases.

Fliegelman and Kruse (1948) examined 20 members of 3 generations in one family; 8 were affected (4 male, 4 female) and two others had probably been affected. Goldman (1940) found 10 examples (5 male, 5 female) in 3 generations of one family (Fig. 95). One of Paul's cases had a similarly affected sister, two brothers, father and grandfather.

Binkley and Johnson (1951) described the case of a woman with epithelioma adenoides cysticum whose affected daughter was otherwise apparently normal. The mother, in addition, had many naevoid abnormalities ; multiple follicular dental cysts with sarcomatous metaplasia and metastasis leading ultimately to death ; rodent ulcer formation ; lipoma of the foot ; fibroma of ovary ; bifid rib ; and agenesis of the corpus callosum. The authors draw attention to similarly widespread disorders that occur in epiloia.

Xeroderma pigmentosum and multiple basal-cell carcinoma

Clinical aspects.—This was first described by Kaposi in 1870. Crocker called it atrophoderma pigmentosa. The skin reacts abnormally to the stimulus of light, particularly ultra-violet rays. Freckles, pigmentation, telangiectasia, localized atrophy, warty growths, superficial ulcers and malignant changes appear, often in that order. The exposed parts are affected, males as often as females. It is a rare disease and even in Australia, with its very high incidence of sunshine and rodent ulcers, Norman Paul could recall no case up to 1933.

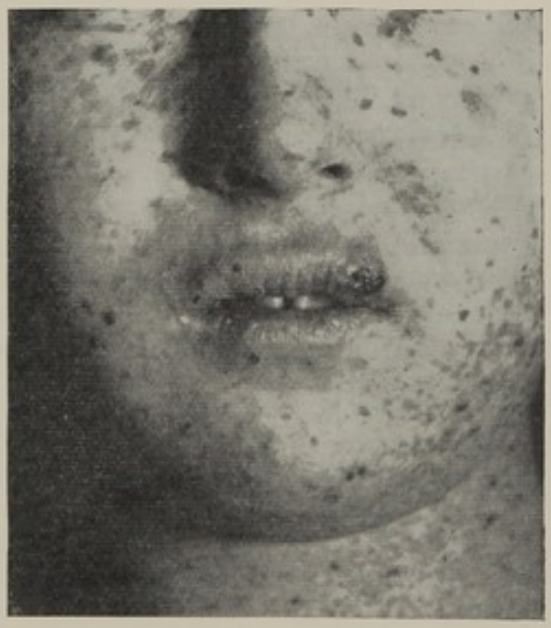


FIG. 96.—Xeroderma pigmentosum with squamous-cell carcinoma of lip. (*By courtesy of Professor D. W. Smithers.*)

The earliest signs are usually reddening and excessive freckling of the exposed parts in the first summer of the infant's life. However, conjunctival injection and photophobia may be seen earlier. As the years go by, the defence mechanism of the skin becomes more active, and hyperkeratosis, melanin pigmentation, telangiectasia and atrophy occur. Histologically, the changes in the early stage consist of epidermal hyperplasia and dermal atrophy, particularly of the papillary processes. Later there is vascular dilatation and much atrophy of the collagen and elastic tissue, associated with hyperkeratosis and sometimes metaplasia. Basal-cell carcinomas develop often, squamous-cell carcinoma more rarely (Fig. 96;

see also Fig. 39 on page 110); melanocarcinoma, sarcoma and even malignant endothelioma have been reported. Malignant changes may also take place on the conjunctiva.

The face and other affected areas may be severely mutilated; the nose, eyelids and ears are particularly vulnerable to the scarring and atrophy. Patients usually die young, before the age of 30 years, but they may, if well cared for, live to old age. Negroes are susceptible to the disease, despite their pigmentary advantages so far as actinic rays are concerned. Jews are said to be affected more often than gentiles.

Heredity.—According to Haldane the condition is due to an incompletely sex-linked recessive gene. He located the gene on the homologous portion of the sex-chromosome between the loci for total colour-blindness (achromatopsia) and congenital night-blindness (Oguchi's disease). Fisher believed that the exact position of the xeroderma pigmentosum gene was farther from the non-paired segment of the chromosome (18·2 crossing-over units as compared with 14 units according to Haldane) (*see* Fig. 33 on page 111). In one of the families described by Koller (1948) the disease was probably due to an independent autosomal gene, or to position effect. It is probable that the heavily freckled relatives of affected patients represent the heterozygous stage.

The appearance of these individuals who are heterozygous for xeroderma pigmentosum is important. The exposed areas of skin are very heavily freckled and unduly sensitive to actinic rays, although not to the extreme degree that is present in the homozygote. The heterozygotes are only recognized when a case of xeroderma pigmentosum is discovered in a family.

In this connexion a disorder described by Paul and sometimes seen in England though much more common in Australia may be related. It was originally called " rodent ulcers of the face, multiple and naevoid " and bears comparison with the heterozygous state for xeroderma. The exposed areas of the face and hands are heavily freckled and telangiectatic ; milium cysts are commonly found ; and " skin tags " are present on the neck and cheeks. The presenting symptom is the presence of multiple rodent ulcers in all stages of development, particularly on the face. The syndrome appears to be inherited as a simple dominant characteristic. It is not by any means certain that it is related to xeroderma pigmentosum, but the resemblance to the heterozygous state is remarkable and has hitherto not been investigated from a clinical or genetical point of view.

The multiple benign superficial epitheliomas (Wise) or erythematoid benign epitheliomas (Little) are probably due to a recessive gene. These cases are usually sporadic but they have been reported in families by Gray and by McFeeters.

Pachyonychia congenita

Clinical aspects.—This is a rare disease which was first described under the above name by Jadassohn and Lewandowsky in 1907. It is characterized clinically by the following features: dystrophy of the nails; hyperkeratosis of the palms and soles, hyperidrosis, follicular hyperkeratosis leading to warty growths around the larger joints, white patches on the tongue and corneal dyskeratosis. Not all the manifestations are present at birth, but the greatly heaped-up, claw-like nails are usually present and are the most constant features of the disease. Occasionally blisters are present, usually in association with the hyperidrosis.

Some authors have noted histological resemblance to Darier's disease, but the

diseases are believed to be distinct. The essential histological abnormality is dyskeratosis with hyperkeratosis and follicular plugging.

Heredity.—According to Cockayne (1933), the disorder was most prevalent among Slavs and Jews of Slavonic extraction, and there was a great preponderance of boys over girls, 21 : 5. The proportion of normal to affected sibs is far from the 1 : 1 ratio expected from a single dominant gene. The Filipino family of Clemente and the Indian family recorded in Fig. 97 show the dominance clearly. Cockayne considered the defect to be due to two autosomal dominant genes, neither of which alone caused abnormality.

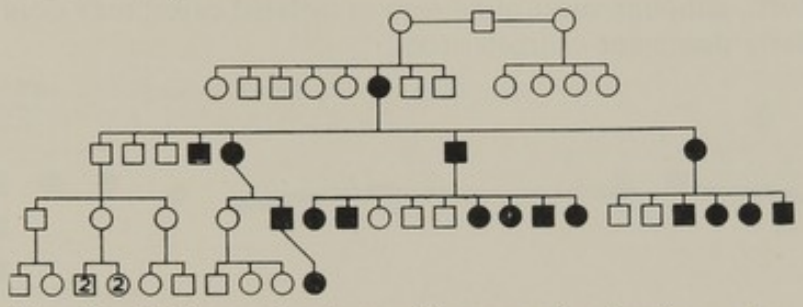


FIG. 97.—Pedigree of pachyonychia congenita showing regular dominant inheritance. (*By courtesy of Dr. D. Tipping.*)

Porokeratosis

Clinical aspects.—This affection, described in 1893 by Mibelli, is a progressive, chronic inherited abnormality which is usually first seen in childhood. The most commonly affected areas are the palms, soles, forearm, legs, face and trunk. The essential lesion is a hyperkeratotic papule or collarette. This collarette enlarges by peripheral extension and the centrally enclosed area of skin may become atrophic and depressed. The growing edge may be hard, raised and thickened, and have a sharp furrow or groove running along its peak. The hairs may be shed and replaced by horny plugging of the follicles. Hyperkeratosis and atrophy are more pronounced on the feet and hands and sites of friction than on the abdomen, thighs and face, where the hyperkeratosis may be mild and confined to the peripheral collar, and the atrophy minimal. Histology shows hyperkeratosis of the entire area involved but most markedly at the edge where there is a horny plug at the site of the groove. Parakeratosis is present. There is acanthosis and later atrophy of the prickle-cell layer, and lymphocytic infiltration of the upper dermis followed later by atrophy of the appendages and collagen degeneration.

Heredity—Numerous family histories have been examined and a regularly dominant autosomal gene is responsible. Gilchrist described 11 cases in 4 generations. Males are twice as commonly affected as females, both in isolated and familial cases, so there is partial limitation to the male sex.

Pili torti

Clinical aspects.—This affection generally appears in children who have been previously bald for the first year or two of life. The hairs of the scalp are usually short and microscopic examination shows them to be twisted through 180 degrees on their own axis at irregular intervals (Fig. 98). They are easily broken and the whole frizzy head gives a strange glint due to unequal reflexion of light from the twisted hairs. Sometimes the eyebrows and even eyelashes are affected (Fig. 100).

The condition has been reported in adults after shedding of the hair, and also localized pili torti following inflammation of the scalp. The cause of the twisting is probably irregular follicular growth.

Heredity.—Touraine in 1938 described pili torti occurring in the mother, 2 daughters and 3 sons; in this pedigree the eyebrows were also affected. Franchi has reported 3 brothers affected. The condition has also been reported in twins. Martin described a Spanish family with 7 affected persons in 3 generations. In the pedigree shown in Fig. 99 there were 5 cases (3 females, 2 males) in 3 generations. The eyelashes were also affected, which has not been hitherto reported.

Thus pili torti, although most often seen in isolated cases, may occur in families as an irregularly dominant characteristic.

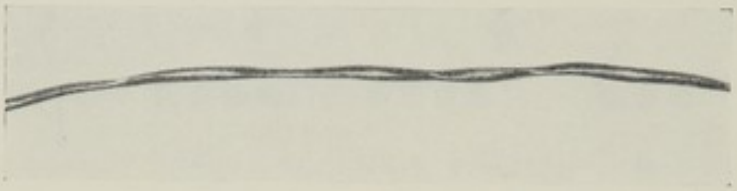


FIG. 98.—Pili torti, showing the hair twisted in several places through about 180 degrees.

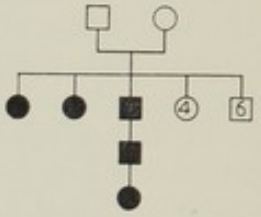


FIG. 99.—Pedigree of pili torti in which hairs of scalp and eyelashes were affected.

FIG. 100.—Pili torti, showing the affected eyelashes emerging at unusual angles.

Monilethrix

Clinical aspects.—This affection, in which there is beading of the hairs, was first described in 1879 by Smith. Its characteristics are its inherited nature, predilection for the scalp, gradually progressing alopecia and associated keratosis pilaris. The first appearance is usually in childhood, when the beading and fragility of the hairs leads to fracture about 5–10 millimetres from the scalp. The beading, which may be observed with a hand lens, consists of alternately normal and atrophic segments of the hair. These are produced by no definite cause, and

terms such as periodic aplasia of the hair follicles, endocrine dysfunction and trophoneurosis show the mystery of the origin. The keratosis pilaris usually occurs in the affected regions, but may extend farther.

Heredity.—Monilethrix is due to a single irregularly dominant gene according to Henck, Gossage, and Siemens. Saboraud describes a family which included 17 cases in 5 generations. A good example is the pedigree of Tobias (Fig. 101). Patients with monilethrix are almost invariably dark-haired, and it has been suggested that there is linkage between the conditions.

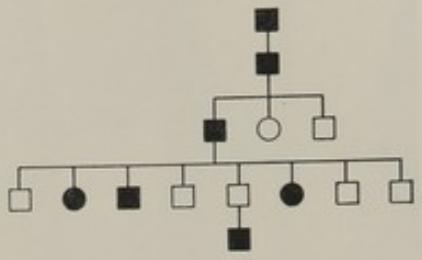


FIG. 101.—Dominant pedigree of monelithrix. (*After Tobias, N. (1923). Arch. Derm. Syph.*, **8**, 655.)

Pityriasis rubra pilaris

Clinical aspects.—This is a chronic exfoliative disease of the skin. It usually appears in childhood and the essential lesion is a discrete acuminate papule situated over the opening of the pilo-sebaceous follicle. The papule is horny. It plugs the opening and projects with the hair in a small cone-shaped spine. The disease usually first appears on the face as dry, adherent scales; similar scales may be seen in most other parts of the body. Later the typical papules appear and give rise to the nutmeg-grater or gooseflesh appearance which is particularly apparent on the backs of the fingers. Scaling becomes more evident and erythema is present. There may be severe palmar and plantar hyperkeratosis. The nails are often roughened and striated transversely. Histologically, there is hyperkeratosis, patchy parakeratosis (particularly around the openings of the hair follicles) and acanthosis. The dermis may show mild chronic inflammatory changes. In a few patients deficiency of vitamin A has been proved, but administration of the vitamin seldom produces change in this disorder. The disease may advance and become generalized, but the health is usually unimpaired. A few fatal cases have been described, however. Spontaneous resolution has been reported.

Heredity.—Many families have been described in which the abnormality is apparently due to a dominant gene which is usually of high penetrance. Werner and Levine (1943) described a family with 39 cases in 3 generations. No associated abnormalities have been described.

Other affections

Piebald

Piebald individuals, who may perhaps be regarded as partial albinos in so far as their absence of pigment is incomplete and inherited, often have a blaze on the forehead, with non-pigmented spotting of the limbs and trunk. In families the picture tends to remain constant (Fig. 102). Most cases are inherited as a simple dominant characteristic (Fig. 103). Gates quotes the extensive six-generation pedigree described by Miller (1915) and states that the origin of the

white forelock goes back even farther to Harry (Hotspur) Percy who was killed at the Battle of Shrewsbury in 1403. Dominant pedigrees have been reported in Negro families and in Negro and white crosses. The anomaly may be of a more widespread affection (*see* Figs. 52 and 67 and relevant text).

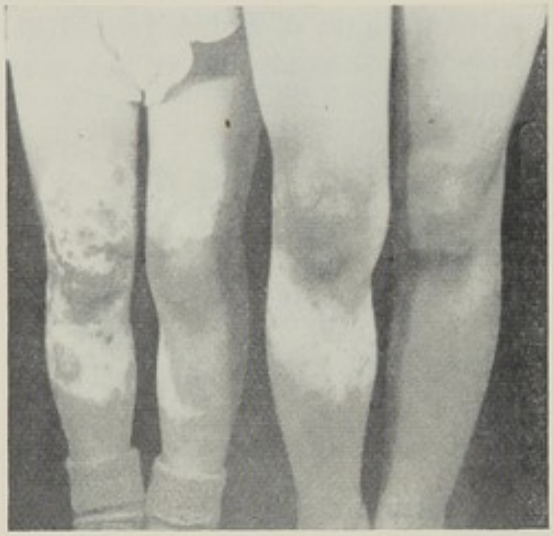


FIG. 102.—Partial albinism: congenital leucodermia in sisters. (*By courtesy of St. John's Hospital and the Institute of Dermatology, London.*)

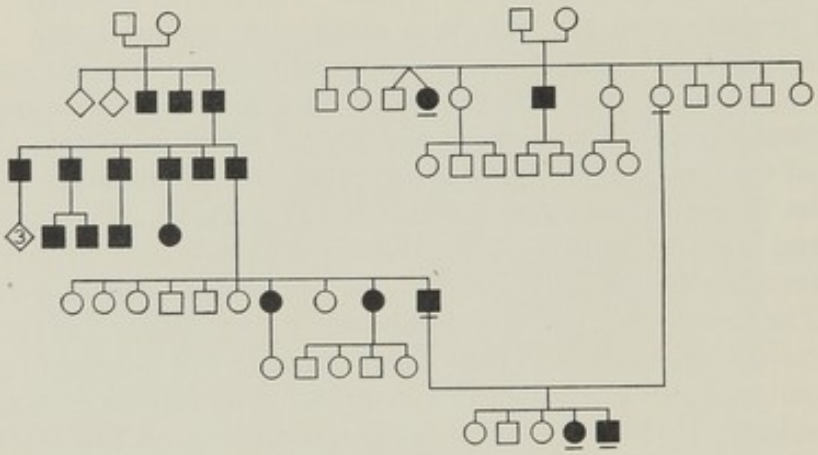


FIG. 103.—Pedigree of white blaze of forehead and congenital leucodermia. (*After Germeraad, H. (1951), Ned. Veren, Derm. Rotterdam.*)

Alopecia

Premature baldness is the most important type of alopecia genetically, and has been discussed elsewhere.

Alopecia congenita is a rare condition in which more or less complete absence of hair is present at birth or occurs soon afterwards. Dominant recessive and sex-linked pedigrees have been recorded which are clinically indistinguishable and which require no description.

Porphyria

Porphyria, primarily a disease of metabolism and excretion of porphyrins, is discussed fully elsewhere. The cutaneous lesions, which are always significant,

first consist of blisters containing clear or blood-stained fluid. These bullae are found on all exposed sites, including the scalp. They heal with atrophic scarring and hyperpigmentation. Milium bodies and telangiectasia may be present. The skin generally is dry, inelastic, and sweating is reduced. Due to recurrent blistering with resulting scars and contractures, the hands may become grossly distorted and useless, and the ears and nose deformed. Hypertrichosis is found particularly in females.

DISORDERS OF MESODERMAL CELLS

Connective Tissue

Epidermolysis bullosa

This is one of the most well-recognized inherited abnormalities of the skin, and was first described in 1879 by Tilbury Fox. It is a rare disease, but large numbers of cases have been recorded. Two types have long been recognized. Physicians speak of the simple and the dystrophic (Kobner) and geneticists of the dominant and the recessive (Siemens). There is not exact correspondence between these classifications, for while the simple form is inherited as a dominant, the dystrophic form may be dominant or recessive. Touraine (1942) has reviewed 1,181 cases of the disease and the percentages given here are taken from his study.

Clinical aspects

Simple epidermolysis bullosa.—This appears in the first year of life—men were affected in 59 per cent of cases. The bullae are always traumatic in origin, are most frequent in hot weather. They occur particularly at the sites of trauma, on the fingers, knuckles, toes and ankles. They are superficial, heal without scarring and leave only temporary pigmentation. There are no epidermal cysts and Nikolsky's sign is absent. The mucosal surfaces were affected in 2 per cent of cases. The bullae are intra-epidermal, small or medium sized, generally very tense, and the contents are clear.

Dystrophic epidermolysis bullosa (*hyperplastic type*).—The disorder begins at any time between birth and puberty. The bullae are usually traumatic, but occasionally occur spontaneously, and are mostly confined to the head and limbs. The mucous membranes are affected in 20 per cent of cases. The bullae are intra-epidermal or at the epidermo-dermal junction, small or medium sized, tense, and the contents are clear, although occasionally haemorrhagic. The deeper sub-epidermal bullae heal with scarring or keloid formation. Epidermal cysts may be present in small numbers. Nikolsky's sign is often present. Pasini described albo-papuloid lesions which occur in this and the preceding groups. The lesions consist of lichenoid white papules, 1–2 millimetres in diameter, situated in the so-called seborrhoeic areas; in the centre of the papules may be seen the dilated opening of the sebaceous duct. The papules are not related to the bullae. Acne vulgaris often accompanies this condition. The following hyperplastic conditions may also occur: ichthyosis, palmar and plantar keratosis and hyperidrosis, keratosis pilaris, mucosal keratoses, thickened deformed nails, and hypertrichosis.

Dystrophic epidermolysis bullosa (*hypoplastic type*).—The onset is usually at or soon after birth. The bullae arise spontaneously at any time of the year and on any part of the skin. The mucous membranes are also usually affected. The bullae generally occur at the dermo-epidermal junction and are accompanied by lesions of the vessels and neighbouring elastic tissue; they are medium sized or large, very often flaccid, and often haemorrhagic (Fig. 104). Epidermal cysts are

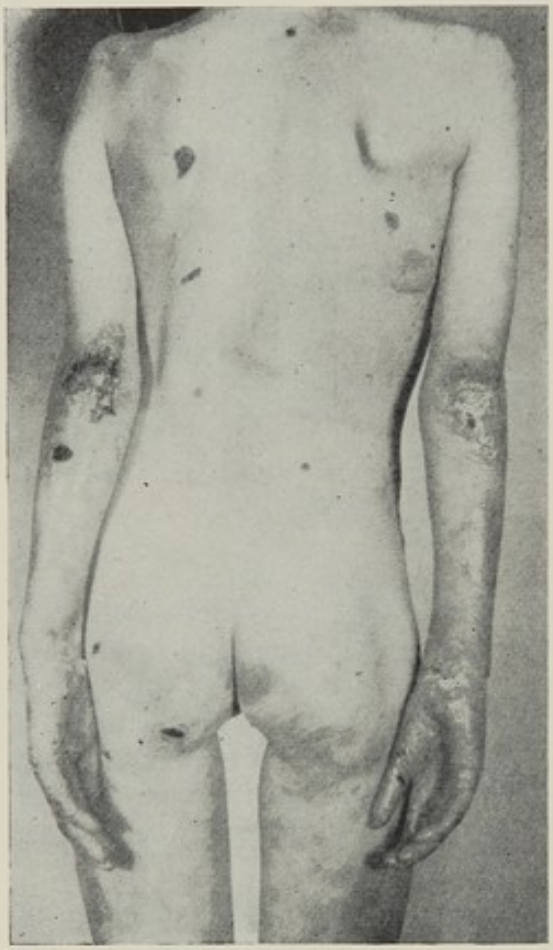


FIG. 104.—Epidermolysis bullosa: hypoplastic recessive type. Note large flaccid bulla below right scapula, atrophic scarring of elbow, forearm and hand. (*By courtesy of Dr. R. T. Brain.*)

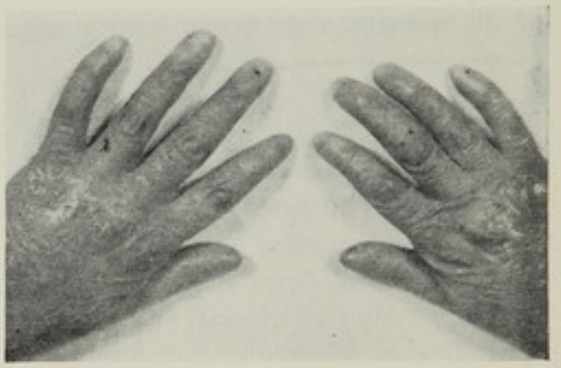


FIG. 105.—Same case as Fig. 104, showing absence of nails and atrophy. (*By courtesy of Dr. R. T. Brain.*)

common and scarring the rule. Nikolsky's sign is often present. The following hypoplastic abnormalities may also occur: thin, xerodermic, presenile skin; absent or rudimentary nails (Fig. 105); atrophic, sometimes acrosclerotic fingertips; hypoplasia, malformation and early caries of teeth. There may also be corneal involvement, hypotrichosis, or porphyria, and blood, endocrine or psychiatric disorders. There are neither cutaneous nor mucosal keratoses. Death may occur *in utero*, in the first few days of life, or later on.

Heredity

Simple epidermolysis bullosa.—The heredity is regularly dominant (Fig. 106) and constitutes 45 per cent of all cases.

Dystrophic epidermolysis bullosa (*hyperplastic type*).—Inheritance is due to a single autosomal gene of high degree of penetrance (Fig. 107). It accounts for some 29 per cent of all cases.

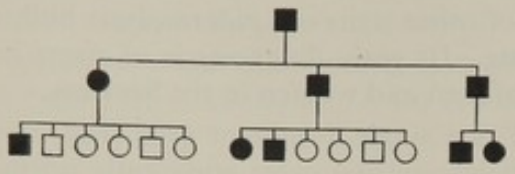


FIG. 106.—Dominant pedigree of simple epidermolysis bullosa. (*After Bamber, G. (1935). Proc. R. Soc. Med.*, **29**, 95.)

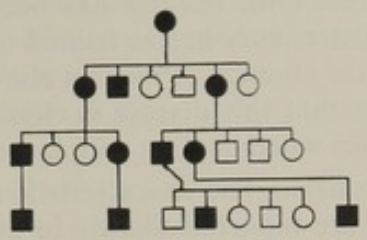


FIG. 107.—Dominant pedigree of dystrophic epidermolysis bullosa. (*After MacKenna, R. M. B. (1937). Brit. J. Derm.*, **49**, 448.)

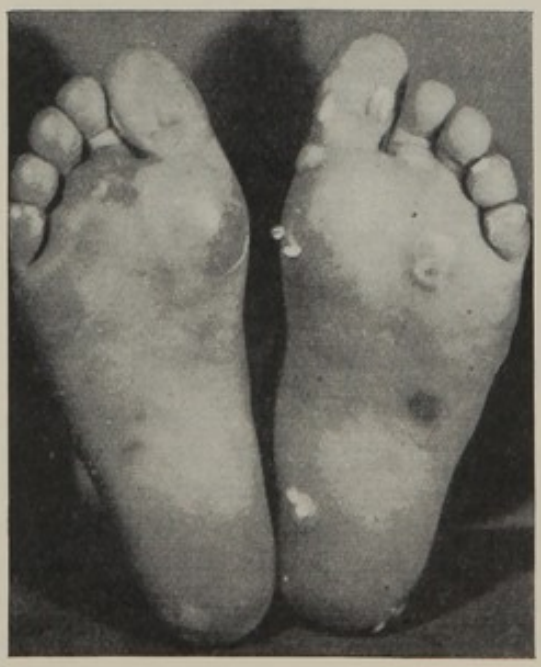
Dystrophic epidermolysis bullosa (*hypoplastic type*).—This group is usually caused by a single recessive gene and accounts for 26 per cent of all cases.

Whilst the classification into three types is clinically and pathologically justifiable, it is not known whether or not there are three genes involved, nor is there any known relationship between the simple dominant and recessive gene. Several other atypical forms of epidermolysis bullosa have been described, but they are excessively rare. One such form was inherited as an incompletely sex-linked recessive, the pedigree of which was traced for 12 generations.

Recurrent bullous eruption of the feet

This affection was first described as a hereditary disease by Cockayne (1938). It had previously been recorded in isolated cases, but has since been recognized by Haldane and Poole (1942), who describe a pedigree of 18 cases (10 males, 8 females) in 4 generations and by Cockayne (1947).

FIG. 108.—Recurrent bullous eruption of feet. (*By courtesy of St. John's Hospital and the Institute of Dermatology, London.*)



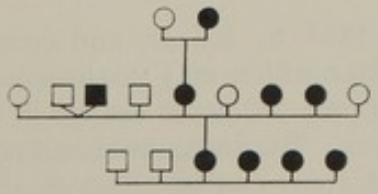


FIG. 109.—Dominant pedigree of bullous eruption of feet.

Clinical aspects (Fig. 108).—The blisters, which are normally first seen in infancy, recur throughout life in the hot summer weather. There is often hyperidrosis of the feet. Disability may be so great that walking is impossible, and the patient must rest until healing has occurred; this takes place without scar formation. The blisters vary in size from 1 to 5 centimetres in diameter. The fact that there is complete absence of blisters elsewhere and of other signs of epidermolysis bullosa suggest that this disease is clinically separate. Its early diagnosis is of some importance when dealing with large numbers of men and women in the Services.

Heredity.—The characteristic is inherited as a single dominant gene (Fig. 109). Males are reported slightly in excess of females; in two cases apparently normal persons have transmitted the disease. The two most striking pedigrees are those of Fourman and Test (1946), containing 145 affected persons. It is not certain however, whether the condition they describe is identical, as the hands were in most cases affected in addition to the feet.

Multiple lipomatosis

Multiple lipomas occur in any situation, and may be very disfiguring. Apart from this they are not clinically important. Several pedigrees have been reported in which there was evidence of a single dominant gene, but isolated cases are more common. The pedigree of Grebe (Fig. 110) is interesting in that it shows the coexistence of achondroplasia and multiple lipomatosis. It has also been reported in association with multiple neurofibromatosis and tylosis palmaris et plantaris.

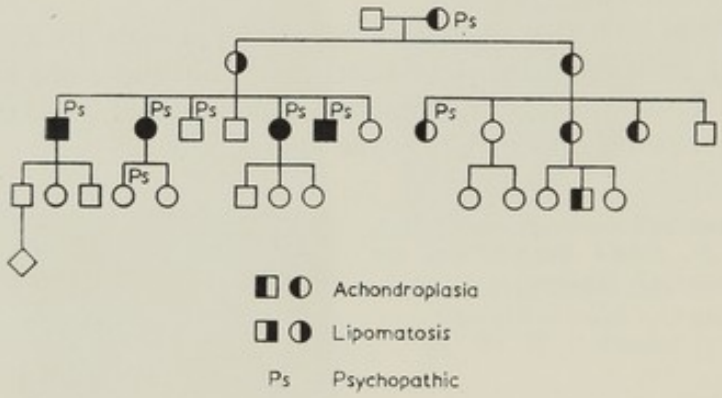


FIG. 110.—Pedigree of multiple lipomatosis, achondroplasia and psychopathic personality. (*After Grebe, quoted by Touraine, A., in Encyclopaedie Médico-Chirurgicale*, 12107, *Paris*.)

Pseudoxanthoma elasticum

Clinical aspects.—This was first described in 1884 by Balzar, and consists of collections of papules 1–5 millimetres in diameter which may coalesce to form plaques or linear arrangement. The papules are pale yellow or orange in colour, and are usually situated in the axillae or on the neck. The antecubital and popliteal fossae and groins are also often affected; most areas can be affected, although the palms, soles and head are usually spared. The neighbouring skin is lax and easily stretched and the normal folds exaggerated. In 1928 Gröndblad described

the association with angioid streaks in the retina, the so-called Gröndblad-Strandberg syndrome. The disease consists of a basophilic degeneration of the elastic tissue in the mid-cutis, which is separated from the epidermis by normal collagen and elastic tissue. The " retinal " changes are probably due to a similar degenerative change in the membrane of Bruch. Similar degeneration has been found in the elastic tissue of the heart.

Heredity.—The abnormality is probably inherited as a recessive and there is perhaps partial limitation to the female.

Vascular Tissue

Hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber)

Clinical aspects.—In this affection there are repeated bleeding, telangiectasia and a family history of one or both of these. It was first described in 1876 by Legg. Since then many reports have appeared and records of the disease have increased so that Garland and Anning (1950) in their comprehensive survey were able to collect together with their own 20 new pedigrees, nearly 1,500 cases

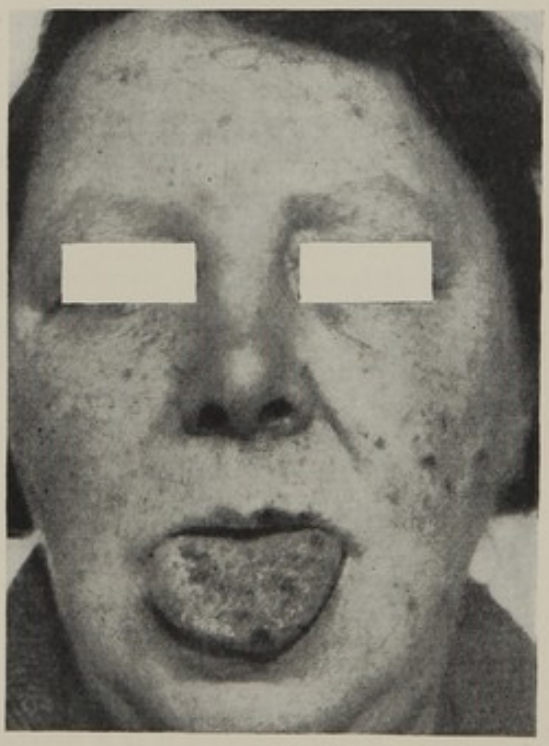


Fig. 111.—Multiple haemorrhagic telangiectasia.

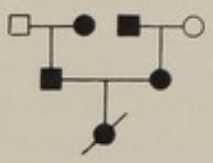


Fig. 112.—Pedigree of haemorrhagic telangiectasia. The infant in the third generation died of multiple angiomatous lesions. Parents and grandparents were affected typically. (*After Snyder, L. H., and Doan, C. A. (1944). J. Lab. clin. Med.*, **22**, 1211.)

in 244 families. The multiple telangiectases appear most commonly on the face (Fig. 111), in the mucous membranes of nose and mouth, on the conjunctivae and beneath the nails. They may be small, of the " spider naevus " type, or large and show a central nodule of vascular tissue. Epistaxis, which may be very severe, is usually the first and commonest single symptom, and it generally precedes the onset of cutaneous telangiectasia. Post-mortem and clinical examinations have

shown that the mucous membranes of the throat, bronchi, lungs, kidneys, bladder and entire gastro-intestinal tract may be involved. This sometimes leads to unexplained bleeding, particularly if more superficial telangiectasia is absent or not sought after. Anaemia is common and death sometimes occurs from haemorrhage. Touraine estimates the death rate from this cause at 4 per cent. The disease usually appears in childhood but may not become manifest until the age of 30 years or over. Some families show a marked tendency for involvement of particular sites. In a family described by Wigley the favoured site was the genito-urinary tract. Histologically, there is proliferation and dilatation of capillaries.

Heredity.—The disease is caused by the presence of a single regularly dominant gene. Males and females are equally affected, and equally able to transmit the disease. Jews are more often affected than gentiles. There is a history of " normal conductors " in the literature but, as Garland and Anning point out, only one of these was examined by the authors concerned. The homozygous case of Snyder and Doan (Fig. 112) led these authors to regard the causal gene as being due to a " semi-dominant lethal ". Their case was that of an infant, born of affected parents (each of whom also had an affected parent), who died aged 2½ months as a result of multiple haemorrhages. Post-mortem examination showed a " fundamental deficiency involving solely the vascular tree, more particularly the capillary bed and small vessels leading to multiple telangiectatic haemangio-endotheliomas involving the entire superficial skin and mucous membranes and the majority of the internal organs including lungs, spleen, liver, intestines, kidneys and brain ". It would therefore seem that although the disease is caused by a single dominant autosomal gene, complete expression is not obtained in the heterozygous state.

Congenital lymphoedema (congenital trophoedema or Milroy's disease)

There is an abnormality of growth of the lymph vessels, almost always confined clinically to the lower limbs. The manifestation is oedema of the non-pitting variety, and the condition may be of congenital or late onset. In the congenital form the disease is inherited as a simple autosomal dominant, not always expressed, but in the late-occurring form although there is dominance, there is a preponderance of affected females and female transmitters. It has been suggested that this is due to another modifying gene on the sex chromosome. An example of congenital ptosis and lymphoedema is shown in Fig. 113.

Urticaria pigmentosa

Clinical aspects.—There are two forms of this disease: the adult and childhood varieties. Pathologically it is a mast-cell naevus, and clinically it is characterized by red-brown or brown pigmented macules and nodules which urticate on friction or when the patient becomes hot, as in bathing. The lesions may be few in number. but are usually distributed symmetrically over the trunk, back and limbs (Fig. 115). Vesicles and bullae are often seen in the congenital cases. As the child grows older they gradually disappear and their place is taken by the typical macules and nodules. There is a tendency for the lesions to fade with age. Little collected 154 cases, and found the disease commoner in fair children.

Heredity.—Nearly all reported cases are sporadic, but a few familial cases have been reported (Fig. 114). Cockayne considered the disease to be inherited, but whether due to a single gene is not certain. Consanguinity has not been mentioned in any cases, but it is possible that it is due to recessive inheritance.

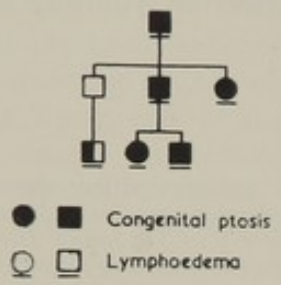


FIG. 113.—Pedigree of congenital ptosis and congenital lymphoedema. (*After Bloom, D. (1941). N.Y. St. J. Med.*, **41**, 856.)

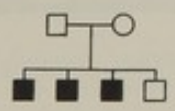


FIG. 114.—Darier's pedigree of urticaria pigmentosa. (*After Touraine, A., in Encyclopaedie Médico-Chirurgicale*, 12107, *Paris.*)

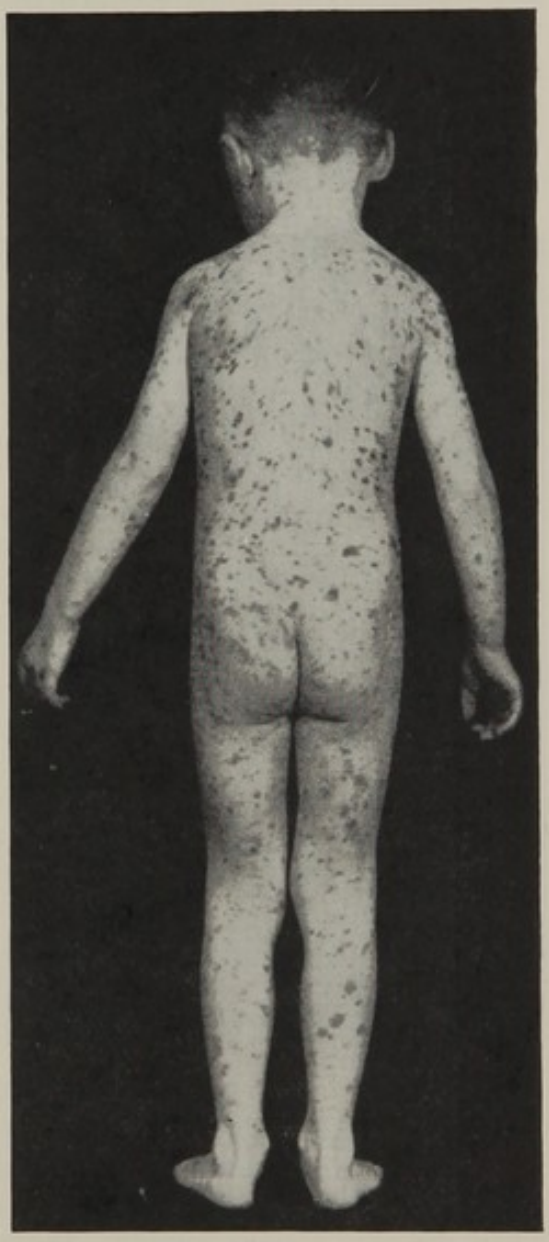


FIG. 115.—Urticaria pigmentosa. (*By courtesy of St. Thomas's Hospital.*)

HISTIOCYTES

Xanthomatosis

This group of diseases with their important cutaneous and general manifestations are discussed in Chapter 12.

DISORDERS OF ECTODERMAL AND MESODERMAL CELLS

Epiloia

Clinical aspects.—This is a rare disease in which mental defect and epilepsy are associated with tumours of the brain, skin and certain viscera, notably the heart and kidneys. The disease was first recognized as an entity by Bournville in 1880 who described the association of the brain tumours—tuberous sclerosis—and skin lesions—adenoma sebaceum. Pringle described the skin lesions in detail, and in 1911 Sherlock used the term epiloia to describe the syndrome of adenoma sebaceum (Pringle), epilepsy and mental deficiency.

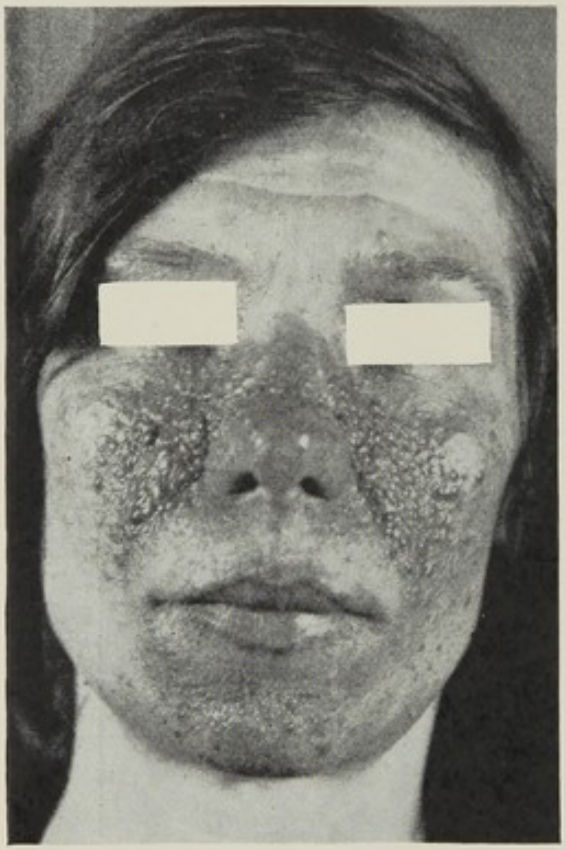


FIG. 116.—Epiloia: patient showing adenoma sebaceum telangiectasia and very greasy skin. (*By courtesy of St. John's Hospital and the Institute of Dermatology, London.*)

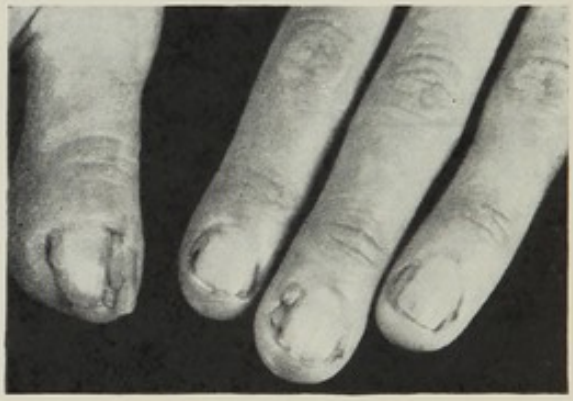


FIG. 117.—Epiloia: showing subungual and peri-ungual fibromas. (*By courtesy of St. John's Hospital and the Institute of Dermatology, London.*)

Adenoma sebaceum is only one feature of the disease process, and should not be separately considered. The disease affects all races; men and women are equally liable to suffer and transmit it. It is usually first manifest in early childhood when the skin lesions appear. These take the form of small papules on the " butterfly " area of the face. With increasing age the papules grow in size and number, and form nodules and small tumours 1–10 millimetres in diameter which are yellow to red-brown in colour. They are usually confined to the face, which is often very greasy (Fig. 116). The upper lip is typically spared. Histologically, there is increased growth of the sebaceous gland tissue and epidermal thinning. Variations in the amount of vascular and fibrous tissue elements are responsible for the different types of adenoma sebaceum described. Telangiectasia may be a

prominent feature and the face may be permanently scarlet. Pigmented and warty naevi of the face may be present and skin tags are common on the neck. Peri-ungual and subungual fibromas are typical (Fig. 117) and similar fibromas may be seen in the mouth and in the nose. Raised, thickened connective tissue plaques, the " shagreen patches ", are found particularly in the lumbo-sacral region. There may be *café-au-lait* pigmentation, indistinguishable from that found in von Recklinghausen's disease.

Associated with these superficial cutaneous manifestations are tumours of the brain, heart and kidney, which are responsible for the severity of the disease. Throughout the brain substance may be found tumours of 5–50 millimetres in diameter consisting mainly of neuroglia and astrocytes. These merge into the surrounding tissue and produce distortion. They often undergo degeneration. Depending on size and situation they may lead to signs such as epilepsy, exophthalmos or mental deficiency. The kidney tumours may be fibromas, sarcomas or hypernephromas. Tumours in the heart are usually multiple, small rhabdomyomas. Tumours have also been reported in the liver, spleen, lungs, duodenum, thyroid and thymus. Retinal tumours, " phakomas ", are occasionally seen.

Heredity.—Epiloia is inherited as an irregular dominant characteristic, which may show variable degrees of expression. Any of the signs of the syndrome may exist independently or in any combination, and this variable expression occurs in different members of the same pedigree. An explanation of this has been given by Penrose (1936), who estimated the mutation rate at 1: 40,000. He believes that modifying autosomal dominant gene *B* may influence the pathogenic gene *M*, and give rise to these various phenotypical or clinical groups. The patients are heterozygous for epiloia (*Mm*), and genotypically are *Mm.BB*, *Mm.Bb*, and *Mm.bb*. These genotypes could then be classified respectively thus: (1) Mild cases which may pass for normal except under close scrutiny; in these the pathogenic gene is modified. (2) Intermediate cases in which only one of the three systems—brain, viscera, skin—are affected; the gene is partly modified. (3) Severe cases in which more than one system is involved; the gene is not modified.

It may be concluded that epiloia is due to a single dominant gene which may be affected by a modifying gene, thus producing the different phenotypes and the clinical variations. Adenoma sebaceum, the cutaneous manifestation, is regarded as only part of the whole disease.

Multiple neurofibromatosis (von Recklinghausen's disease)

Clinical aspects.—This condition is fairly common. It has been found in most races and in either sex, and is characterized by the presence of multiple sessile or pedunculated tumours irregularly disseminated over the skin (Figs. 118 and 119), similar tumours along the course of the deep and subcutaneous nerves, and brown pigmentation of the skin and mucous membranes. The tumours may be soft or firm, and range in size from several millimetres in diameter to 10 centimetres or more. They are nerve-sheath tumours and may occur singly; they are often found on the acoustic nerve. When situated in or near deep organs such as the suprarenal, pituitary, thyroid, parathyroid or brain, they produce the expected changes from pressure or destruction. These changes are of course secondary, and deafness, mental disorder, skeletal defects and pituitary dysfunction are examples. Tumours

may undergo sarcomatous metaplasia, but this is uncommon and probably occurs in less than 5 per cent of cases. The pigmentation varies in intensity, is patchy, and may occur independently of the subcutaneous tumours. The disease is essentially benign but disfiguring.

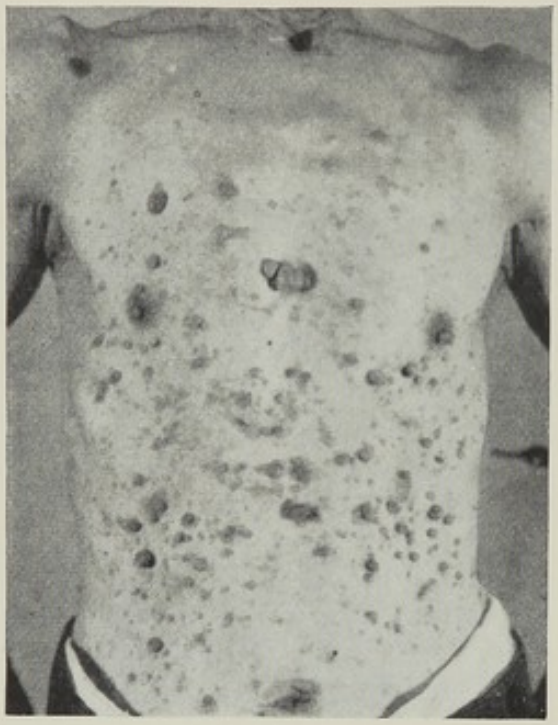


FIG. 118.—Multiple neurofibromatosis. (*By courtesy of St. Thomas's Hospital, London.*)

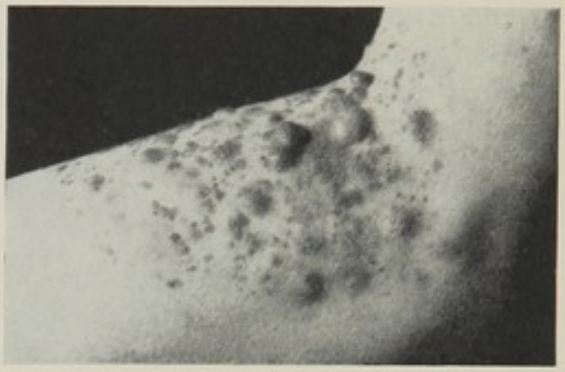


FIG. 119.—Neurofibromatosis showing localized tumours on the forearm. (*By courtesy of St. John's Hospital and the Institute of Dermatology, London.*)

FIG. 120.—Pedigree of multiple neurofibromatosis: III/I died of fibrocarcoma with metastases.

Heredity.—There is a tendency for affected members of the same family to show more or less similar clinical pictures, although different families may vary somewhat in the degree of tumour formation or of pigmentation, and in the situation of deeper neurofibromas. Cockayne describes over 100 families in which neurofibromatosis was inherited as a strictly dominant character. Nearly all the pedigrees described by the numerous authors on the subject indicate the presence of a single dominant gene with a high degree of penetrance and variable degree of expression (Fig. 120). This may be partly explained, however, by the fact that pigmentation or deep-seated tumours have passed unnoticed; and, of course, not all the family is usually examined by a critical physician. It is possible that a modifying gene may influence the pathogenic gene, as in epiloia. Certainly the clinical picture is definite and circumscribed but it must be remembered that not all the features of the disease are necessarily present in every patient. Whether the dominant pedigrees of bilateral acoustic neurofibromas, which have been reported in absence of other signs of von Recklinghausen's disease, are due to the same gene is not so certain. Several authors have suggested that adenoma sebaceum and multiple neurofibromatosis are part of one disease, but clinical and genetical evidence against this seems to be overwhelming.

Psoriasis, an exceedingly chronic disease, is responsible for about 5 per cent of all out-patients seen in dermatology. Its essential lesions are red-brown, scaly papules which form aggregations of various shapes and sizes and are labelled by such descriptive terms as guttate, gyrate, follicular and pustular. The most commonly affected areas are the scalp and the extensor aspects of the limbs, particularly the knees and elbows. The nails may be affected by brittleness, pitting or great thickening, and the so-called pustular psoriasis occurs on the palms and soles. In such a common disease rheumatoid and other forms of arthritis are often seen. The term arthropathic psoriasis is reserved for those cases in which the terminal interphalangeal joint is typically affected. The aetiology of psoriasis is obscure. There is no doubt that it " runs in families ", and the more carefully the family history is examined the higher is the proportion found of patients with affected parents and siblings. Probably as much as one-third of all patients have such a family history. Lerner (1941) studied the family trees of 172 private but otherwise apparently unselected patients. He found an incidence of 42 per cent in immediate relatives. He quotes the very extensive work of Hoede who found a " familial incidence " of 39 per cent in 539 cases. The disease is probably due to a single autosomal gene of irregular dominance. Recessive pedigrees have been reported, a good example being that described by Snyder (Fig. 121). Dominance is usual, however, as is shown in Fig. 122. A case has been seen recently in which the mother and all 13 children were affected (7 males, 6 females).

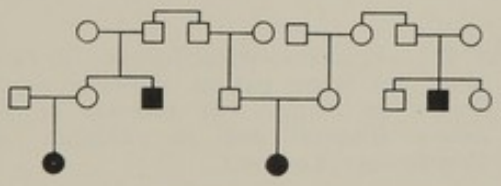


FIG. 121.—Recessive pedigree of psoriasis. (*After Snyder, L.H. (1941), Medical Genetics, p.54. Duke University Press.*)

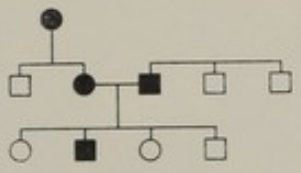
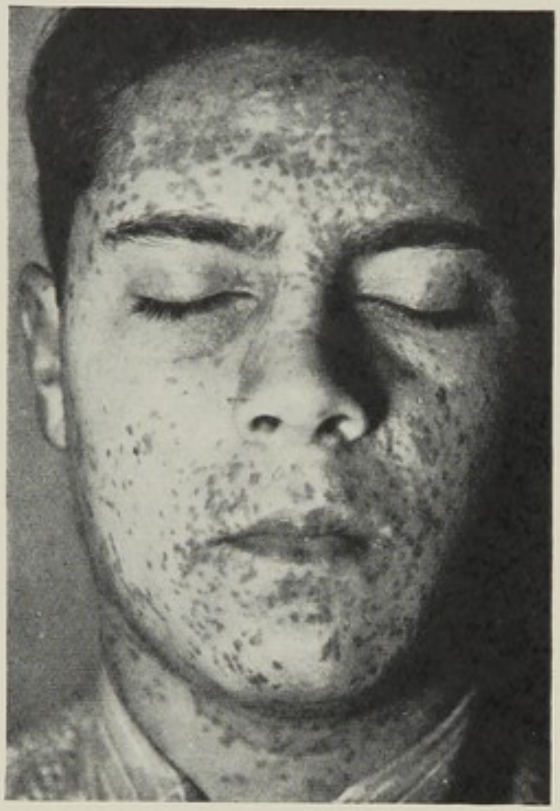


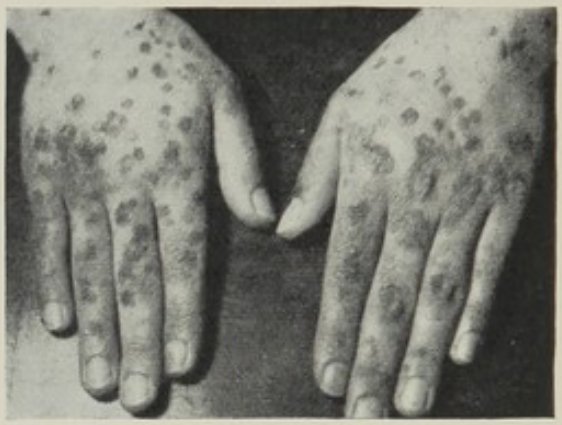
FIG. 122.—Pedigree of psoriasis showing dominance.

Epidermodysplasia verruciformis is the ponderous name given to a disease first described in 1922 by Lewandowsky and Lutz. Other names suggested are " congenital dyskeratotic verruca " and " verrucosis generalisata " The appearance is of flat, polygonal papules which usually appear first on the extremities. The face, neck and dorsal surfaces of the hands and feet are most often affected (Fig. 123*a* and *b*); occasionally, lesions are scattered over the whole body. Clinically, there is resemblance to juvenile or plane warts and to acrokeratosis verruciformis (Hopf). The diagnosis can be confirmed only by biopsy. Histology shows acanthosis and vacuolation of the prickle cells and hyperkeratosis with the typical " basket weave " appearance of the stratum corneum. The disease is regarded by some as a pre-cancerous state, for superficial basal-cell carcinomas have been found not infrequently on the facial lesions. The majority of cases have a family history of consanguinity (Touraine, Wise). Inheritance is probably by a single recessive autosomal gene.

Eczema.—The so-called eczema-asthma-hay fever syndrome is frequently found in several members of a family. This type of eczema usually begins in infancy or early childhood, and exacerbations often occur when teeth are being cut. There is a tendency for the skin condition to improve with time, and probably less than 10 per cent of affected infants still have eczema at puberty. Many irregular dominant pedigrees have been described, but mental and physical environmental influences play a major part in the evolution.



(*a*)



(*b*)

FIG. 123.—Epidermo-verraciformis. (*a*) *Face view.* (*b*) Same patient showing warty lesions on hands. (*By courtesy of St. John's Hospital and the Institute of Dermatology, London.*)

Alopecia areata has often been found in several members of a family. Its precise cause is unknown. In the familial cases, which are much less numerous than the sporadic cases, inheritance seems to be due to a single dominant gene.

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CHAPTER 14

SKELETAL SYSTEM, INCLUDING JOINTS

HAROLD F. FALLS

THE EXTENT and range of inherited human skeletal and joint abnormalities, as well as normal variations, are very wide. Probably more abnormalities of the bone and joint system are known than for any other part of the body, with the exception of the eye and the skin. Many bone anomalies pertain to more than one system whereas others are restricted to minute structural alterations of a specific part. As is true of other inherited human pathology, the skeletal diseases may present similar phenotypes which originate from different genotypes, and furthermore, intra-uterine noxious agents, such as rubella, toxoplasmosis, dietary insufficiency, exanthems, and others may effect structural changes indistinguishable from those due to a gene influence.

Skeletal as well as other specific systemic abnormalities may be present in an affected individual and may be transmitted as a unit, comprising what is known as a syndrome. As in most syndromes it is the exception rather than the rule to find the complete syndrome in one affected individual.

I. GENERALIZED AFFECTIONS OF THE SKELETAL SYSTEM*

CHONDROMATOSES

Clinical aspects

Diaphyseal aclasis (*multiple cartilaginous exostoses*)

The distinguishing feature of diaphyseal aclasis is the formation of exostoses near the extremities of the diaphyses of the long bones (Fig. 124). They may be present as multiple, more or less symmetrical, cartilaginous and osteocartilaginous growths in and upon the skeletal system, generally benign, and resulting from a disturbance in proliferation and ossification of bone forming cartilage.

Enchondromas (*Ollier's dyschondroplasia*)

In Ollier's dyschondroplasia multiple enchondromas of the shafts of the tubular bones are irregularly distributed in the skeleton, but tend to be unilateral and characteristically produce shortening deformities of the affected bones. Fairbanks (1948) insisted on the restriction of endosteal changes to this disease and differentiated it from multiple exostoses or diaphyseal aclasis. A bizarre combination of enchondromas with multiple cavernous haemangiomas (Fig. 125) passes under the name of *Maffucci's syndrome*.

* The writings of H. A. T. Fairbanks (1948, 1949, 1950) have been freely utilized in this section.

FIG. 124.—Multiple exostosis of femur, tibia and fibula.

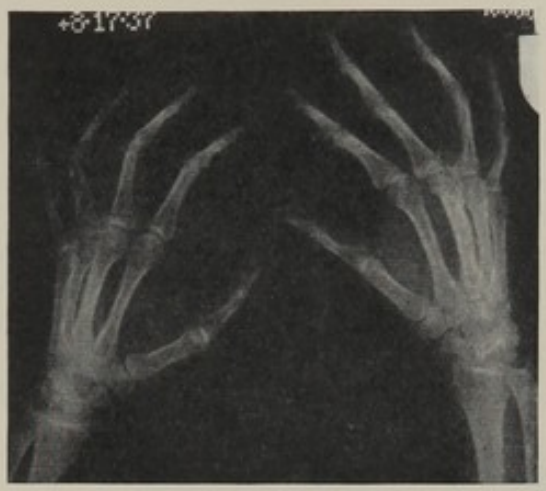


FIG. 125.—Hands in Maffucci's syndrome, note presence of phleboliths.

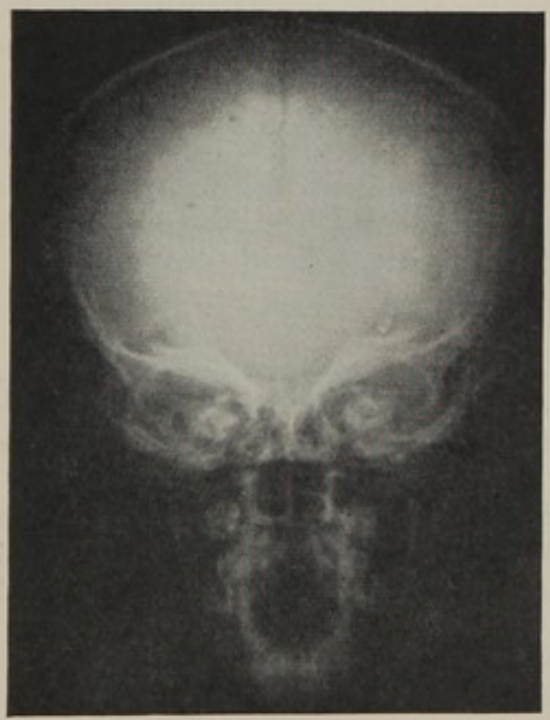


FIG. 126.—Achondroplasia. Constriction of the base of the skull and dilated calvarium.

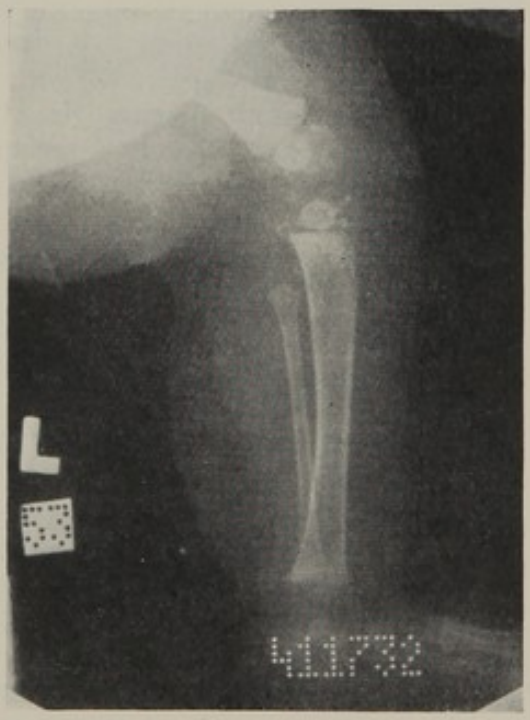


FIG. 127.—Dysplasia epiphysitis punctata. Epiphyseal dysgenesis. Left lower extremity. Female, aged 10 months.

Achondroplasia (*chondro-dystrophia foetalis*)

Achondroplasia is characterized by congenital dwarfism of the short limb type, trident hands, and a large head (Fig. 126). These manifestations vary considerably. The disease is dependent upon defective development of the chondral ossification

with involvement of the epiphyses of the long bones. All races of man have been affected. A slightly higher incidence of affected females is known.

Dysplasia epiphysitis punctata (*chondrodystrophia calcificans congenital*)

Dysplasia epiphysitis punctata, a rare disorder, is characterized by the presence of a number of discrete centres of unusual density in many cartilaginous epiphyses and apophyses (Fig. 127). The affected individual presents dwarfism, with a large head, bossing of the skull, flexion contractures of the joints, congenital cataract, dulled intellect, blunt, short fingers, and a generalized weakness. The disorder is considered congenital. Females are affected in slightly greater numbers. Hypothyroidism has not been observed in the familial cases.

Osteochondrodystrophia deformans (*Brailsford-Morquio dystrophy*)

In osteochondrodystrophia deformans there are widespread skeletal abnormalities. Kyphosis develops in early childhood, there is undue prominence of the lower thorax, and a resultant short, thick trunk with a moderate degree of micromelia. The child is a deformed dwarf with several cardinal manifestations : normal head, short neck and trunk, kyphosis, multiple deformities of the extremities, with knock-knee and flat-foot due to relaxation of the musculature and tendons. The shortening of the neck and trunk is the result, roentgenologically, of a universal vertebra plana. Sorsby (1951) believes that the skeletal abnormalities attributed to Morquio's disease are part of the clinical picture of gargoylism ; however, the bright and cheerful disposition, with absence of skull involvement, strongly contrasts this child from the gargoyle. Both sexes are affected.

Silverskiöld's syndrome is a variant of this affection. It is characterized by slight changes in the vertebral column, but with the major skeletal changes localized especially to the extremities. The extremities are shortened and curved with plump articular regions, genu valgum and genu varum. The sex incidence is equal.

Chondro-ectodermal dysplasia

Chondro-ectodermal dysplasia is an apparently new syndrome featuring a tetrad of cardinal signs : (1) dysplasia of hair, teeth and nails; (2) chondrodysplasia and shortening of tubular bones; (3) polydactyly; and (4) an occasional congenital malformation of the heart.

In all of the patients the ectodermal dysplasia has apparently been of the hydrotic type since no disturbance of the sweat glands or sebaceous glands was evidenced. The clinical manifestations are congenital but become more marked with advancing age.

Polyostotic fibrous dysplasia (*Albright's syndrome*)

Polyostotic fibrous dysplasia is a rare, bizarre disease of the childhood skeleton characterized by a peculiar fibrous dysplasia of the bones with cystic changes, patchy brown pigmentation of the skin and precocious sexual changes. The latter occurs chiefly in females, but has been recently observed in males. The bony dystrophy, cystic lesions, roentgenographically develops in multiple sites with irregular distribution throughout the entire skeleton, but most commonly at the extremities of the diaphyses. The deformities may be unilateral or rarely generalized.

The base of the skull and calvarium may obtain enormous thickening, resulting in optic atrophy and other cranial nerve pressure. A great deal of variability exists, with many incomplete syndromes or *formes frustes*. Fairbanks does not regard leontiasis ossea, occurring alone, as different and distinct from the hyperostosis of the skull seen in many cases of polyostotic fibrous dysplasia.

Osteopetrosis

This is a relatively rare generalized dystrophy of the skeleton characterized by a widespread but uneven heavy amorphous sclerosis (marble bones) (Fig. 128). The thickened cortex encroaches upon the medullary cavity which reduces the haemopoietic function and results in a progressive severe anaemia. The bones

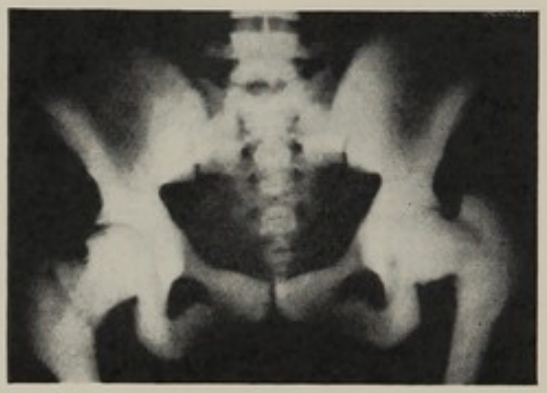


FIG. 128.—Osteopetrosis. Generalized osteosclerosis of the pelvis.

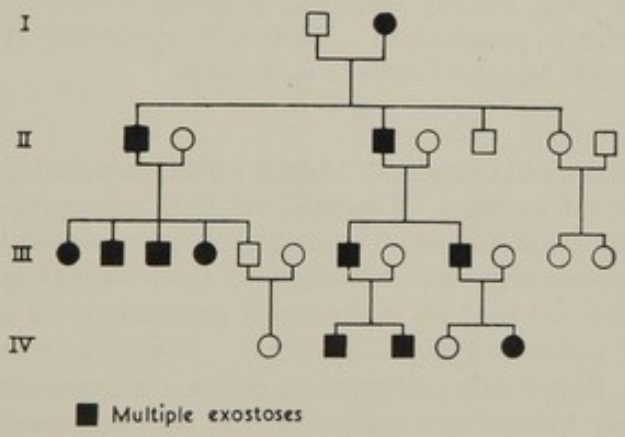


FIG. 129.—Diaphyseal aclasis. Pedigree showing dominant inheritance. (*After Bauer, K. H., and Bode, W. (1940). "Erbpathologie der Stützgewebe beim Menschen." Ed. by G. Just. Handb. Erbbiologie Des Menschen*, 3, 105.)

are fragile, in many cases, and fracture easily. Retarded growth, hydrocephalic changes, imperfect dentition and basilar irregular thickening of the skull are encountered. Optic atrophy and nystagmus are not uncommon.

Madelung's deformity

There is a striking bayonet-like projection of the hand on a shortened forearm. Defective development of the inner one-third of the growth cartilage at the lower end of the radius results in a carrying forward of the hand and carpal at the radiocarpal joint. The deformity is usually bilateral. The clinical picture is rather constant. The affected individuals are of short stature. Not infrequently

multiple cartilaginous exostoses are encountered in affected individuals as well as other associated anomalies.

Heredity

Diaphyseal aclasis

The monograph by Stocks and Barrington (1925) showed that of the then 1,124 recorded cases of diaphyseal aclasis 64·7 per cent gave amnesic evidence of the occurrence of the disorder among antecedents and relatives. Their data, further substantiated by other reviews (Ehrenfried, 1917 ; Jaffe, 1943), indicated that the inheritance is dominant (Fig. 129). There was a marked male predominance (70 per cent). In addition an affected father tends to transmit the disease to rather more of his offspring than does an affected mother. Female transmitters may themselves be phenotypically normal (25 per cent). Males with the abnormal genotype seldom fail to exhibit clinically the disorder.

A rather considerable degree of intra-familial variability in expression exists, yet there is a slight trend toward the single or multiple character of the exostoses.

Enchondromas

In contrast to the strong dominant influence observed in diaphyseal aclasis there is some evidence that dyschondroplasia may be a recessive disease. Brailsford (1948) was unable to demonstrate hereditary evidence in 10 cases in which he carefully searched for such evidence. According to Stocks and Barrington (1925) the first evidence of multiple enchondromas being observed in several members of a family was reported in 1845. An analysis of the rather sparse literature suggests that multiple enchondromas are quite rare, usually sporadic, possibly dominant in inheritance, but exhibiting a very low penetrance. Maffucci's syndrome is reported to be recessive in its inheritance, but the evidence is slender.

Achondroplasia

On comprehensive studies in Norway and Denmark, Mørch (1941) concluded that achondroplasia is always dominant in man. He believed that achondrodystrophy arose frequently through mutation and in all cases was of a genotypical origin. The frequency of achondrodystrophy was estimated to be 1:44,000 in the Danish population. Stephens (1943) (Fig. 130) described 3 generations of a Utah family in which the affected numbered 40:52 normal. The gene was transmitted in a dominant pattern. Bonnevie's pedigree, recessive transmission of achondroplasia, was re-examined by Mørch who claimed it was misdiagnosed. However, Weinberg (1912), J. Bauer (1923), Verschuer and Paroli (1931) have published reports which suggest a recessive form of transmission.

Dysplasia epiphysitis punctata

A genetic background is emphasized by the multiple occurrence among siblings but the mode of inheritance is not known. Resnick (1943) described the disorder in an Italian woman and her monozygotic twin sons. Raap (1943) who reported the disease in 10-month-old twins, an affected male sibling and a questionably involved female sibling, believed the lesion shows a tendency to resolve with advancing age. Maitland (1939) has observed 2 affected members in the same family.

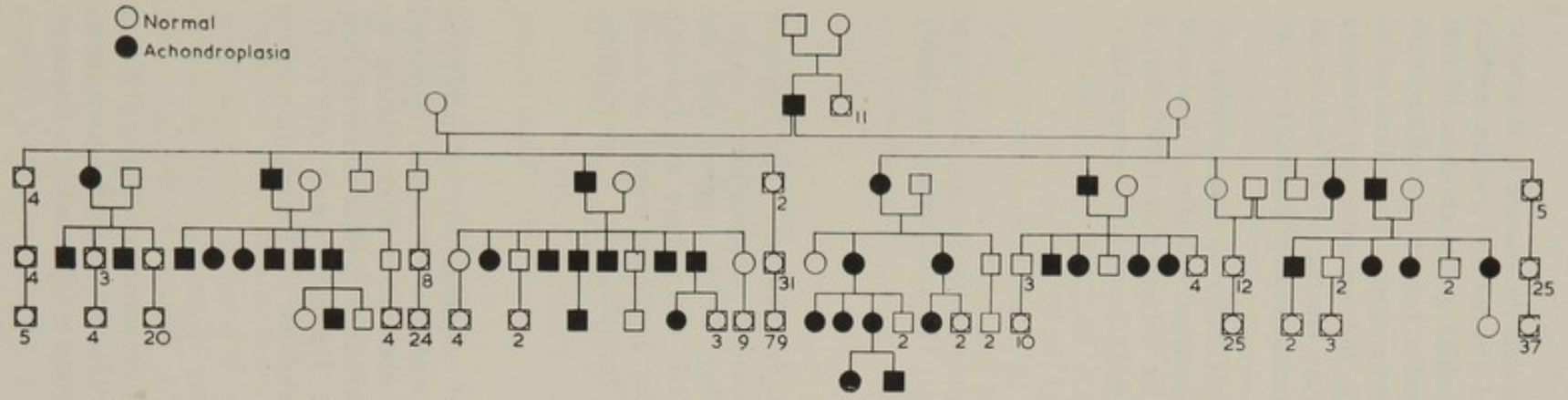


FIG. 130.—Achondroplasia. Pedigree showing autosomal dominant inheritance. (*After Stephens, F. E. (1943). J. Hered.*, **34**, 229.)

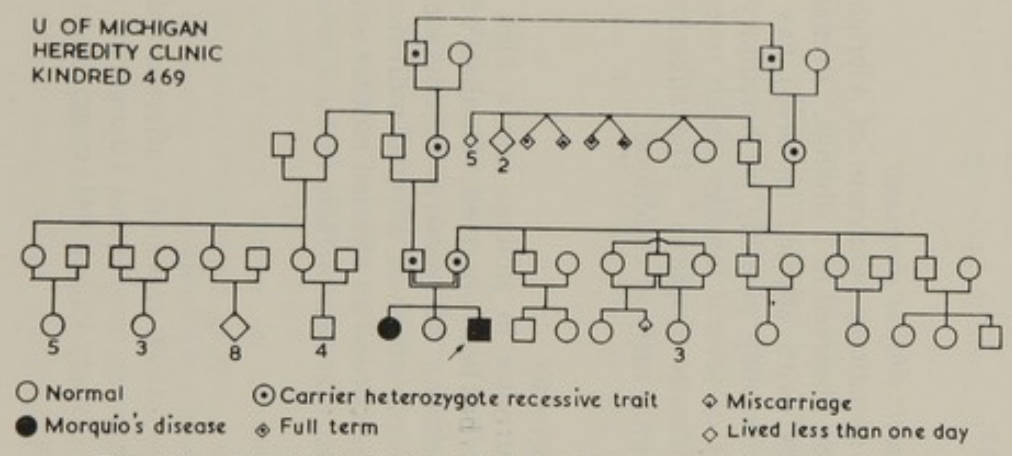


FIG. 131.—Morquio's disease. Pedigree showing recessive inheritance and illustrating consanguinity.

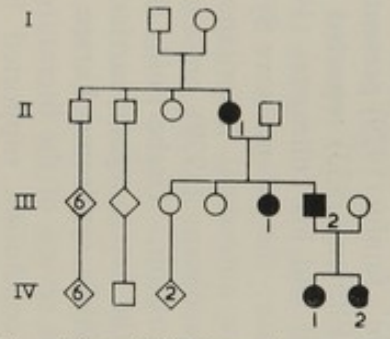


FIG. 132.—Silverskiöld's syndrome. Pedigree showing autosomal inheritance. (*After Helweg-Larsen, L., and Mφrch, E. T. (1945). "Genetic Aspects of Osteochondrodystrophy: Silverskiöld's and Morquio's Syndromes." Separatum Acta Pathologica*, **22**, 4.)

Osteochondrodystrophia deformans

A common familial incidence (8 families) suggests that the disease is of genetic origin. Morquio's family (1929) presented 4 affected sibs out of 5 and the parents were cousins. Ellman (1933) reported an affected child in the children of first cousins. Farrell and his colleagues (1942) described a brother and sister with Morquio's disease; the parents were Syrians and first cousins. These findings all suggest recessive autosomal inheritance (Fig. 131), but an extensive pedigree published by Jacobsens (1939) presents an excellent illustration of sex-linked recessive transmission. Grebe holds that slight roentgenographic changes may be detected in the heterozygotic carriers.

For Silverskiöld's syndrome Larsen and Morch (1945), on their studies of 3 families and a review of the literature (Fig. 132), assume autosomal dominant inheritance, a conclusion supported by reports by Silverskiöld (1925–26), 2 generations; Snoke (1931), 2 generations; Hirsch (1937), 5 cases in 2 generations; and by Guldager (1945), 5 cases in 2 generations.

Chondro-ectodermal dysplasia

Ellis and Van Crevald (1940) described 3 cases in their family studies, 2 boys and a girl. In 2 families the parents were first cousins. The syndrome is probably recessive.

Polyostotic fibrous dysplasia

The hereditary behaviour of Albright's syndrome is unknown. The dysplasia has been observed in 2 siblings. Premature or precocious menstruation in several mothers (with affected children) has been reported, which suggests that the syndrome may possibly be hereditary. In leontiasis ossea there are available records of several families which reveal an irregular dominant pattern of facial bone fibrous dysplasia. The affection has been recorded over 4 generations, developing early in childhood.

Osteopetrosis

Occurrence in siblings and a high incidence of consanguinity of unaffected parents has been observed. Hanhart's Swiss family studies of the disease supported a conclusion of recessive inheritance. On the other hand Peak (quoted by Brailsford) observed affected individuals in 3 generations, and in addition Pirie (1930) recorded an affected mother and 3 children. Herzenberg and Levit (1931) believed that one of their cases, a heterozygote, exhibited mild expression of the trait.

Madelung's deformity

Roget (1899) reported 3 affected individuals in 3 generations; Segrist (1908), a grandmother, mother and 3 daughters; and Reich (1927), 7 women in 3 generations. In a full study Paus (1941) concluded that the affection is inherited in a dominant manner.

OTHER GENERALIZED BONE DISEASES

Clinical aspects

Osteogenesis imperfecta (*van der Hoeve syndrome; fragilitas ossium*)

In this affection there is fragility of the bones in which multiple fractures may occur in intra-uterine or early infantile life. Seedorff (1949) distinguishes three clinical types: osteogenesis imperfecta congenita (Type I) which he characterizes by multiple prenatal as well as intra-partum fractures and failing ossification of the skull; this is the most severe type and the prognosis is extremely poor. Osteogenesis imperfecta tarda is subdivided into Type II and Type III. In Type II the patients present a liability to fractures at birth and this continues throughout life; in Type III the fractures first appear around 2–3 years of life and seem to decline in frequency at about puberty.

The cardinal signs of the disease are blue sclerotics, bone fragility and deafness (otosclerosis). This combination has been frequently designated as van der Hoeve syndrome. Seedorff (1949) found blue sclerae in all of his patients, while bone fragility occurred in 61 per cent and deafness in 26 per cent. The combination of blue sclera and bone fragility appeared in 61 per cent of his cases, blue sclera and deafness in 4 per cent. The entire syndrome appeared in the frequency of 23 per cent. The literature indicates that blue sclera, bone fragility and otosclerosis may be encountered as true independent entities in specific families.

Osteitis deformans

Paget's disease is a chronic and progressive disease of the skeleton in which thickening and rarefaction appear to be the principal changes. Thickening of the calvarium, bowing of the extremities, dwarfing of the stature and a waddling gait are frequently observed characteristics. The course of the disease is slow and insidious. The sex incidence appears to be slightly greater in the male, although many reports indicate equal sex incidence. The aetiology is unknown. The age of onset is difficult to ascertain, but the first symptoms usually appear during middle life.

Vitamin resistant rickets

Vitamin D resistant rickets is a rare metabolic disorder of childhood which differs from ordinary infantile rickets in that spectacularly large doses of vitamin D are required to prevent recurrences. The blood chemistry in refractory rickets simulates that of infantile rickets except for a persistent low serum phosphorus level. An increased faecal excretion of calcium and phosphate points toward decreased absorption of these substances from the intestinal tract. The disease exhibits varying degrees of severity presenting short stature in the affected individual, enlargement of all palpable epiphyses, Harrison's groove, rachitic rosary and frontal bossing. A ligamentous instability of the joints exists.

Osteopoikilosis (*spotted bones*)

This is a rare abnormality of ossification characterized by the presence of multiple ovoid or rounded islands of compact bone in the cancellous tissue

(Fig. 133). The condition is frequently accompanied by a dermatosis, *dermatofibrosis lenticularis disseminata*. All of the bones appear susceptible except the skull. Under observation the skeletal lesions fluctuate greatly. The condition has been observed at birth and at 60 years of age. The disease is symptomless.

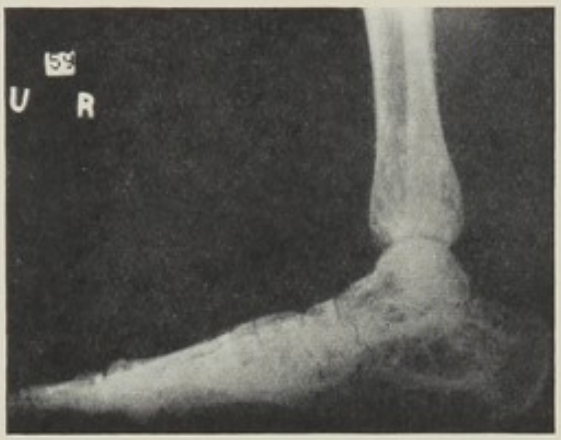


FIG. 133.—Osteopoikilosis. Lateral view of foot and tibia. Male, aged 23 years.

Aseptic osseous necrosis is the basic pathological aberration in a rather extensive group of entities which together constitute an important part of orthopaedic pathology. Despite an extensive literature the aetiology is more obscure than that of the epiphyseal osteochondritides. Most of the secondary and even primary epiphyses have, alone or in combination, been observed as the sites of an osteochondritis (Fig. 134). Among the many suggested aetiological agents are: (1) trauma; (2) infection; (3) endocrine imbalance; and (4) heredity.

The following clinical varieties are recognized:

(*a*) *Legg-Perthes' disease*

Since the appearance of Perthes' classical report in 1913, accumulating data has indicated that there is a much higher incidence in boys than in girls, and that the disease appears most frequently between the ages of 8 and 12 years. Bilateral involvement is rare. No racial immunity is evident.

(*b*) *Aseptic necrosis of the tibial tubercle*

Osgood-Schlatter disease presents localized pain and tenderness over the affected tibial tubercle. The disease affects chiefly males about the interval between 11–15 years of age.

(*c*) *Osteochondritis of the tarsal navicular*

In 1908 Kohler described osteochondritic changes in the tarsal navicular. The disease develops in young children usually before the age of 6 years.

(*d*) *Osteochondritis of the carpal lunate*

Aseptic necrosis of the lunate bone was described by Keinbock in 1911.

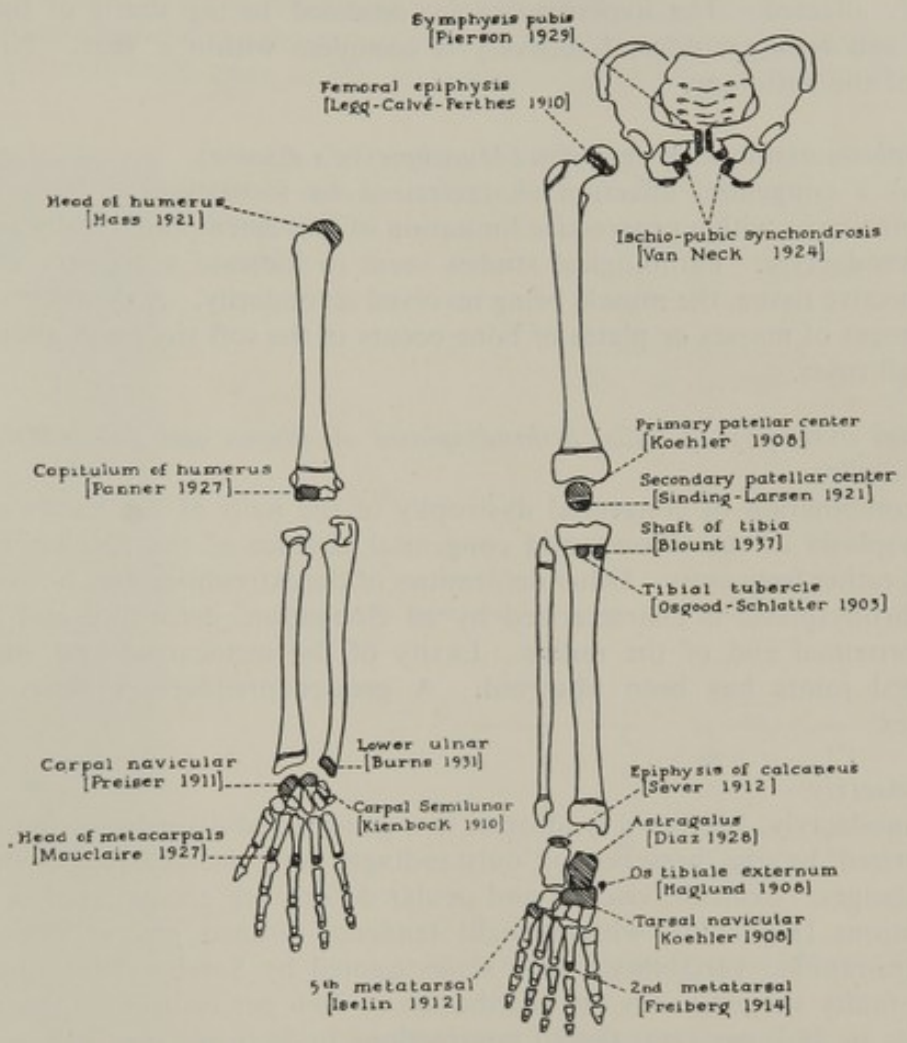


FIG. 134.—Aseptic necrosis. Nomenclature, sites of occurrence. (*Redrawn from Caffey, J. (1945)). Pediatric X-ray Diagnosis, 1st ed. Chicago; Year Book Publishers.*)

(*e*) *Osteochondritis dissecans*

In contrast to the widespread necrosis of the epiphyseal osteochondritis, osteochondritis dissecans involves only a small, well circumscribed, superficial area. It may be observed most commonly in the cartilaginous surfaces of the knee and elbow joints. Both sexes may be affected, but there is a male excess.

Infantile cortical hyperostosis

Infantile cortical hyperostosis, reported by Caffey and Silverman in 1945 is characterized by three chief manifestations: (1) hyperirritability, (2) swellings of the soft tissues; and (3) cortical thickenings of the underlying bones. The soft tissue swellings precede the hyperostoses, and involute slowly without suppuration. An uneven, protracted clinical course is characterized by unpredictable remissions and relapses. Cortical hyperostoses have been revealed in all of the tubular bones of the body, and the flat bones may also be involved. The mandible is

invariably affected. The hyperostoses are confined to the shafts of the bones. Clinical and roentgenological recovery is complete within a year. Nothing is known of the aetiology.

Fibrodysplasia ossificans progressiva (*Munchmeyer's disease*)

This is a congenital affection characterized by formation of bony columns in the soft tissues with a progressive limitation of movement and usually associated with microdactyly. Pathological studies seem to indicate a primary change in the connective tissue, the muscle being involved secondarily. A slowly progressive development of masses or plates of bone occurs in the soft tissues in about 75 per cent of all cases.

Congenital dystrophy of nails, arthrodysplasia of elbows and congenital absence of patellae

The combination of congenital dystrophy of the nails of the hands and feet, arthrodysplasia of the elbows, and congenital absence of the patellae has been reported rather frequently. Other deformities of the extremities may be associated. The arthrodysplasia is characterized by an elongation, deformity and luxation of the proximal end of the radius. Laxity of the metacarpal and metatarsal phalangeal joints has been observed. A greater predilection exists for the female sex.

Arachnodactyly

Arachnodactyly, Marfan's syndrome, is a generalized disorder of the skeleton characterized by the presence of outstandingly long metacarpals, metatarsals and phalanges. Skeletal, visceral and ocular defects are encountered in varying combinations (Fig. 135), with a slight tendency toward greater inter-familial than intra-familial variability. In a series quoted by Sorsby (1951) there were poor or faulty subcutaneous fat distribution in 76·6 per cent of 60 cases, spinal anomalies in 58·3 per cent, fascial contractions in 56·6 per cent and congenital heart lesions in 36·6 per cent, malformations of the ear in 25 per cent and abnormal masculature in 20 per cent. The sex incidence of the syndrome is equal. The disease is congenital.

Brachymorphia with spherophakia

Marchesani is credited with having described the association of brachymorphia with spherophakia—a condition that contrasts with arachnodactyly. The affected individual usually presents short limbs and some degree of brachydactyly. Other mesenchymal abnormalities may be associated.

Cleido-cranial dysostosis

Cleido-cranial dysostosis exhibits two main components: (1) hypoplasia of the clavicles; and (2) slow and incomplete ossification of the calvarium. The aetiology is apparently a partial failure of the normal process of ossification in membrane with but little involvement of the bones originating in cartilage.

Klippel-Feil syndrome

In the Klippel-Feil syndrome congenital anomalies may occur at the upper

dorsal and lower cervical spine and result in shortening of the neck. Moderate to severe limitation of motion may coexist. There is usually a reduction in number of the vertebrae with more or less synostosis. Spina bifida may be present with

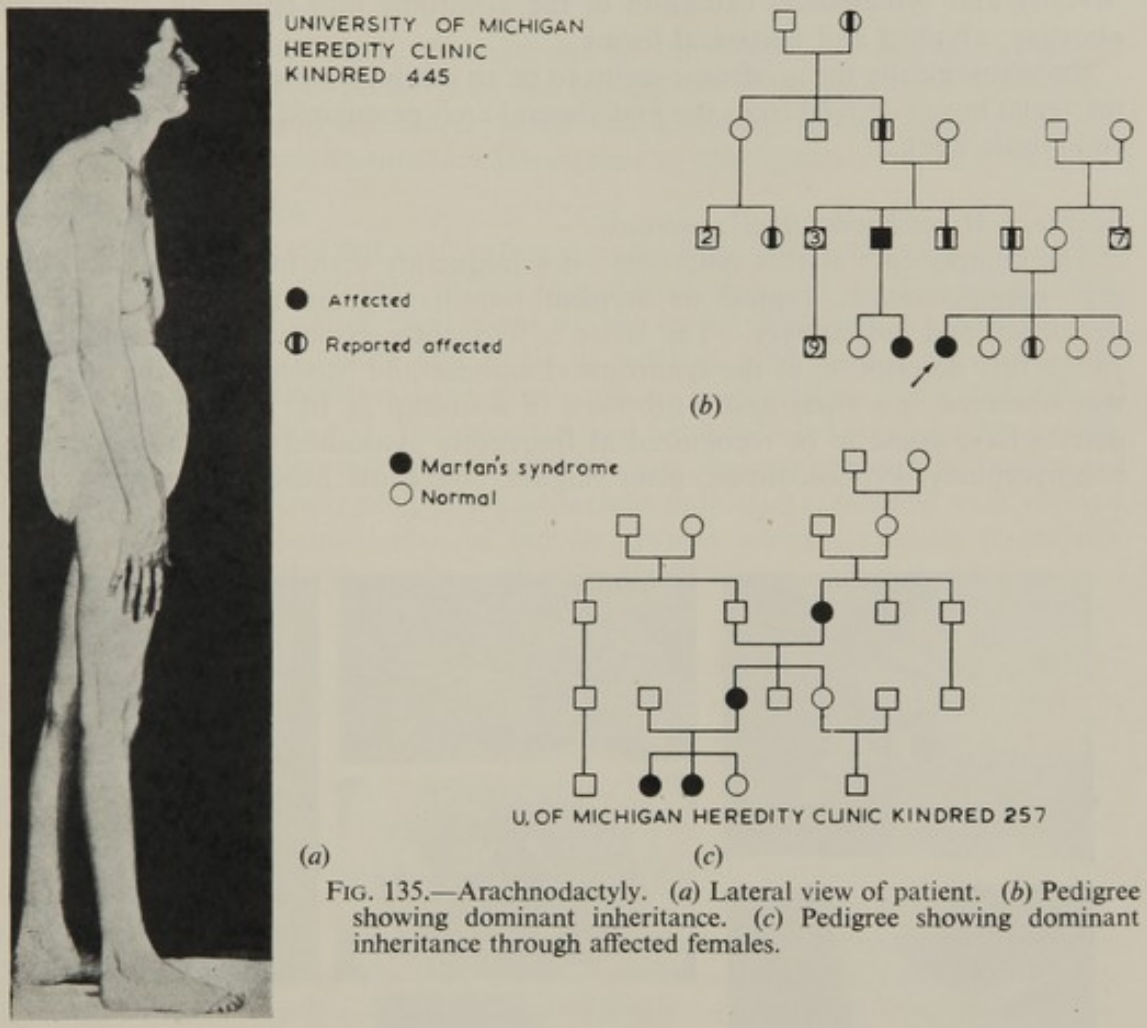


FIG. 135.—Arachnodactyly. (*a*) Lateral view of patient. (*b*) Pedigree showing dominant inheritance. (*c*) Pedigree showing dominant inheritance through affected females.

an accompanying variety of neurological disorders. Other congenital anomalies may be present: pterygium colli, low hair line, winged scapulae or undescended scapulae, and an associated scoliosis.

Mandibulo-facial dysostosis

Franceschetti and Klein (1949), claim the mandibulo-facial dysostosis syndrome to be a distinct and independent clinical entity. The syndrome is chiefly recognized by the presence of a characteristic anti-mongoloid obliqueness of the palpebral fissures and an S-shaped appearance of the lower lids. Other features of the syndrome are: a fish-like facial physiognomy, colobomas of the outer part of the lower lids and occasionally in the middle part of the upper lids. Triangular-shaped palpebral fissures may be noted, as may be hypoplasia of the squamous portion of the malar and zygomatic process of the temporal bones. The zygomatic

arches may be rudimentary. The mandible is rather frequently hypoplastic. The external ear is bilaterally malformed and middle-ear deafness is common. Macrostomia and blind fistulous prolongation of the angle of the mouth toward the ears may be observed. The syndrome can be subdivided according to the severity and symmetrical extension of the syndrome into complete, incomplete, abortive, atypical and unilateral forms.

Embryologically the syndrome seems to be an inhibitory process chiefly affecting the facial bones derived from the first visceral arch postulated at about the seventh embryonic week.

Laurence-Moon-Bardet-Biedl syndrome

The components of this syndrome—not frequently seen in full combination—are: hypogenitalism, typical or atypical retinitis pigmentosa, obesity, mental deficiency and polydactyly. The latter is frequently associated with syndactyly. In the first description of the syndrome (Laurence and Moon, 1866) the affection was observed in a sister and 3 brothers, in a sibship of 10. A number of other defects have come to be recognized as frequently associated such as oxycephaly, brachycephaly, kyphoscoliosis, genu valgum, congenital heart disease, dwarfism,

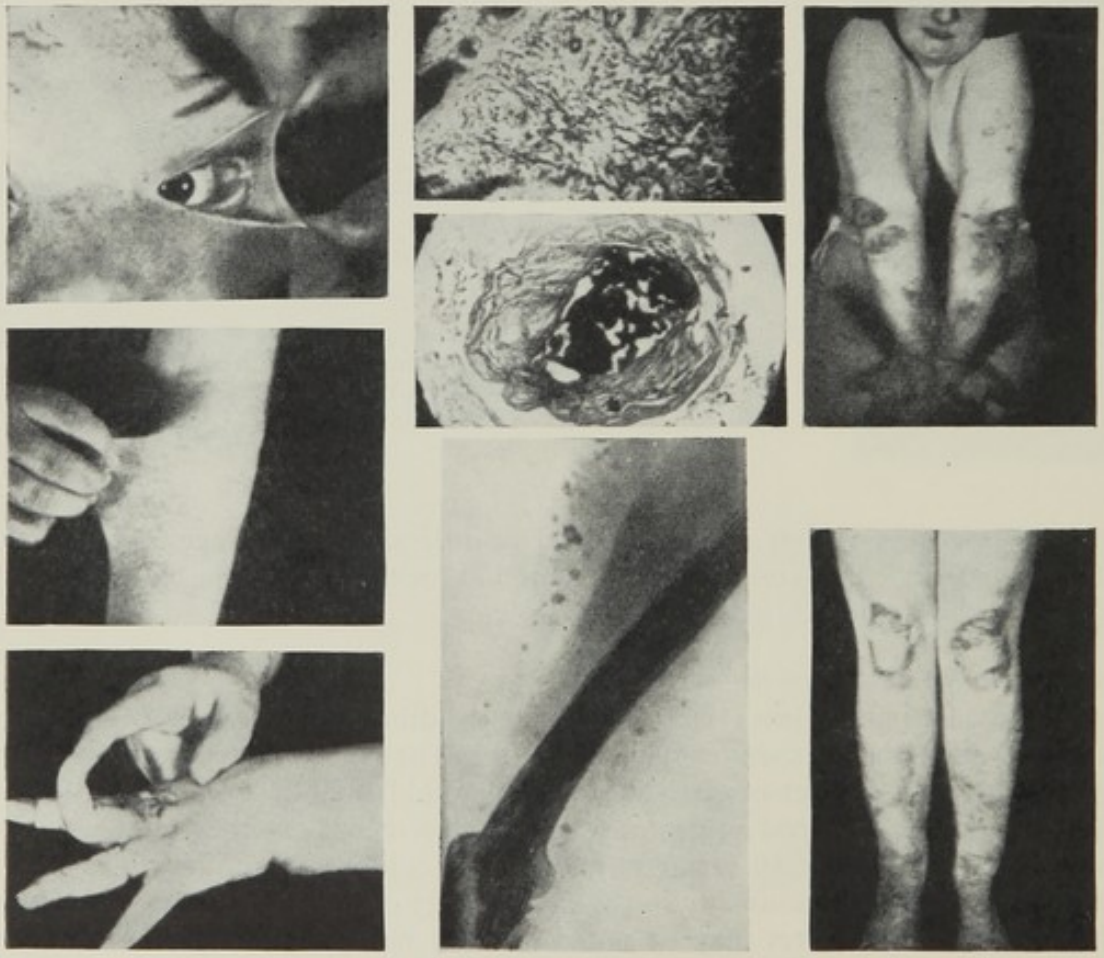


FIG. 136.—Ehlers-Danlos syndrome. Composite picture.

coxa vara, ataxia, nystagmus, muscular weakness and deaf-mutism. Obesity and polydactyly may be the only congenital indications of the presence of the disease and even the former may be absent at birth. The retinal degeneration and mental deficiency may be slowly progressive.

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome is characterized by (1) hyperlaxity and hyperextensibility of the joints; (2) hyperelasticity and hyperlaxity of the skin; and (3) friability and fragility of the skin and blood vessels with breaking, splitting and formation of hematomas and pseudo-tumours subsequent to the slightest trauma (Fig. 136).

Status Bonnevie-Ullrich

Ullrich (1936) pointed out that certain congenital human anomalies of the head and extremities might find their embryological explanation in the damaging action of wandering cerebrospinal fluid blebs as shown by Bonnevie to apply to the mutations observed by Bagg and Little in radiated mice (*see* page 16). Two principal anomaly complexes have thus come to be described under the title of " status Bonnevie-Ullrich". The asymmetrical form, which Ullrich believed to be attributable to an identical wandering bleb mechanism, consists of congenital nuclear defects (especially abducens and facialis paralysis) combined with various abnormalities, chiefly unilateral, of the ear, ocular adnexa, muscles (especially pectoralis defect), and extremities (especially the hands).

Sarcoidosis (Besnier-Boeck disease)

Sarcoidosis is a chronic, granulomatous inflammation which occasionally may affect the bones of children and rarely of infants. The aetiological agent has not been established.

Heredity

Osteogenesis imperfecta

The disease is inherited as a simple autosomal dominant. One pedigree (Hirschmann, 1934) suggested the possibility of Y-chromosome transmission.

Seedorff holds that the disease may represent mutation in five closely linked or even adjacent loci and suggested that these are arranged in the following order : (1) deafness gene; (2) blue sclerae gene; and 3(a), 4(b), and 5(c) being genes controlling bone fragility. He believed that his Type III represents a mutation involving the locus for blue sclera plus gene (a) for bone fragility. Type II represents a mutation involving the locus for blue sclera plus genes (a) and (b) for bone fragility. Type I includes a mutation embracing the gene for blue sclera and (a), (b) and (c). Van der Hoeve's syndrome involves a mutation of the entire complex. Types II and III, he admitted, may be the same mutation, but exhibiting variation effected by modifying genes.

The more generally accepted view is that a single dominant gene with a pleiotropic effect is involved (Fig. 137).

Osteitis deformans

The frequent involvement of siblings suggests that the disease may have a genetic background. Roberts and Cohen (1926) found 14 cases of familial incidence in the literature. Subsequently Kay and his colleagues (1934) reported an affected brother and sister, and Dickson and his colleagues (1945), 7 affected individuals in 4 generations. Eleven affected males in 4 generations with involvement of the

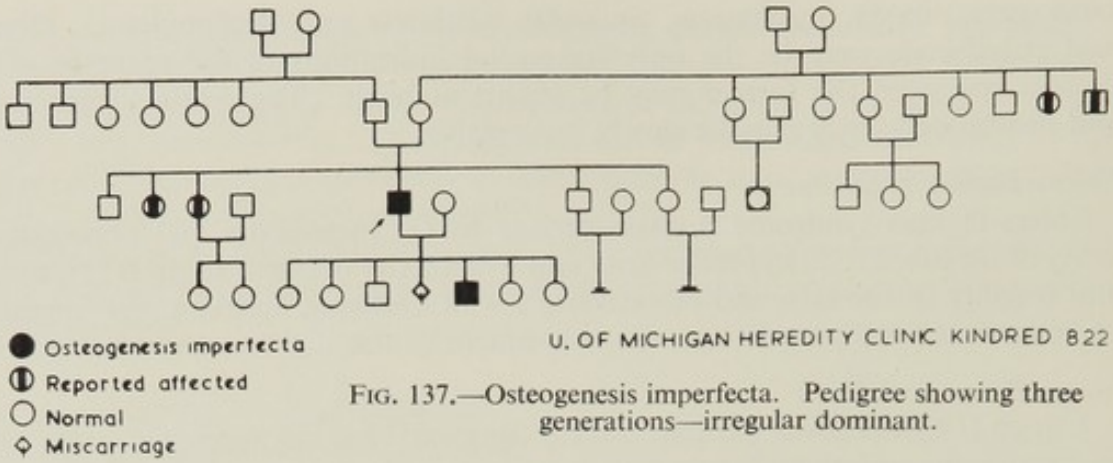


FIG. 137.—Osteogenesis imperfecta. Pedigree showing three generations—irregular dominant.

lower extremities only were reported by Camurati in 1922, while Koller (1946) reported 2 affected siblings and 1 of their sons was likewise affected. Boyd (1947) mentioned 2 families in each of which 3 cases occurred. Crumpacker reported 3 affected siblings.

Paget's disease is probably a dominant with incomplete penetrance. That the predisposition to Paget's disease, when inherited, was transmitted as an incomplete dominant gene carried on the X-chromosome, is suggested by Montagu (1949) in his review of the available literature.

Vitamin resistant rickets

The relatively frequent occurrence of the disease in siblings suggests a hereditary tendency. Pedersen and McCarroll (1951) investigated 25 patients, of whom 16 fell into 10 family groups; one parent in each group presented similar deformities and characteristic histories, thus suggesting that a dominant gene is responsible.

Osteopoikilosis

Heredity is probably an important factor. Wilcox (1932) observed an affected father and son. Voorhoeve (1924) described a variant of the disease characterized by longitudinal striping of the bones; he observed the disease in an affected father, his son and daughter. Moreau and his colleagues reported both forms in the same individual. Kraft (1931) reported an affected mother and 2 affected sons. Kadrnka and Hirlemann (1933) recorded an affected father with 2 of his 3 children being likewise involved. Risseuw (1936) observed 3 generations; an affected father, 6 children and a grandson. The reported cases

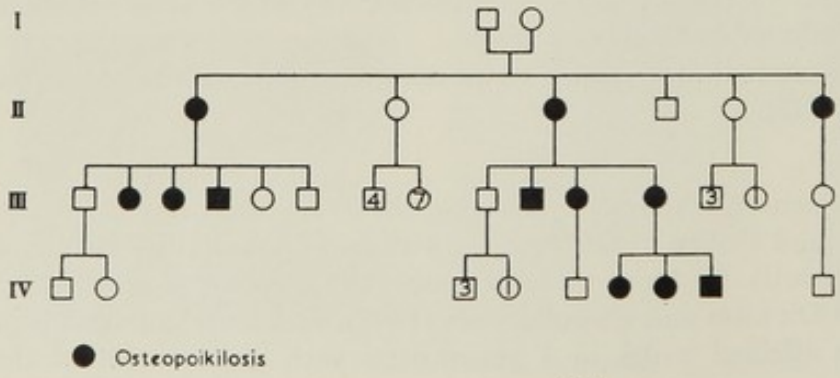


FIG. 138.—Osteopoikilosis. Pedigree showing dominant inheritance. (*After Busch, K. F. B. (1937). Acta Radiol.*, **18**, 693.)

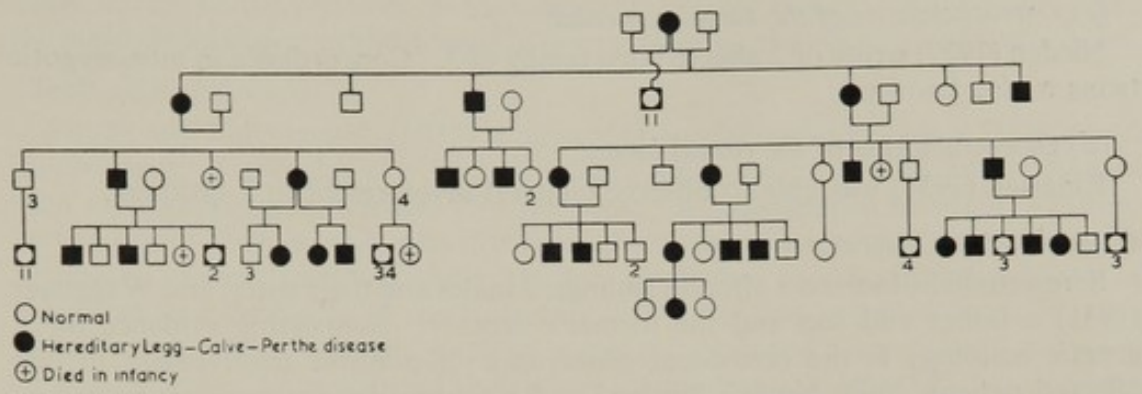


FIG. 139.—Legg-Calve-Perthe disease. Pedigree showing dominant inheritance. (*After Stephens, F. E., and Kerby, J. P. (1946), J. Hered.*, **37**, 153.)

show a greater incidence in the male sex and suggest dominance, possibly sex influenced. Recessive inheritance cannot be ruled out. Busch (1937) reported 3 generations in which 12 affected individuals appeared (Fig. 138).

Aseptic osseous necrosis

(*a*) *Legg-Perthes' disease*

Some of the more interesting pedigrees suggest that an autosomal dominant gene may be responsible. Kehl (1925) and Brill (1927) have reported a family in which 26 members in 6 generations were affected with hip joint changes suggestive of Perthes' disease. Stephens' (1946) Utah family indicated a dominant inheritance pattern with marked penetrance (Fig. 139). Even as early as 1906 Küttner had reported a family of 3 generations of " coxitis deformans juvenilis ". Perthes (1943) reported 2 affected brothers.

(*b*) *Aseptic necrosis of the tibial tubercle*

The disease has been described as being concordant in monozygotic twins by Spaich and Ostertag (1935). Several families have been reported in which more than one affected sibling have appeared.

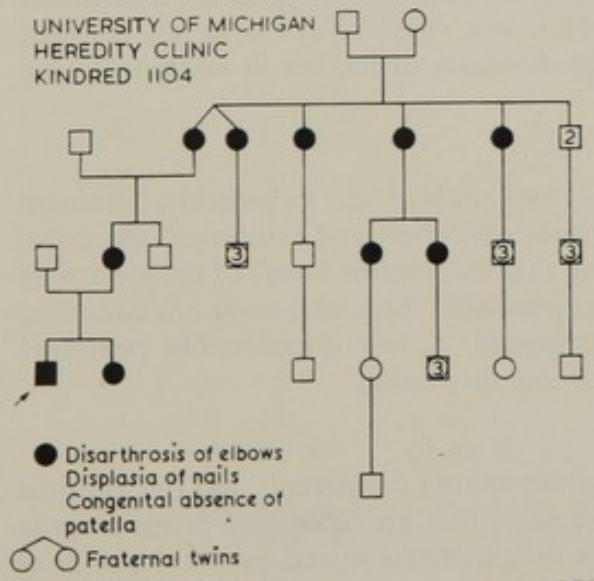


FIG. 140.—Congenital dystrophy of nails, arthrodysplasia of elbows and congenital absence of patella. Pedigree showing dominant inheritance.

(*c*) *Osteochondritis of the tarsal navicular*

Nieden (1927) wrote of 2 affected in a family of 3. Concordance in monozygotic twins is also known.

(*d*) *Osteochondritis of the carpal lunate*

Ringsted (1931) was able to observe bilateral involvement in 2 brothers.

Osteochondritis disecans

Bernstein has observed 3 affected siblings, 2 males and their sister, and Waggoner (1931) a father and son and the former's brother. Supporting evidence for a genetic aetiology is the occasional observance of multiple involvement in one affected patient. Van Necks', Perthes' and Koehlers' lesions have all been seen in one individual (Caffey, 1951).

Infantile cortical hyperostosis

Boyes and Demy (1951) reported the occurrence of the disease in 2 sibs of their family, a boy aged 12 months and a girl aged 2 weeks.

Fibrodysplasia ossificans progressive

Sympson reported a case in a father and son in which both had the finger deformity, but the father did not develop myositis. Burton-Fanning reported a family in which a father and son were afflicted with similar deposits. Most cases are sporadic, and the affection is generally regarded as non-hereditary. However, the association of congenital deformities of the hands and feet with early onset of the disease, as well as an occasional association with other known inherited dysplasias, suggest a genetic factor.

Congenital dystrophy of nails, urthrodysplasia of elbows and congenital absence of patella

An autosomal dominant gene, exhibiting considerable variability of expressivity, appears to be responsible for the syndrome (Fig. 140). Little (1897) reported 18 cases in 4 generations with those affected presenting only a partial expression of the syndrome. Senturia and Senturia (1944) presented 30 affected individuals in 4 generations with an excess of affected females. Lesters' (1936) family revealed an involvement of the shoulder joint and dysplasia of the iris in addition to the other features of the syndrome.

Arachnodactyly

The hereditary nature of the syndrome is well established. In general a dominant autosomal gene is responsible, having a pleiotropic effect and exhibiting occasional failure of penetrance (Figs. 135*b* and *c*), so that incomplete forms of the syndrome are not uncommon and may readily be overlooked. Sporadic cases are common, and they may represent dominant mutations. A few questionable pedigrees suggest that a recessive gene for the syndrome may exist.

Brachymorphia with spherophakia

The rather high frequency of consanguinity among the parents and the multiple occurrence of the syndrome in siblings suggests that an autosomal recessive gene is responsible. A question of incomplete dominance is raised by the presence of

short stature in the relatives of Marchesani's original family. Holstein recorded the multiple incidence of the disease in several siblings, the offspring of first cousins.

Cleido-cranial dysostosis

Stocks and Barrington's (1925) summary of the literature revealed: (1) bilateral involvement of the clavicles 82·2 per cent; (2) obvious cranial vault changes such as large frontal eminences 25·5 per cent; (3) undeveloped maxillae; (4) high arched palate 43·9 per cent; and (5) dental aberration 55 per cent. Other frequently associated defects included short stature, small face and hyperextensibility of the joints and flaccidity of the ligaments. Of their 144 collected cases 96 gave hereditary histories. Stocks implied a greater tendency toward male offspring of affected males to be affected than when the mother was affected. More recent literature does not support this observation. Tatum (1934) reported dominant transmission of the trait, having observed 7 affected cases in 3 generations. An old observation of Gegenbauer (1864) showed affected offspring of an affected woman and 2 apparently normal mates.

Kahlers' (1939) pedigree reported 6 generations illustrating dominant inheritance. Fitchel (1929) reported clavicular dysostosis affecting 6 cases in 3 generations. These and other pedigrees indicate that fractions or components of the syndrome may be encountered in specific families.

Valentin (1928) reported 14 affected cases in 4 generations (Fig. 141). The dysostosis is usually transmitted as a dominant with good penetrance and exhibits considerable variability. This variability is greater between unrelated families. The sporadic cases are assumed to be the result of mutation.

Klippel-Feil syndrome

The mode of inheritance is not known. Recessiveness has been suggested. Hangarter and Dieker (1938) reported a family in which many skeletal degenerations were scattered over 3 generations in addition to a solitary case of Klippel-Feil. Jarcho and Levin (1938) reported an affected Negro brother and sister; their mother had a minor defect of the fifth cervical vertebra. Bauman (1932) described a case whose parents were normal but whose cousin and aunt were affected.

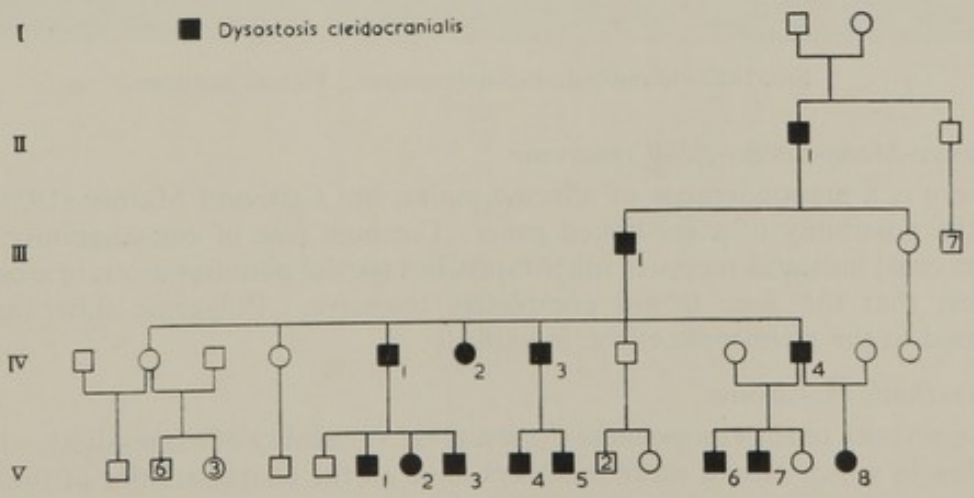


FIG. 141.—Cleido-cranial-dysostosis. Pedigree showing dominant inheritance. (*After Valentin, B., and Mestern, J. (1934). Erbartzt.*, **1**, 62.)

Mandibulo-facial dysostosis

The syndrome is transmitted in an irregular autosomal dominant mode. Debusmann (1940) reported a pedigree in which 9 typical cases appeared in 3 consecutive generations. Leopold, Mahoney and Price (1945) and Brohm and Kluska (1949) have likewise reported transmission of the syndrome through 3 generations. Falls has observed 2 families in which the syndrome has appeared in 3 generations. A wide intra-familial variation of expressivity is to be anticipated (Fig. 142).

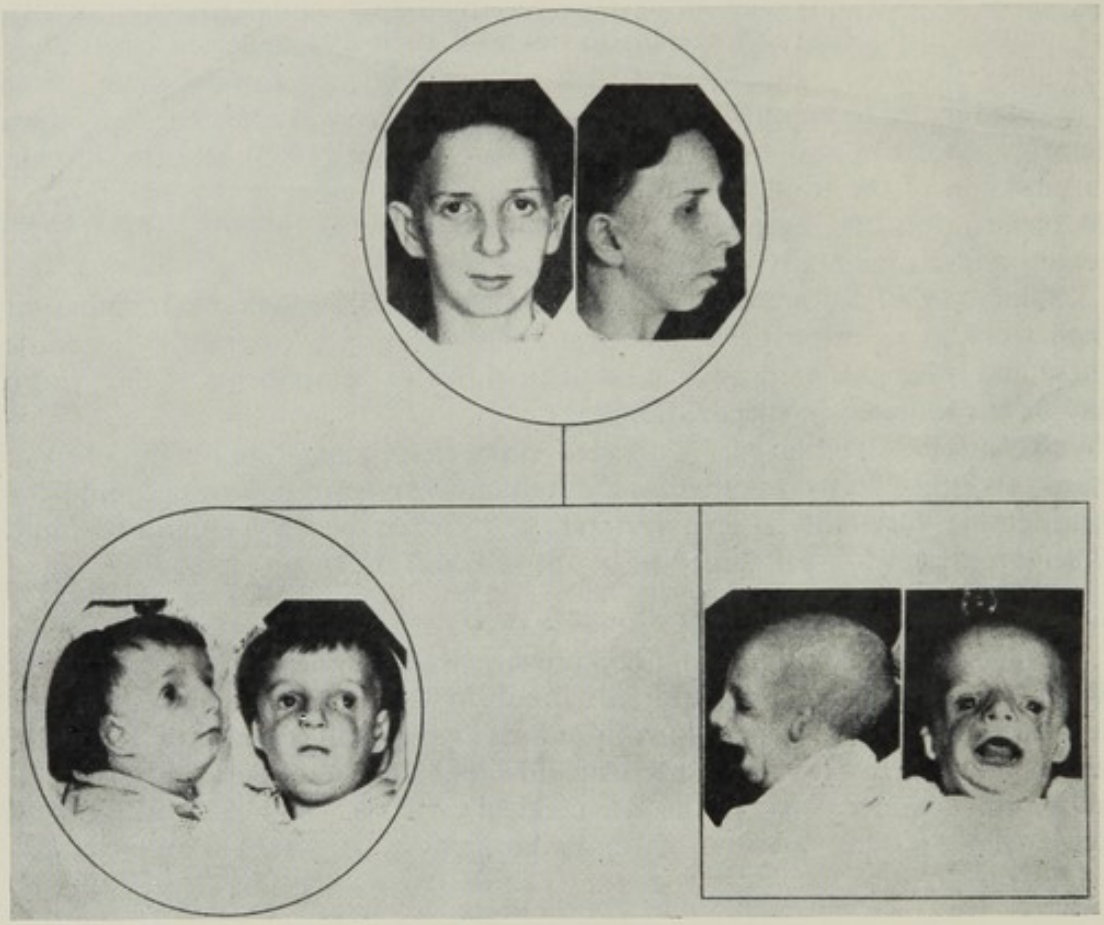


FIG. 142.—Mandibulo-facial dysostosis. Picture pedigree.

Laurence-Moon-Bardet-Beidl syndrome

There is a preponderance of affected males, but Csik and Mather (1938) ruled out the possibility of a sex-linked gene. The high rate of consanguinity (about 33 per cent) indicates recessive inheritance, but partial manifestations in ascendants suggest that the gene is not completely recessive. Polygenic inheritance, as opposed to the pleiotropic effect, is unlikely.

Ehlers-Danlos syndrome

The severity of the components show a great variability of expressivity. In some families in which one or more members have all the characteristics of the Ehlers-Danlos syndrome other members may only have one or two of the characteristics in mild form. Johnson and Falls (1949) reported 32 affected among 123 individuals;

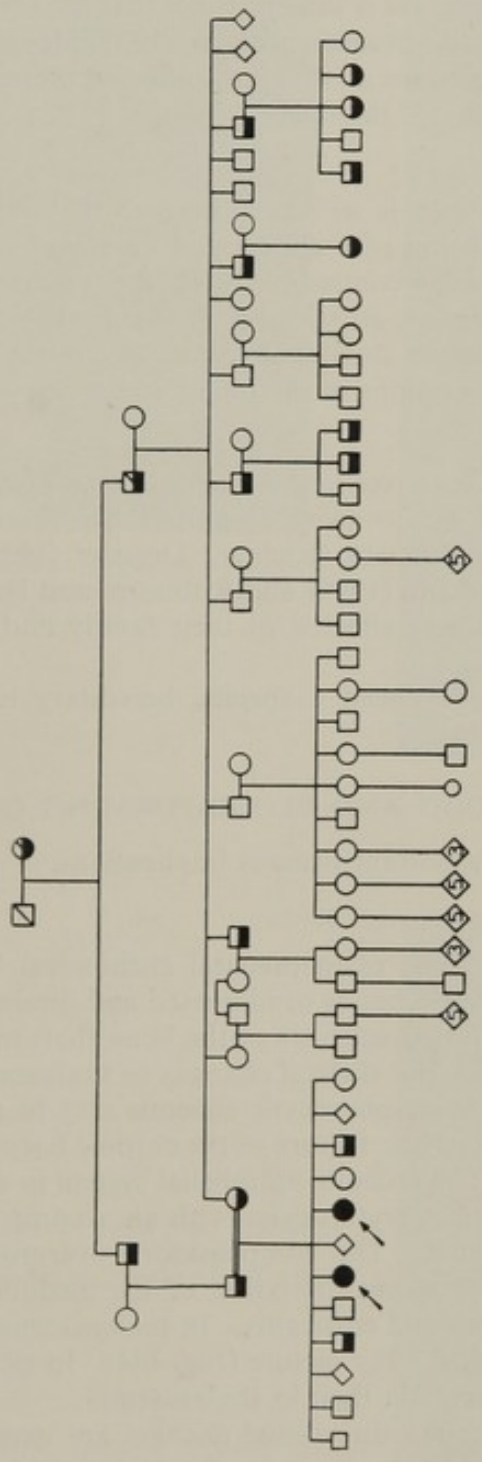


FIG. 143.—Ehlers-Danlos syndrome. Pedigree showing dominant inheritance.

21 men and 11 women had the syndrome (Fig. 143). This pedigree suggests dominant inheritance. Two severely affected daughters in one family resulting from the mating of mildly affected cousins suggests that the girls could represent the homozygous state of the syndrome. It is thus possible that the gene is not totally dominant in the heterozygous state. Stuart's pedigree (1937) presented incomplete dominant transmission in 4 generations in which the affected presented a tendency toward excessive hyperextensibility of the finger joints.

Status Bonnevie-Ullrich

No clear evidence of inheritance is as yet available. Cotterman and Falls (1949) reported 2 sisters in a sibship of 6 children of unrelated parents showing unilateral developmental anomalies compatible with the asymmetrical form of status Bonnevie-Ullrich syndrome. Rossi and Howald (1947), on indefinite evidence, incriminated a facultative dominant gene. Cotterman (1948) found scattered manifestations in 2 generations of the family in his case.

Sarcoidosis

That hereditary factors may play a role in this constitutional disease is suggested by its appearance in identical Negro twins, reported by Sherer and Kelley. There are many records of affected sibs (Richter, Dressler (1938-39), Boggilds (1944), MacComac (1940), Bergmann (1939) and Robinson and Hahn. Sellei and Berger (1926) found 5 of 7 siblings affected in their family and Robinson and Hahn noted 4 affected male sibs.

It appears that the disease may need a specific hereditary background, the nature of which is as yet unknown.

DISEASE OF THE BLOOD AND BLOOD-FORMING ORGANS

Some of these affections have important osseous implications.

Clinical aspects

Erythroblastosis foetalis.—In some cases prenatal enchondral bone formation is disturbed and there are transverse bands of increased and diminished density in the ends of the shaft. Rarely, diffuse sclerosis of the bone shaft may occur.

Chronic haemolytic anaemias.—The skeletal changes in thalassaemia, sickle-cell anaemia, and familial haemolytic or spherocytic anaemia may be pathognomonic, and are perhaps the most characteristic feature of the chronic haemolytic anaemias other than the blood picture. The reticulo-endothelial system in all three diseases prematurely destroys the abnormal erythrocytes with an accompanying excessive proliferation of the bone marrow. The compensatory overgrowth of marrow within expansile young bones produces dilatation of the medullary cavities and pressure atrophy of the spongiosa and corticallis. In thalassaemia the hyperplasia of the bone marrow gives a typical x-ray picture (Fig. 144). In sickle-cell anaemia there is less bone marrow hyperplasia than in thalassaemia.

In congenital haemolytic anaemia the cranial changes are usually more severe than those observed in the long bones.

Heredity

This is discussed in the chapter on Serology.

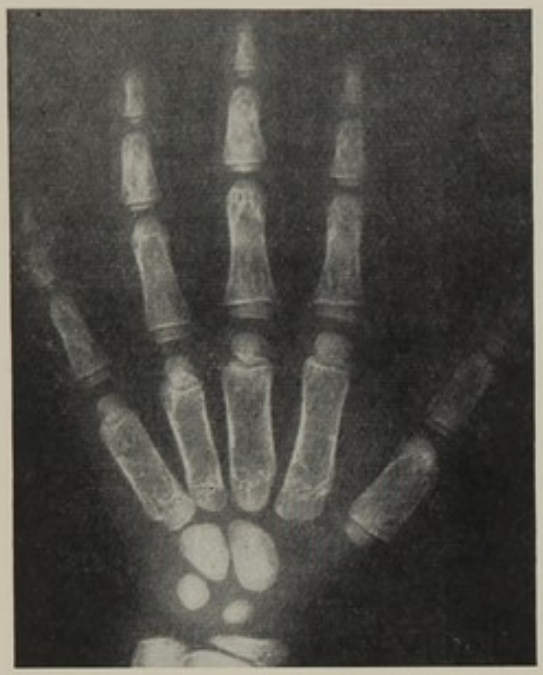


FIG. 144.—Thalassaemia, trabeculated osteoporosis, cortical atrophy and swollen tubular bones of the hand.

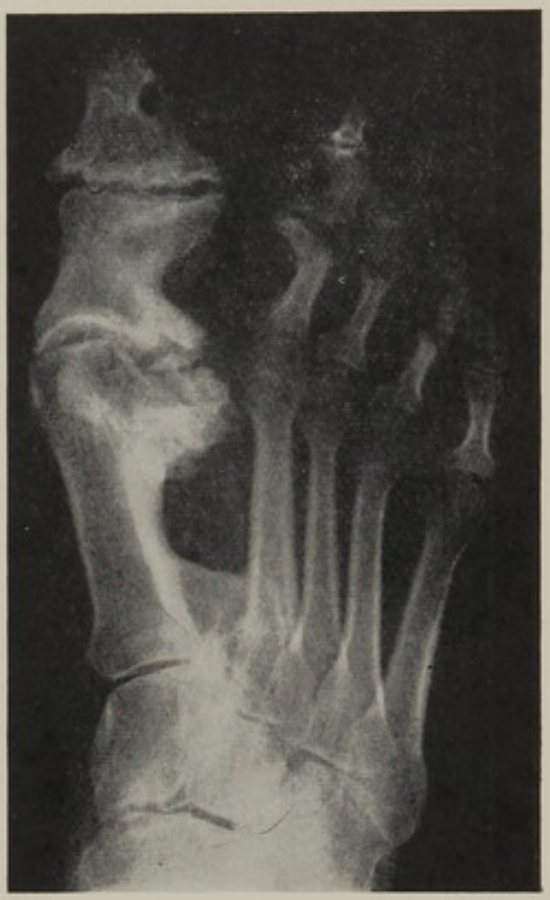


FIG. 145.—Neurofibromatosis. Gigantism of the foot and great toe.

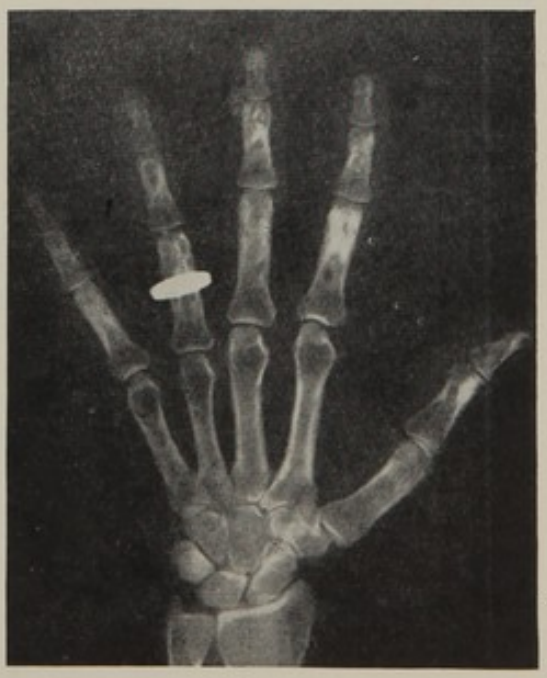


FIG. 146.—Tuberous sclerosis. Multiple areas of cystic destruction and massive changes in the tubular bones of the hands.

PHAKOMATOSES

These too have significant osseous lesions.

Neurofibromatosis.—This is discussed on page 232. Various osseous changes have been recognized as associated with neurofibromatosis; they include scoliosis, abnormalities of growth (usually elephantiasis), subperiosteal bone cysts, and pseudo-arthrosis (Fig. 145). Skeletal manifestations are present at least in 1 case in 10 and it appears that overgrowth of the affected part is the most common lesion in childhood.

Tuberous sclerosis (*epiloia*)—This too is discussed elsewhere (page 231). The skeletal system may present bone cysts (Fig. 146), melorheostosis, and generalized fibrosis especially of the metatarsal and metacarpal bones and phalanges.

Sturge-Weber syndrome (*cephalo-facial angiomatosis*).—The Sturge-Weber syndrome shares with other phakomatoses the presence of congenital naevi (or phako spots), cystic lesions of the viscera, congenital malformation of structure and the central nervous system. Characteristic of the syndrome is the presence of facial angiomatosis and the associated angiomas of the meninges on the affected side. Atrophy and localized homolateral skull anomalies may be seen.

Koch (1940) reported several people affected in a 4-generation pedigree suggesting a dominant form of transmission but with considerable intra-familial variability of expressivity. The author has personally encountered an affected mother and her one son among 3 siblings.

OTHER AFFECTIONS

On the following possibly hereditary diseases the available genetic information is as yet incomplete.

(1) Pyle's disease—a congenital symmetrical splaying of the long bones.
(2) Fibroplastic diathesis—Badgley (1953)—characterized by the extensibility of joints and hyperelasticity of the cutaneous tissue.
(3) Arthrogryposis multiplex congenita—maldevelopment of the mesenchyme (muscle).
(4) Turner's syndrome—ovarian dysplasia.
(5) Engelmann's disease—progressive diaphyseal dysplasia.
(6) Melorheostosis—questionably associated with epiloia.
(7) Familial fibrous swelling of the jaws.
(8) Osteochondral dystrophy—François (1949).
(9) Milkman's disease—multiple spontaneous idiopathic symmetrical fractures.
(10) Osteopathia striata—vertical striations in the metaphyses of the long bones.
(11) Hyperostosis frontalis interna, Stewart-Morel syndrome.
(12) Hereditary multiple diaphyseal sclerosis—Ribbing (1950).

II. Regional Affections of the Skeletal System

SKULL

Minor variations of the skull contour are particularly common and many may have demonstrable genetic background. The Hapsburg lip (prognathism) and Catlin mark may serve as examples. Specific familial physiognomy is well known and within the intimate experience of all. Some skull anomalies are marked and are of pathological significance.

Clinical aspects

Congenital dysplasias of the skull

Meningocele, meningo-encephalocele, and cranium bifidum occultum are of infrequent occurrence, but when present they are median plane defects usually located in the vicinity of the occipital and accessory fontanelles. These defects frequently may be associated with spina bifida of the upper cervical spine. Mental defects of varying grades of severity exist. Many other associated developmental anomalies of the skeletal system are encountered.

Lacunar skull of the newborn

In the lacunar skull of the newborn irregular circular or oval thickenings appear on the inner surface of the skull with a corresponding thinning. A multiple soap-bubble appearance is observed roentgenologically. The defect is always associated with abnormalities of the central nervous system—spina bifida of the thoracic region—and is attributed to foetal increased intracranial pressure.

Enlarged parietal foramina

Enlarged parietal foramina may appear as varying sized defects of the posterior angles of the parietal bones. These defects apparently arise from a failure of mineralization of the membranous bones of the skull. Approximately 10 per cent of the skulls present small defects in this region. They are not associated with other skeletal defects. The sex incidence appears to be equal. The question of the relationship of the defect to the parietal foramen is still controversial.

Congenital craniostenoses

The craniostenoses represent a group of malformations of the skull effected by premature synostoses of two or more of the cranial bones associated with obliteration of the involved sutures. A defective development of the mesenchymal capsule of the skull, of unknown aetiology, is thought responsible and is frequently associated with other congenital anomalies. A localized expansion of the growing skull is prevented or limited in a direction perpendicular to the long axis of the obliterated suture. This results in a compensatory overgrowth of the skull in other directions. It is becoming increasingly evident that the craniostenoses may be associated with generalized bone marrow disorders such as congenital haemolytic anaemia and pernicious anaemia.

Oxycephaly.—The most striking feature in oxycephaly (tower skull) is the great height of the skull. Exophthalmos and defects of muscle balance are commonly associated as is secondary optic atrophy. Males are more frequently affected.

Acrocephalosyndactyly (Apert's syndrome or acrobrachycephaly).—In Apert's syndrome the head is flattened in the anterior-posterior plane and the vault is abnormally high. The forehead is excessively broad and there is frequently an associated hypertelorism. Syndactyly of the hands and feet is a most frequent association. Other skeletal anomalies may be associated : polydactylism, lobster-claw hand, ankylosis of the radius and ulna and so forth.

Craniofacial dysostosis.—Crouzon's disease is characterized by a central prominence of the frontal region of the skull, a peculiar beak-like nose, prognathism of the mandible, exophthalmos, and exotropia. Considerable variability in the type of skull malformation may exist and there is usually an associated underdevelopment of the maxillae and nasal fossae atresia. The mentality varies but is usually normal. Optic atrophy is not infrequently encountered. Vogt has suggested that a transition stage between Crouzon and Apert diseases may exist, exhibiting the skull defect of Crouzon's disease and the syndactyly of Apert's.

Hypertelorism.—Hypertelorism is a rare form of craniofacial deformity presenting excessive intrapupillary distance, mental deficiency, brachycephaly and a depressed nasal bridge. The forehead is frequently marked with a vertical groove, suggesting a mild cleft face. Grieg (1924) showed that the deformity is the result of malformation of the sphenoid bone (pre-formed in cartilage) in that the greater wings are smaller and the lesser wings larger than normal.

Microcephaly.—Any child with a cranial circumference of less than 17 inches should be suspected of having microcephaly. True microcephaly, a defect of development, presents: a very small head with a narrow forehead, a flattened occiput, recession of the fronto-parietal bones, mental deficiency, receding chin, large outstanding ears, and a prominent nose. The fontanelles may be more or less completely closed at birth. A minor degree of dwarfism exists. There is great variation in the mental status, but as a rule there is severe amentia.

Anencephaly

Anencephaly (rhachischisis, cranioschisis, acrania, holocrania) constitute a series of brain anomalies presumed by Böök and Rayner to have a common origin. They believed the basic developmental failure is a defective closure of the medullary plate. It was believed that the deficiencies in skeletal and muscle development seem to be only secondary to the primary anomaly of the central nervous system.

Anomalies of the skull in generalized affections

Alterations of the skull associated with general affections of the skeleton have been considered under their appropriate categories. The more important have been noted under (1) cleido-cranial dysostosis; (2) osteogenesis imperfecta; (3) chondrodystrophy; (4) dysostosis multiplex; (5) polyostotic fibrous dysplasia; (6) vitamin resistant rickets; (7) diseases of the blood; and (8) reticuloses.

Heredity

Congenital dysplasias of the skull

Ford (1937) reported cortical blindness and cranium bifidum occultum in 2 brothers. The heredity is not known. Sporadic occurrence of the defects is most common.

Lacunar skull of the newborn

Schamburow and Stilbau (1932) were able to present 12 short pedigrees which included 23 affected individuals. They concluded that the heterozygous state of the gene was responsible for spina bifida occulta and the homozygous state for spina bifida aperta. Multiple appearance in siblings has been observed. It is most likely that several genotypes may be responsible.

Enlarged parietal foramina

Goldsmith (1922) reported 56 affected members of the Catlin family. The defect was transmitted as an autosomal dominant. Pepper and Pendergast (1936) reported 9 affected individuals in 3 generations. Inheritance was again dominant.

Congenital craniostenosis

Oxycephaly.—Oxycephaly is usually sporadic. Müller (1893) reported 3 affected brothers Velhagen (1904) an affected mother and daughter, Schob (1920) observed the affection in 3 generations, while Manchot (1911) noted it in 3 generations and 4 affected females. Many other families have been reported. A

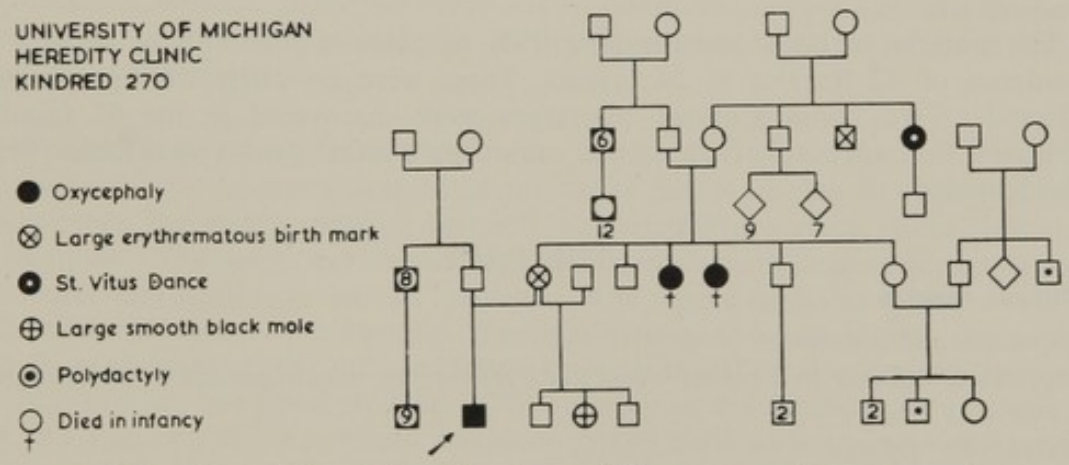


FIG. 147.—Oxycephaly. Pedigree showing multiple occurrence in two generations.

dominant character for the trait has been suggested but recessiveness has been considered (Fig. 147). It has been observed in association with hereditary haemolytic jaundice.

Acrocephalosyndactyly.—The inheritance is perhaps an irregular dominant, although a few pedigrees suggest a recessive gene. Carpenter (1900) reported two affected sisters. Weech (1927) observed an affected mother and daughter. Mohr (1939) reported an affected father and 5 of his 9 children. Waardenburg (1935) observed 8 cases in 4 generations.

Craniofacial dysostosis.—The available evidence suggests that Crouzon's disease may be transmitted as a dominant trait with fair penetrance of the gene. Günther (1933) reported an affected mother, her 2 daughters and a son. He also wrote concerning 4 affected males appearing in 3 generations in another family. Fogh-Andersen (1943) wrote of an affected female transmitting the defect to 3 of her

5 children, to 2 sons by her second husband and to a daughter by her first husband. Concordance in monozygotic twins has been observed (1938, Liebenam).

Hypertelorism.—There is rather frequent occurrence of this disease in families. Abernethy (1927) was able to demonstrate the trait in 5 affected individuals in 3 generations. Walsh (1947) reported an affected brother and sister. Waardenburg (1932) reported 4 affected in 3 generations. Many sporadic cases have been published. It is possible that the disease may be determined by both dominant and recessive genotypes.

Microcephaly.—Frequently there are several affected children in the family. Identical twins (Ford, 1937) have demonstrated microcephaly of the same degree. Halperin (1944) described 8 cases of microcephaly in 3 sibships; there were 19 normal siblings, which supports strongly the conclusion that an autosomal recessive gene is responsible. Spencer (1920) reported 2 microcephalic sisters, children of a consanguinous marriage, in which he believed the defect due solely to disturbance of the development of the calvarium. Allan and his colleagues (1944) reported 3 cases of microcephaly in 3 generations which they presumed was recessive transmission.

Anencephaly

The material of Böök and Bender (1950), 67 cases of anencephaly, showed sex incidence of 42 females to 24 males. There were no other siblings similarly affected. Two consanguinous marriages were discovered in the 67 families. The view that anencephaly in man is caused by a lethal genotypical factor seems well founded.

THE FACE

Clinical aspects

Zygomatic arch defects

Zygomatic aplasia is a rather consistent feature in *mandibulo-facial dysostosis.*

Mandibular defects

The mandible may be involved in vitamin resistant rickets, thalassaemia, reticuloses, polyostotic fibrous dysplasia, mandibulo-facial dysostosis, leontiasis ossea, anhidrotic ectodermal dysplasia, multilocular cystic disease, and status Bonnevie-Ullrich—all are discussed elsewhere.

Pierre-Robin syndrome.—Pierre-Robin syndrome is characterized by hypoplasia of the mandible, fore-shortened geni-glossi muscles, difficulty in swallowing and inspirational retraction of the sternum. Death may result unless mechanical and surgical relief is provided the most severely affected. Among the many associated errors of development are protruding ears, kyphosis, strabismus and cleft palate.

Heredity

Zygomatic arch defects

High cheek bones may appear as a dominant trait in certain families.

Mandibular defects

Whitney (1942) holds that a receding chin was recessive to a straight chin, a

pointed chin was recessive to a wide chin, and a long chin dominant to a short chin. As for the Pierre-Robin syndrome, this has been seen in siblings, and Dingman (1951) has observed the trait in an affected father and his daughter. The expressivity varies greatly as to degree of severity.

THE SPINE AND THORAX

Clinical aspects

Developmental arrest of the vertebral bodies

Hemivertebrae.—Hemivertebrae is the result of the failure of ossification centres for the two halves of the vertebrae to fuse. The resultant halves are usually asymmetrical. Caffey (1951) presented familial dwarfism in a brother and sister, ages 10 and 8 years. Roentgen study revealed multiple hemivertebrae at nearly all levels of both spines. Hemivertebrae have been observed associated with localized alopecia of the scalp, follicular atrophy of the skin and unilateral extremity anomalies. Brailsford (1948) estimates the incidence at 0·3 per cent.

Wedge-shaped.—In wedge-shaped vertebrae one-half of the vertebrae may be absent or incompletely developed. A congenital scoliosis may be associated.

Congenital absence of the vertebrae.—The odontoid process and sacrum have been reported as absent, usually associated with severe degrees of spina bifida manifesta or meningoceles.

Developmental arrest involving arches

Spondylolysis.—In spondylolysis the site of the cleft is frequently but not always the isthmus, the narrow portion between the articular processes. This cleft may be bilateral. The defect occurs most frequently in the fifth lumbar vertebrae, but the fourth and third may also be involved. The degree of defect varies.

Spondylolisthesis.—In congenital spondylolisthesis a separation of the neural arch from its body occurs and the bony anchorage is lost most commonly between the fifth lumbar body and its arch. The stability of the lumbosacral junction is lost and a gliding of the involved vertebrae results until, as in the case of the fifth lumbar vertebra, it may come to lie entirely in front of the first sacral segment. Any degree may exist.

Spina bifida.—In spina bifida a defect of several of the vertebral lamina or neural arch exists. In spina bifida occulta no herniation of the contents of the canal results. In spina bifida manifesta there is usually a large, central tumour covered with an atrophic, thin skin. A frequent association with peripheral symptoms and signs may exist such as (1) motor and sensory disturbances; (2) club-foot and claw-foot deformity; and (3) flaccid paralysis. More severe forms may exist in the case of spina bifida manifesta—meningocele, myelocele and syringomyelocele.

Errors of differentiation of the vertebrae

The vertebrae number is fairly constant, but when the number in one section of the spine is increased or decreased it is usually at the expense of the neighbouring section. A process called assimilation occurs when an increase in one section of the spine may be offset by a reduction in another.

Congenital fusion of the cervical vertebrae.—Isolated synostosis of one or more

vertebral bodies is not rare and when present affects a limitation of motion. Massive synostosis may occur in the Klippel-Feil syndrome, with which may be associated: Sprengel's deformity, neurotropic symptoms, a cervico-dorsal scoliosis and multiple hemivertebrae.

Occipitalization, cervicalization, sacralization and lumbarization.—The first cervical vertebra may undergo cranial assimilation (occipitalization). The seventh cervical may show a caudal assimilation by the dorsalization of the lumbar vertebrae. Sacralization of the lumbar vertebrae, lumbarization of the sacral vertebrae and finally sacralization of the coccygeal may also occur.

Sacralization represents a caudal assimilation of the fifth lumbar to the sacrum and is a very common finding. All degrees of sacralization may exist. In lumbarization all degrees may also be evident. The reduction of spinal stability in lumbarization may contribute to sacralgic pain.

Errors of differentiation of ribs

Cervical rib.—The cervical rib, according to Kühne, is an error in differentiation due to the assimilation of the seventh cervical to the dorsal segment—caudal assimilation. Marked variation in degree exists: rudimentary, complete posterior half, attached to first rib and attached to sternum.

Anatomical variants.—The first rib may fail to reach the sternum. An exostosis or bifid rib may be formed. A pseudo-arthrosis may be found.

Congenital absence of rib.—A partial or total absence of a rib may occur. Concomitant deformities of the vertebrae may coexist. The rib is closely related to the transverse process of the vertebrae, for when the rib is absent so is the transverse process. Associated defects of the overlying skin and underlying viscera may be associated. This latter is especially true in the asymmetrical form of status Bonnevie-Ullrich. Pectoralis muscle defects are probably the most common of thoracic congenital anomalies.

Lumbar rib.—The lumbar rib may be a rudimentary or a fully developed (floating) rib.

Congenital funnel chest

In congenital funnel chest the defect may be so severe that the lower sternum may be held against the vertebral column by a contracted and malformed diaphragm. The severity of the lesion varies greatly within the same family, but even to a greater degree between unrelated individuals. The defect is not rare and frequently cardiac pathology may be associated.

Sprengel's deformity

Sprengel's deformity—congenital non-descent of the scapula—may be observed alone or in association with other widespread congenital anomalies—Klippel-Feil syndrome. It may be unilateral or bilateral, but is usually unilateral. Spina bifida, scoliosis, and other vertebral column anomalies are usually associated.

Generalized skeletal dystrophies

The vertebral column can be involved in a large number of general skeletal dystrophies discussed elsewhere, rheumatoid arthritis, ankylosing spondylitis, the

reticuloses, the haemolytic anaemias, the chondromatoses, dysostosis multiplex, and other affections.

Heredity

Experimental study among mammals, especially the rodents (Green (1939), and Sawin (1945)) has implicated a complex number of genes which seemingly affect localized embryonic areas (ossification centres) as to rate and time of onset. A predilection was demonstrated toward aberrant modification at the divisional points between the various types of vertebrae—cervico, thoracic, lumbar, sacral.

In his extensive studies of the anatomical variations of human vertebral variations, Kühne (1931) maintained that the human vertebral column demonstrates rhythmical waves of change, during development, from one end of the column to the other. Thus the entire column will demonstrate " a unit of continuous change " and with the greatest variability occurring at the four critical points of vertebral change. He observed that if the first thoracic evidenced features of a cervical vertebra then the variation is cranialward, the caudalward variation is illustrated by the last thoracic assuming characteristics of a lumbar vertebra. Kühne concluded that most vertebral aberrations were dependent upon a pair of allelic genes, Cr ↑ (cranialward variation) and cr (caudalward variation). Individuals may then be of genotypes Cr Cr, Cr cr, or cr cr. Cr ↑ proved to be dominant to cr ↓ and presented incomplete penetrance. The homozygous state Cr Cr presented greater intensity of variability than did the heterozygous state Cr cr. In 1936 Kühne presented supportive evidence in an intensive study of twins. The normal individual is assumed to be a balance between the two genic states, a failure of penetrance either of Cr cr or cr cr.

The incidence is 2 ↑ :1 ↓. The identical twins disclosed 100 per cent concordance and the dizygotic twins 70·8 per cent concordance.

Other than for a relatively few studies such as Kühne's our void of genetic knowledge on the many congenital anomalies of the vertebral column is great.

Developmental arrest of the vertebral bodies

Hemivertebrae have been observed in monozygotic twins and in the Klippel-Feil syndrome.

Wedge-shaped vertebrae.—The presence in several siblings (Faber, 1936) in a family with the trait suggests the role of a genic influence.

Congenital absence of the vertebrae in association with spina bifida and meningoceles implicates a genic influence.

Developmental arrest involving arches

Spondylolisthesis.—Stewart (1931), in an extensive study among the Eskimos, concluded that the defect—that is, both minor and severe degrees—is the result of a gene influence, most likely a dominant, with varying degree of expressivity but with good penetrance. Most orthopaedists are aware of at least 2 generation families of the trait.

Spina bifida.—The incidence of the trait has been variously estimated at from 3·5 to 24 per cent of the population. It is evident that the gene must be very common. It appears to have a greater incidence in the male sex. Schamburow

and Stebans (1932) suggested that spina bifida occultum represented the heterozygous state of the gene and spina bifida aperta the homozygous condition. Hindse and Nielsen (1938) reported data on 124 cases of spina bifida manifesta ; they found 28 additional affected siblings among 548 examined. Schroder (1939) reported 2 brothers affected; meningocele and club-foot were associated. Meyers (1930) described twin girls and another sibling with spina bifida; a fourth child was normal. Twin studies have revealed greater concordance in monozygotic pairs for the trait.

It is possible that many genotypes—irregular dominant, conditional dominant, recessive and even sex-linked recessive—may exist for the trait.

Errors of differentiation of the vertebrae

Congenital fusion of the cervical vertebrae.—Sicard and Lermoyez (1923) reported an affected mother, 3 affected sons and an affected daughter with the syndrome, but exhibiting variation in expressivity. The author has studied a family in which 2 of 6 siblings present moderately severe manifestations of the syndrome.

An irregular dominant gene may be responsible. Recessive inheritance has not been ruled out.

Occipitalization, cervicalization, sacralization and lumbarization.—As suggested by Kühne (1931, 1936) the process is the result of two allelic genes, cranialward assimilation being dominant to caudalward assimilation.

Errors of differentiation of ribs

Cervical rib.—The trait is sex influenced in that more females are affected. Kühne's genetic explanation applies to cervical ribs.

Congenital funnel chest

Troisier and Monnerot-Dumaine (1930) reported 10 affected in 4 generations. Their pedigrees revealed dominant inheritance. Snyder and Curtis (1934) recorded 7 affected individuals in 3 generations. Failure of penetrance occurred once in this family. Stoddard (1939) described a very extensive pedigree revealing dominant transmission of the defect.

Sprengel's deformity

Aschner (1928) believed Sprengel's deformity to be recessive. Schwarzweller (1937) and Kühne (1931) both suggested that Sprengel's deformity is due to the same gene which determines the defects of the vertebral column previously discussed.

THE PELVIS

Clinical aspects

The abnormalities of the pelvis are frequently found on radiography.

Accessory secondary ossification centres.—These centres occur in the spine of the ischium and in the superior margin of the acetabulum. They may be unilateral or bilateral.

Ischiopubic osteochondrosis.—Ischiopubic osteochondrosis is closely allied to

ischaemic necrosis occurring in other parts of the skeleton, such as Perthes' disease and Osgood-Schlatter's disease.

Persistence of infantile type of pelvis.—Persistence of the infantile type of pelvis may be associated with unilateral hypoplasia of one of the wings of the sacrum and presents an obliquely contracted pelvis. A rare, transversely contracted pelvis may result from under-development of both wings of the sacrum. These and other pelvic anomalies may be associated with developmental anomalies of the vertebral column.

Open pubic arch.—The pubic arch may be open and the bodies of the pubic bones may be spread apart in exstrophy of the bladder.

Deep acetabulum and intrapelvic protrusion.—In this condition the inner acetabular wall protrudes into the pelvis, the acetabular cavity is usually enlarged, especially inward and upward. The head of the femur—essentially of normal contour—is displaced into the deepened acetabulum. The lower extremity is usually shortened. The condition is usually bilateral and commoner in women.

Congenital luxation and dislocation of hip.—Hypoplasia of the rim of the acetabulum and a small, shallow acetabular cavity associated with congenital anomalies of the hip is probably the most important anomaly of this region. Many theories have been evolved to explain the aberrations of the hip joint (Badgley; Hart, 1942), and all assume a hereditary factor. The primary gene variation theory implies a localized aplasia (germinal aplasia) from which the different forms and degrees of the deformity develop. Preluxation, subluxation and dislocation merely represent degrees of the aplasia. Mechanical factors are secondary (Badgley). In the majority of cases subluxation exists at birth and may or may not develop into dislocation. A sex influence favouring females is present.

Generalized skeletal dystrophies.—The following general skeletal dystrophies, discussed elsewhere, may effect pelvic aberrations: (1) osteogenesis imperfecta; (2) chondrodystrophy; (3) diaphyseal aclasis; (4) osteopetrosis; (5) cleidocranial dysostosis; (6) reticuloses; and (7) thalasseamia.

Heredity

There are few genetic studies of these anomalies.

Accessory secondary ossification centres.—Twin studies have revealed that the accessory ossification centres are genetically determined, but as yet nothing is known about the hereditary mechanism.

Ischiopubic osteochondrosis.—Twin studies and the occasional association of ischiopubic osteochondrosis with other forms of osteochondritis in the same individual suggest that genetic factors may play a significant role.

Persistence of infantile type of pelvis.—Genetic factors are instrumental, but the hereditary mechanism is not known.

Open pubic arch.—This disorder is most frequently associated with other genetically determined anomalies of the spinal division of the central nervous system such as spina bifida manifesta and meningoceles.

Deep acetabulum and intrapelvic protrusion.—Three of Rechtman's cases (1936) suggested a hereditary background. In 1 family 7 individuals were believed affected in 2 generations. In a second family 6 affected individuals appeared in 3 generations. The trait appears to be due to a dominant gene.

Congenital luxation and dislocation of the hip.—Faber's studies (1935, 1937), based on intensive roentgenological observation, indicated that a dominant gene is responsible—a view shared by Hart (1942). The gene penetrance is fair and the variability of expression is rather extensive (*see* Fig. 4, page 22). Dubriel-Chambardel (1908) presented an extensive pedigree disclosing an irregular dominant pattern of transmission. The frequent association of other congenital skeletal anomalies in affected individuals is also strong evidence for the hereditary factor active in the disorder. While statistics vary from report to report an estimated 20 per cent of the cases reveal the presence in the family of other affected relatives.

THE UPPER EXTREMITIES*

An exceptionally large number of abnormalities of hand and finger have been described.

Clinical aspects

The fingers

Apical dystrophy.—There is a total or partial absence of the terminal portion of the distal phalanx of the second through the fifth fingers. The thumb may be involved alone in specific families. The fingernails may be incompletely developed or absent.

Brachydactyly.—Many varying types of brachydactyly have been recorded. Pol's (1921) classification included such entities as: (1) brachyphalangy—(a) brachytelephalangy, (b) brachymesophalangy, and (c) brachybasophalangy—(2) brachymetacarpy and brachymetapody. All may contribute to the clinical picture of brachydactyly. The anomaly usually affects equally the fingers and toes and is not infrequently associated with short stature. Total or incomplete absence of a phalanx (hypophalangy) or abnormal segmentation of the phalanges, ankylosis of the interphalangeal joints and shortened metacarpals may all effect brachydactyly.

Symphalangism.—There is an ankylosis, bony or fibrous, between the interphalangeal joints. A frequent association of symphalangism is observed with brachydactyly. Typically, the middle interphalangeal joints of digits two through five on both hands are affected and many variations exist.

Clinodactyly.—The term tends to be confined to clinodactyly to describe fingers bent in a radial direction. Brachydactyly is often, and possibly always, present. The anomaly may originate from an irregularity in the shape of the phalanges or metacarpals, or joint and tendon abnormalities. Hyperphalangy may coexist. The little finger is most frequently affected.

Camptodactyly.—The term is applied to a permanent flexure of a finger or fingers. The little finger is most frequently affected, being bent or flexed toward the palm of the hand. Dupuytren's contracture chiefly involves digits four and five, a result perhaps of palmar aponeurotic aberration.

Polydactylism.—Part of the general phenomenon of reduplication, is widely distributed throughout a large proportion of the animal world. The variability of expression of the trait is tremendous, ranging from complete reduplication of a limb,

* The monographs by Müller, by Birch-Jensen and by Bauer and Bode have been freely used for this section.

or parts of a limb, to bifurcation of a distal phalanx, or a mere fleshy protrusion (pedunculated post-minimus). In hexadactyly, the most common form, the accessory finger may be radial or ulnar in position. All possible inter-gradations may exist. Syndactyly and other congenital anomalies may be associated findings, but on the whole, the affected individuals are generally normal in every other respect.

Syndactyly.—Here a fusion of the digits can exist in any degree from a cutaneous webbing to synostosis of the phalanges. The webbing usually involves the second and third digits. Polydactyly, brachydactyly, and other congenital anomalies of development are frequently associated. The term zygodactyly has been suggested for the cutaneous webbing between the second and third toes with no change in the bone structure. The term syndactyly is employed for actual bony fusion. There is a greater incidence for the male sex. Any race may be affected.

Hyperphalangy of the thumb.—Extra phalanges may occur and are especially common in the thumb. Hyperphalangism of the fingers appeared associated with brachydactyly in Unterrichter's family (1934).

The hand

Split hand (*lobster hand*).—Birch-Jensen (1949) describes two types: (1) complete or partial absence of one or more of the three central rays and the two radial rays; and (2) is considered as a particularly pronounced degree of type 1, the radial rays being cut off proximally so that there is no cleft formation. He further subdivided type 1 into subgroup (a) characterized by a more or less pronounced cone-shaped cleft formation tapering proximally. The hand is divided into two parts which are moved toward each other—lobster-claws. Syndactylism of the fingers of each side of the cleft is a frequent association. Polydactylism may also be associated with syndactylism. A marked range of variability may exist both interfamilially and intrafamilially (Fig. 148).

Atypical split hand.—According to Birch-Jensen this shows characterized by absence of some of the central rays, but differs from the typical split hand in that there is a reduction of the remaining rays. The trait is usually unilateral. The Danish incidence at birth was estimated to be 1 in 150,000. Syndactylism is a frequently associated congenital anomaly.

Ectrodactylism.—Birch-Jensen uses this term for cases involving total or partial absence of rays where there is no reduction of the remaining bony parts. The variability of ectrodactylism can include partial absence of fingers, or total absence of fingers, hypophalangy, and polydactylism.

Radial defects

Defects of the radius and radial rays are often present in the same individual. Birch-Jensen stressed the frequency of unilateral involvement, and the frequent association with other widespread congenital anomalies. He gives the incidence at 1 : 30,000 births.

Absence of the radius alone with the radial ray of the hand intact.—In partial defect the lower portion of the radius is most frequently involved while the upper end of the radius is less frequently affected. The hand may be deflected radially (club-hand).

Total defect presents the radial rays of the hand to be intact. The missing radius is replaced by fibrous strands and the ulna is curved, thickened and short.

Total or partial absence of radius with aplasia of radial rays of hands and fingers.—The defect affects all or part of the radius in addition to an associated absence of the first metacarpal and thumb. There may be in addition an absence or under-development of the radial carpal bones. The muscles of the thumbs may be defective or absent.

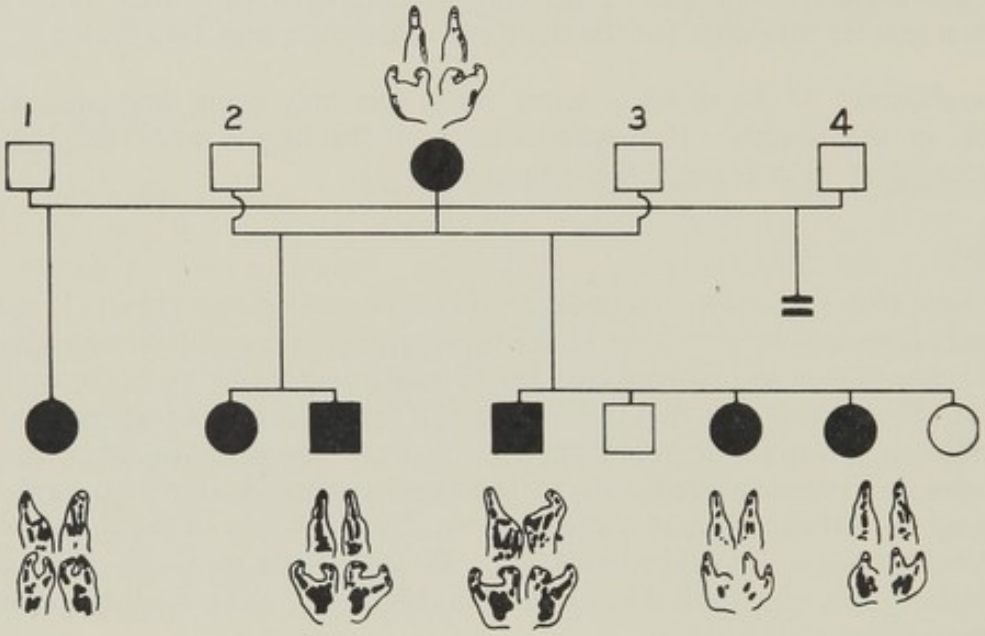


FIG. 148.—Split hand. Pedigree showing dominant autosomal inheritance and intra-familial variability of expression. (*After Stern, C. (1949). Principles of Human Genetics. San Francisco; Freeman.*)

Ulnar defects

Total or partial absence of ulna.—Total or partial absence of the ulna is a very rare anomaly. The forearm is shortened and an associated ulnar club-hand is present. A frequent association is radio-ulnar synostoses, especially when a portion of the ulna persists.

Total or partial absence of ulna with associated defects of ulnar rays.—In addition to the defect of the ulna there may be associated anomalies of the ulnar carpal bones and digits four and five (phalanges and metacarpals).

Radio-ulnar defects

Absence of radius and ulna (phocomelia).—In this defect the forearm is absent but the hand is present and is continuous with the humerus. The latter is usually shortened or poorly developed. The rays of the hands vary from four to two.

Congenital radio-humeral, ulna-humeral synostosis

Congenital radio-humeral, ulna-humeral synostosis is a fusion between the humerus and the ulna or the radius. If not complete a rudimentary elbow joint may develop. The defect is not too rare. Over 50 per cent of the cases are bilateral. Greater male sex incidence is reported.

Congenital amputations

In the cases of amputations there may be found rudimentary fingers or hands. The absence of scar or exposed bone suggests congenital amputation rather than so-called spontaneous amputation.

The rays of the hand are reduced to rudimentary fingers of almost the same size. Birch-Jensen suggests the term symbrachydactylism for this condition, especially where the ray reduction is not complete or one or more of the rudimentary digits are considerably larger than the others.

Heredity

The fingers

Apical dystrophy.—Inheritance is dominant. MacArthur and McCullough (1932) reported a Canadian family in which 15 cases appeared in 3 generations. Sorsby (1935 and 1951) reported apical dystrophy of the hands and feet in which 8 affected individuals appeared in 3 generations; bilateral macular colobomas were also present in all of the affected individuals.

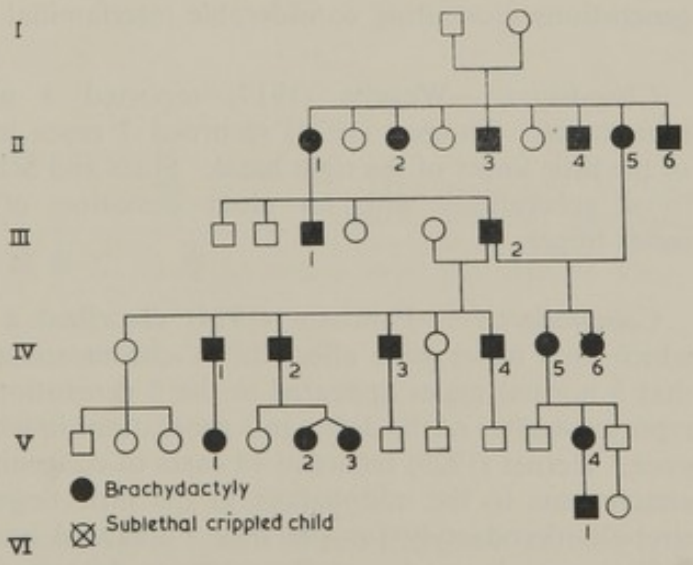


FIG. 149.—Brachydactyly. Pedigree showing dominant inheritance and possible homozygous state. (*After Mohr, O. L., and Wriedt, C. (1919). Carnegie Inst. Wash. Publ.* 295.)

Brachydactyly.—This was one of the first traits shown to conform Mendelian principles in man. As early as in 1905 Farabee presented a 4-generation pedigree of brachydactyly and demonstrated the expected 1:1 Mendelian ratio demanded of dominant autosomal inheritance.

Ziegner's (1903) family presented a brachymesophalangy of the index finger with an associated radial clinodactyly in which the trait appeared in 4 generations; 13 of the affected also illustrated brachymesophalangy of the toe. Mohr and

Wriedt (1919) (Fig. 149) also presented a family with a similar brachymesophalangy. The defect showed variability ranging from nearly normal to severe involvement. The inheritance was dominant. In one instance intermarriage of affected individuals produced a very severely affected child without toes or fingers and very mis-shapen, who probably represented the homozygous state of the trait. Webb (1901) reported 17 affected individuals in 3 generations with brachymesophalangy involving the second through the fifth digits. Brachymetacarpy pedigrees have been reported by Chevallier, Fontana and Vacchelli (1902), and Gillette (1931). Brachytelephalangy of the thumbs (short thumbs) and great toe was traced through 5 generations by Fränkel. Brietenswischer (1923) and Sayles and Jailer (1934) have reported dominant pedigrees. Brachymetapody, short metacarpals and metatarsals, were reported by Stiles (1939) in 5 affected individuals in 2 generations who showed considerable variability of expression.

Symphalangism.—Drinkwater (1917) described a family in which there was evidence that the defect had been transmitted through 14 generations in a dominant manner.

Walker (1901) reported 10 cases in 5 generations with symphalangism between the proximal and middle phalanges of digits three and five, hypophalangy was also associated. Cole (1935) observed dominant inheritance of symphalangism affecting the terminal interphalangeal joint in the index finger only; there were 9 affected members in 5 generations. Hefner (1924) recorded 23 cases in 6 generations illustrating considerable interfamilial variability.

Clinodactyly.—Wegelin (1917) reported 3 generations showing dominant inheritance. Thomas (1926) recorded 7 cases in 3 generations of clinodactyly of the little finger of the right hand. Stiles and Schalck (1945) reported 34 affected in 4 generations with an ulnar deviation of the distal phalanges of the index finger.

Camptodactyly.—Fantham (1924) described a severe degree in a family in which only males were affected. Y-chromosomal inheritance was likely, except that 5 normal males appeared in the 5 generations. Moore and Messina (1936) reported 8 cases of the defect in 3 generations in which lack of penetrance appeared once. Hefner (1929) recorded 14 cases of congenital shortness of the ligamentous attachments to the midphalanx of the little finger. He recommended the term strebolomicrodactyly for the trait. Bilateral and unilateral appearance of the defect were observed as well as varying degrees of severity. Leri's pleonosteosis demonstrated contracture of most of the digits of the hands and feet and this was transmitted as a dominant trait. In Dupuytren's contracture inheritance is an incomplete or irregular dominant, exhibiting a marked male sex incidence.

Polydactylism.—Most pedigrees indicate dominant inheritance (Fig. 150). Brandeis described a pedigree depicting an irregular dominant pattern with several instances of failure of penetrance. Gates (1947) had collected 27 pedigrees of

polydactyly in the Negro; nearly all showed ulnar duplication with a strong frequency of a " pedunculated post-minimus."

A recessive gene for polydactylism probably does exist, but is less common. Polydactylism is a cardinal manifestation of the Laurence-Moon-Bardet-Biedl syndrome, which is a recessive affection. Gates (1946) suggested a sliding scale of values, from absolute to variable dominance with such a low penetrance that it cannot be distinguished from recessiveness. The recessive form of polydactyly seems to be a very mild form of the trait contrary to other recessive genes which seem to exert a strong deleterious effect.

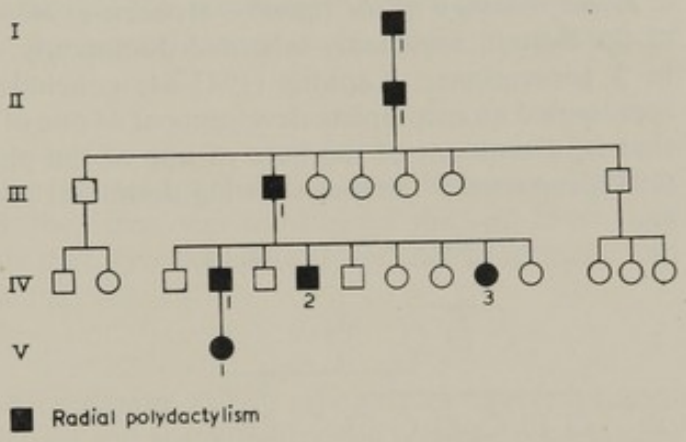


FIG. 150.—Radial polydactylism. Pedigree illustrating dominant inheritance. (*After Manoiloff, E. O. (1931). Amer. J. phys. Anthrop.*, **15**, 503.)

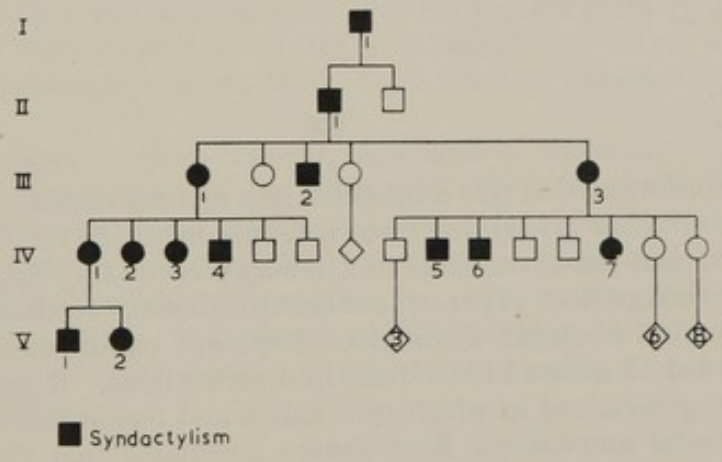


FIG. 151.—Syndactyly. Pedigree showing dominant inheritance. (*After Murphy, D. P. (1925). J. Amer. med. Ass.*, **84**, 576.)

Syndactylism.—Pipkin and Pipkin (1945) reviewed the literature on and concluded that certain pedigrees (Hurlin, Wright, Pfitzner, Wolff and Heston) strongly suggested that the trait is dependent upon a partially sex-linked gene. Kemp and Ravn (1932) presented 44 cases in 6 generations in which the affected presented both polydactylism and syndactyly. The latter, present in 29, was usually confined to a synostosis of the fourth and fifth metacarpals. Considerable variability of expression existed. The transmission was regular dominant, there were three examples of failure of penetrance. Schlatter's pedigree showed 5 generations of syndactylism inherited as a dominant trait. One marriage appeared to be between

a homozygous male and a heterozygous female; all of their offspring were affected in a manner similar to their parents. Schofield (1922) recorded a unique pedigree which illustrated male-to-male (possibly Y-chromosome) transmission over 4 generations. The webbing was cutaneous and between digits two and three. Gates in 1946 tabulated most of the pedigrees, then available, and concluded that a single dominant gene is responsible for the trait, but having a 2 : 1 greater incidence in the males.

It is perhaps best to conclude that syndactylism may be the effect of several genotypes: (1) simple autosomal dominant (Fig. 151); (2) Schofield's Y-linked holandric pedigree; (3) sex-linked dominant; and (4) simple recessive.

Hyperphalangy of the thumb.—Roberts (1943) reported a family of triphalangy of the thumb, apparently inherited dominantly. It was present in 13 individuals in 3 generations. Lapidus (1943-44) concluded that the triphalangeal thumb represented an incomplete development of one of the phalanges of the bifid thumb, that is, a remnant of the base of one of the phalanges of a bifid thumb. Haas (1939) reported 3 families showing dominant inheritance of the trait.

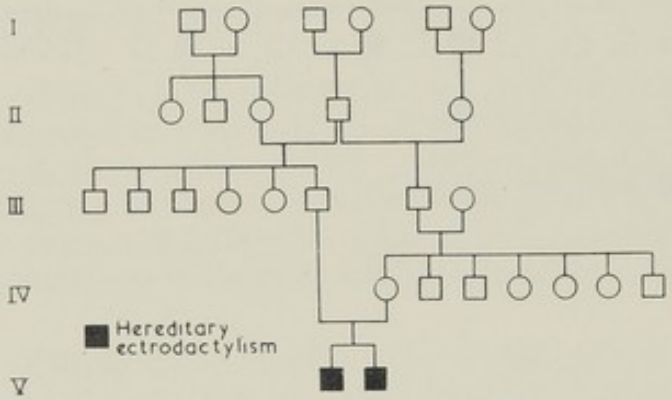


FIG. 152.—Hereditary ectrodactylism. Pedigree presenting recessive inheritance and illustrating consanguinity. (*After Klein, I. J. (1932). Amer. J. Dis. Child.*, **43**, 136.)

The hand

Split hand.—Pearson (1908) showed that this is inherited in a manner consistent with autosomal dominance. Fischer (1922) described a family in which the inheritance seemed to be autosomal recessive, while in a family recorded by Scott (1933) there was irregular dominance (lack of penetrance occurred once). Hoffman (1936) and Hanhart (1945) also observed incomplete dominant transmission, while Anderson (1886) recorded 13 affected individuals in 4 generations. Klages and Jacob (1940) observed 4 generations in which split hands and feet appeared associated with other congenital anomalies. Birch-Jensen concluded that syndactylism is included in the typical split hand and foot picture and that the transmission of split hand is often dominant. An estimated frequency of 1 in 90,000 births was given for the Danish material.

Atypical split hand.—Birch-Jensen saw only sporadic cases. The inheritance pattern is not known. Klein (1932) reported 2 affected siblings, offspring of a consanguinous union of sound parents.

Ectrodactylism.—Birch-Jensen believed the inheritance pattern to be dominant and observed the frequent association of hypoplasia or polydactylism of the distal phalanx. The gene may rarely be recessive (Fig. 152).

Gates (1946) cited 5 cases of monodactyly in 3 generations in which only the little finger was present and the feet were somewhat similarly involved. A dominant inheritance pattern was present.

Radial defects

Total or partial absence of radius with aplasia of radial rays of hands and fingers.—Joachimsthal (1895) reported an affected mother and 5 children, Steinsleger (1921) an affected father and daughter, and Funston (1932) a mother and daughter with bilateral absence of the radius and club-hands. Recessive inheritance is suggested by Kato.

The gene appears to be dominant and the presence of a very minor defect in one individual may be followed by a much more severe form in subsequent generations.

Ulnar defects

Total or partial absence of ulna with associated defects of ulnar rays.—Roberts (1886) reported a family in which the defect was transmitted through more than 2 generations. Birch-Jensen holds that the ulnar defects are chiefly sporadic and are associated with other joint lesions.

Radio-ulnar defects

Absence of radius and ulnar.—Grandmaire (1897) reported an affected grandfather; the father had hyperphalangia and the daughter and son had phocomelia. In Kutzenok's (1929) first generation 2 sibs presented partial absence of the radius while a son and daughter had phocomelia. Birch-Jensen believed the incidence at birth to be 1 in 75,000, and thought the defect was usually bilateral and the inheritance was recessive. Starr holds an irregular dominant gene as responsible.

Congenital radio-humeral, ulna-humeral synostosis

Davenport and his colleagues (1942) were able to present several pedigrees demonstrating a dominant inheritance. In one, Y-chromosomal inheritance was suggested. Abbot (1892) recorded an irregular dominant pedigree and Thomas (1926) 3 cases in 4 generations. A recessive gene is suggested by Roth (1926). In Vogeler's (1925) family an affected man transmitted the disorder to his grandsons through normal daughters, suggesting recessive sex-linkage or male sex-limitation.

Congenital amputations

Bohomoletz (1930) and Koehler (1936) recorded a sibship of 12, the offspring of normal parents who were consanguinous; there were 6 affected displaying congenital amputations of the arms and legs. There is, however, some doubt as to the accuracy of the diagnosis in the affected cases. Schwarzweller (1939) reported 5 out of 8 siblings, children of normal parents, displaying a large range of limb defects including congenital amputations. Birch-Jensen's material consisted mostly of sporadic cases, and he concluded that a recessive, incompletely dominant and a dominant genotype may exist for the trait. Symbrachydactylism he believes to be inherited as a recessive trait.

THE LOWER EXTREMITIES

Clinical aspects

The developmental anomalies and minor aberrations of the lower extremity are largely similar to those of the upper extremity. The basic anatomical structural differences do present specific entities which require further discussion.

The toes

Brachydactyly.—As previously mentioned the feet and toes are shortened in brachydactyly. The foot may be involved alone, but the combined foot and hand affection is more common. The big toe, the metatarsals and even the long bones of the lower extremity may display shortening. The metatarsals are less frequently affected than the metacarpals.

Length of toes.—There exist, according to several authorities, two major types of feet in respect to the length of the toes. In type 1 the great toe is the longest and the other toes slope backward in an oblique line. In type 2 the second toe is the longest. Many variations exist and one foot may present type 1 while the other falls into type 2. Type 1 is believed dominant to type 2.

Syndactyly.—Webbing, or union between the toes, may apply to all digits. It is more frequently found to affect the second and third toes. Syndactyly is more frequent in the foot than the hand.

Polydactyly.—The little toe is most frequently affected. The extra toe may be complete (including the metatarsal) or may be so reduced as to present only a slight excrescence of the expected site. The large toe is occasionally duplicated.

The metatarsus

Alterations in the normal form of the forefoot are rather common and in general chiefly concern anomalies of the first metatarsal.

In metatarsus varus there is supination and adduction of the forefoot, the metatarsal bones being deflected inward and occasionally superimposed.

In metatarsus brevis the first metatarsal bone is shorter than normal and its head may be situated behind the head of the second metatarsal. The metatarsal is often abducted.

In metatarsus hypermobilis the first metatarsal is unduly mobile.

The foot as a whole

Congenital pes planus.—This is a congenital deformity of the bony segments of the long arch of the foot, of the plantar ligaments, or of the postural activity of the tibial group of muscles, and may singly or in combination contribute to a flat-foot. The sole of the affected foot is usually boat-shaped, being higher in the front and in the back. The tendon Achilla is frequently shortened, as are the extensors of the toes. There are many variations and degrees of the affection.

Congenital club-foot.—There are several aberrations. The incidence of the affliction has been variously estimated from 1:1,000 to 1:1,500. A sex ratio of 2 affected males to 1 affected female was reported by Debrunner (1940) from his summary of the literature.

As aetiological factors: (1) congenital skeletal anomalies; (2) dystrophic muscular aberrations usually secondary to (3) neurogenic anomalies of the central nervous system have been suggested.

Pes cavus.—This presents a deformity of the foot in which clawing of the toes is combined with a high, long arch of the foot. When it is congenital the defect may not be apparent until the child reaches the age of 6–7 years. Other developmental anomalies and even degeneration of the central nervous system or muscular diseases may be associated with or may be the causative agents of pes cavus (spina bifida occulta, myelodysplasia, Friedreich's ataxia, and peroneal atrophy).

Tarsal synostoses.—Many congenital synostoses of the various tarsal bones have been reported.

Cleft foot.—Cleft foot, or split foot, closely parallels and is associated with cleft hand.

Long bones

Congenital defects of fibula.—A primary aplasia of the fibula may be congenital. There may be an absence or a deficiency of the lower half of the bone. A fibrous strand or even a pre-formed cartilaginous *anlage* may exist. Associated congenital malformations of other parts of the body are not infrequently present. The lower limb is usually shorter than normal and the tibia may present anterior bowing. A dimple in the skin frequently overlies the bony defect. The foot is usually in an equino-valgus position. There may or may not be a reduction in the tarsus and a reduction or absence in the fourth and fifth digital rays. Associated muscular defects are frequently encountered.

Congenital defect of tibia.—Congenital defects of the tibia are rather rare. The degree of aplasia varies considerably from complete absence to only partial absence of the distal end of the tibia. The distal end of the femur and the foot may be involved on occasion. The metatarsal and first and second digits may be absent. Anomalies of the related musculature may be associated. Total absence of the tibia is not too uncommon and is frequently unilateral.

Congenital angulation and pseudarthrosis of tibia.—Congenital angulation of the tibia is regarded by some as a specific entity distinct from pseudarthrosis of the tibia. It may be unilateral or bilateral. It is frequently associated with other congenital skeletal anomalies. Posterior as well as medial bowing has been reported. The bowing usually occurs at the junction of the middle and lower one-third of the diaphyses. Pseudoarthrosis—a rare affection—may be associated with neurofibromatosis.

Congenital deformity of the femur.—Congenital aplasia of the femur is not a very rare anomaly. The partial defect may vary greatly in extent and character. A short femur is frequent in coxa vara. There may be a rudimentary development of the head, neck and upper portion of the shaft, with a fairly intact femur. The femur is not infrequently synostosed with the tibia. The entire limb is shortened and there are often associated other deformities of the lower limb and foot.

Phocomelia of lower extremities

A peripheral rudiment, digits or a thick skin pad may be attached to the remaining portion of the affected extremity.

Other anomalies

Hammer toe.—This is a deformity consisting of dorsiflexion of the proximal phalanx, plantar flexion of the second and usually flexion (or extension) of the distal phalanx. The second toe is usually involved, but others may likewise be affected. The affection may be bilateral. There is a frequent association of the defect with hallux valgus.

Hallux valgus

Hallux valgus.—This consists of extreme adduction of the proximal phalanx of the great toe towards the midline of the foot. This defect may be associated with varying degrees of varus of the first metatarsal.

Hallux rigidus.—This presents a stiffened metatarsophalangeal joint of the great toe, chiefly characterized by the absence of dorsiflexion.

Heredity

Developmental anomalies of the metatarsus

Several of the clinical features of the metatarsal defects suggest their inclusion in the group of hereditary anomalies of the foot: the symmetry of the defect and the very frequent association with other hereditary congenital abnormalities.

Metatarsus varus has been observed in sibs (Madier and Massart; Mettenleiter; Kite) and also in mother and son (Weil) and in mother and daughter (Kite). Kite reports a normal woman who had an affected daughter by one marriage and 2 affected children by her second husband.

Tarsal synostoses are rare and usually occur only as sporadic cases. Hereditary causation may be thought of since they are not infrequently symmetrical, bilateral and associated with other congenital anomalies.

Boyd (1944) reported 3 cases occurring in 3 generations of synostoses of the navicular and talus. A marked enlargement was observed over the medial end of the navicular portion. Webster and Roberts (1951) reported the discovery of a talo-calcaneal synostosis in 2 sisters. They also observed symmetrical calcaneo-navicular synostosis in an 11-year-old boy and pointed out the relationship between tarsal anomalies and peroneal spastic flat-foot. Weitzner (1946) associated talo-navicular synostosis with the hereditary multiple ankylosing arthropathies. Rothberg and Feldman (1935) reported a hereditary synostosis of the astragalus and scaphoid.

The foot as a whole

Cleft-foot appears to be the effect of the same gene as for cleft-hand. A close association is observed between syndactyly and cleft-foot.

Congenital pes planus

Lamy (1934) has shown that the convex valgus foot is inherited as a dominant factor.

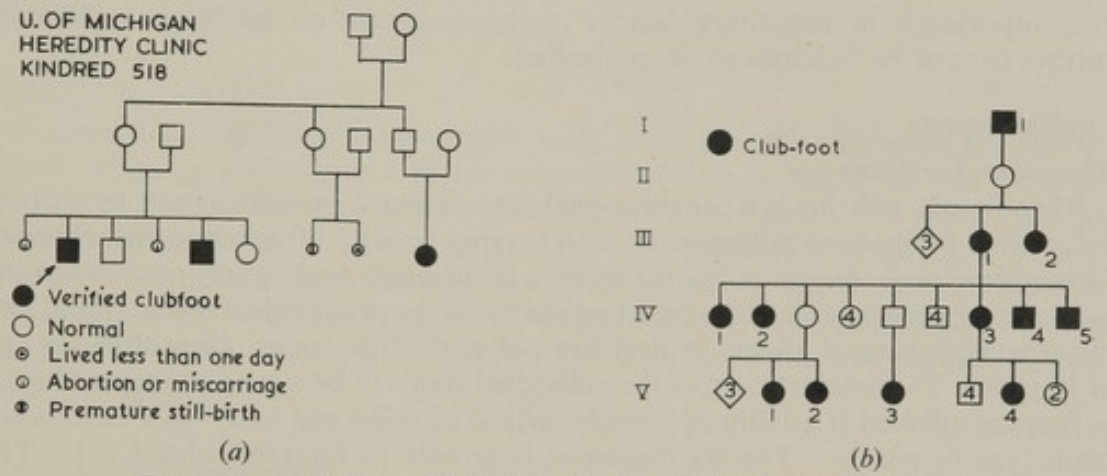
Congenital club-foot.—Irregular dominance (Fig. 153), probably sex influenced, is suggested by Koch (1934), Kite (1949) and Scaglietti (1934). This gene exhibits poor penetrance and considerable variability in expressivity. Unilateral, or bilateral symmetrical as well as interchanging forms of club-foot are known to

have existed in specific pedigrees. A recessive gene (Müller, 1926 and Debrunner, 1936) has also been suggested. Both writers were impressed by the lack of penetrance of the gene. Isigkeit (1928) contended that his material supported a sex-linked recessive form of the disease.

Pes cavus.—Davidenkov (1940) showed that this can occur in normal members of families with Friedriech's ataxia.

Long bones

Congenital defects of fibula.—Volkmann (1873), describing his family, observed 7 affected individuals; most cases have been sporadic.



(*a*) (*b*)

FIG. 153.—Club-foot. (*a*) Pedigree showing multiple occurrence of club-foot in kindred 518. (*b*) Pedigree showing irregular dominant transmission of club-foot. Lack of penetrance appears twice. (*After Stewart, S. F. (1951). J. Bone Jt. Surg.*, 33A, 577.)

Congenital defect of tibia.—Ollershaw (1925) observed monozygotic twin girls with unilateral aplasia of the tibia and associated club-foot and hallux valgus. Vonnegut (1926) recorded a 3-generation pedigree in which 2 cases of tibial aplasia appeared. Other defects present in other members of the family included: polydactyly, club-foot and shortening of the extremity. Gray (1948) suggested a dominant hereditary pattern.

Congenital deformity of the femur.—Bauer and Bode (1940) hold that the defect is genetic in origin. The mode of inheritance is unknown.

Phocomelia of lower extremities

Most reports are of sporadic cases, but the association of the trait with other skeletal aberrations suggests genetic factors.

Other anomalies

Hammer toe.—Gutmann (1925) reported 7 affected individuals in 5 generations in which the second toe on the right foot was involved. There was one instance of failure of penetrance. The transmission pattern was dominant.

Hallux valgus.—McElvenny (1944) concluded that hallux valgus may be hereditary, and probably dominant. Hardy and Clapham (1951), from amnestic

evidence of 63 per cent of their 91 cases, revealed other affected members in the families.

Hallux rigidus.—An affected father and 2 of his 3 sons have been observed at the University Clinic of Ann Arbor.

III. ARTHRITIDES AND RHEUMATIC DISEASES

Chronic rheumatic disease affects approximately one in each twenty of our population. The chronic morbidity, the economic loss of manpower, the years of disability and pain is most appalling. It has been said that arthritis and rheumatism cause more years of disability and crippling than all accidents combined. The importance of hereditary factors in the incidence of the following disease entities cannot be overlooked or minimized.

Clinical aspects

Rheumatoid arthritis

Rheumatoid arthritis is a constitutional disease which manifests itself by chronic deforming, progressive polyarthritis with varying severity of systemic disturbances. This symmetrical chronic polyarthritis may be accompanied by soft tissue swelling, pain and tenderness and with special reference to the proximal interphalangeal and metacarpophalangeal joints. Ninety-five per cent of the cases occur after the age of 16 years. The temperament of the individual seems to be a most important factor in that the affected is usually of " ready fatigue of mind and body "—a vasomotor labile type of person. The sex incidence is greater in females—about 2:1. The white race seems more susceptible than the black.

Ankylosing spondylitis (*spondylitis rhizomélique*)

Considerable controversy still exists in the literature as to whether this disease is a variant of rheumatoid arthritis. The essential pathological lesion is an arthritis of the sacro-iliac joints followed by a primary synovitis of the joints formed by the intervertebral facets, calcification of the paravertebral ligaments and finally rigidity of the spine. A marked male sex incidence is observed 10:1.

Degenerative joint disease

Osteoarthritis.—Degenerative joint disease affects almost all of the population past the age of 50 years (Comroe, 1941), although about only 5 per cent have symptoms. The essential pathological lesion is an erosion and degeneration of the hyaline articular cartilage with hypertrophy of the adjoining cartilage and bone. The terminal phalangeal joints of the fingers, lumbar vertebrae, knees, sacro-iliac, lower cervical vertebrae and hips are most frequently noted in that order. The patient is usually obese.

Heberden's nodes are enlargements of the terminal interphalangeal joints of the fingers due to degenerative joint disease. Multiple fingers on both hands are involved. Age is the most important single factor in the occurrence of the disease, but a hereditary background is apparently necessary. Women are by far the most frequently affected.

The close correlation of the development of the nodes with the onset of the climacteric (+0·46) suggested a causal relationship or, better, a common aetiology.

It was further suggested that the effect of the climacteric on the production of Heberden's nodes may be due to alterations in the peripheral circulation.

Periodic arthralgia

Periodic arthralgia, according to Reimann and Angelides (1951), is a disorder characterized by pain in the joints at regularly recurrent short intervals over many years. No permanent disability has been recognized.

Reimann believes the disorder to be a member of a group of periodic disorders which include: periodic fever, periodic abdominalgia, cyclic neutropenia, intermittent arthralgia, angioneurotic oedema, anaphylactoid purpura, and periodic paralysis.

Haemophilic arthritis

Haemophilic arthritis is associated with a hereditary haemorrhagic disease characterized by prolongation of the coagulation time of the blood and excessive bleeding occurring spontaneously or associated with trauma. In one review of 76 haemophilic patients, 44 demonstrated some evidence of changes in the bones or joints. Permanent joint deformity occurred in nearly 50 per cent of the latter. The knee, ankle and elbow joints, in that order, are most frequently involved. The chief arthritic manifestations are: acute haemarthrosis and chronic haemophilic arthritis.

Non-articular rheumatism

In an excellent review of non-articular rheumatism Freyberg (1951) makes a plea for consideration of the complex disease state as a clinical entity. He refers to those conditions which affect the non-articular connective tissue directly and without accompanying joint disease and without systemic febrile illnesses. These conditions include fibrositis (most common), lumbago, panniculitis, herniated subcutaneous fat, reflex neuromuscular dystrophy, rheumatic manifestations of psychoneurosis, and painful stiff neck. In general the conditions are generally mild, slow to improve, but carry a good prognosis. They usually affect young to middle-aged adults.

Sjögren's syndrome

Sjögren's syndrome is a general constitutional or systemic disturbance of unknown origin characterized by a chronic polyarthritis, keratitis sicca, and a poly-mucous gland involvement with dryness of the nose, pharynx, trachea and bronchi. This disorder is observed chiefly in women in and past the menopause. Males may be effected. The extreme chronicity of the complaint suggests the possibility that the menopause is only an aggravating factor in an already established condition.

Other conditions

Gout, alkaptonuria and psoriatic arthropathy and rheumatic fever are dealt with elsewhere.

Heredity

Rheumatoid arthritis

Kroner (quoted by Weitz, 1936) reported 4 generations of the disease transmitted through the females. Papp and Tepperberg (1937) wrote of 11 cases in 4 generations, chiefly females. Kaufmann and Scheerer (1928) exhibited a greater degree of concordance for the disease in monozygotic twins than exhibited by dizygotic twins and triplets, 17·5 per cent: 22 per cent.

Short and his colleagues (1952) concluded that rheumatoid arthritis occurred more often in the families of arthritic patients than in the families of controls. Their statistics indicated that there was a percentage incidence of other affected members in the family of 11·9 in contrast to 5·1 in their controlled series.

Stecher and his colleagues (1952) state that 5 per cent of 738 relatives of patients with rheumatoid arthritis had the disease in comparison to 0·1 per cent of 2,437 relatives of the controls. The disease occurred 50 times as commonly in relatives of patients as in relatives of controls.

Ankylosing spondylitis (*Figs. 154 and 155*)

Gerlinger (1918) described 5 affected individuals in 3 generations. Fischer and Vontz (1930) observed 4 affected patients in 3 generations. Ray (1931) described concordant male twins. In fact, there are 3 pairs of concordant monozygotic twins now known. Riecker and Neel (1951) (Fig. 155) described 6 affected individuals in 3 generations. Hersh and Stecher (1950) have most capably analysed the literature and have recorded 69 families involving a total of 139 affected individuals. These writers emphasized that some individuals with the genetic constitution for ankylosing spondylitis develop the trait and others do not. There appears to be a lack of penetrance of the gene. Sex-linkage is ruled out by father-to-son transmission in at least 12 instances. Hersh concluded that the gene is probably an autosomal dominant with incomplete penetrance but with a distinctly lower penetrance in females than in males. Stecher and Hersh believe the gene has a 70 per cent penetrance in males and 10 per cent in females. It was further deduced that the presence of affected women in a pedigree has a stabilizing effect upon penetrance, making it almost complete in both sexes. Especially is this true if the mother has spondylitis.

Stecher and his colleagues (1952) stated that ankylosing spondylitis occurred in 3·4 per cent of 235 relatives of patients with the disease compared to 0·005 per cent of 1,904 relatives of the control series. The disease, therefore, occurred 70 times as commonly in relatives of patients as in relatives of controls.

Degenerative joint disease

Heberden's nodes.—Stecher (1949) felt that a strong genetic factor has been demonstrated in that the mothers of affected women have the disease twice as frequently and the sisters three times as often as the population in general. These same authors suggested that Heberden's nodes depended upon a single autosomal gene which is sex influenced so that it is dominant in women and recessive in men. It appears only in men who are homozygous for the trait and may be expected in less than 3 per cent of the male population over the age of 50 years. Stecher estimated that 30 per cent of the female population are genotypically conditioned to develop the abnormality.

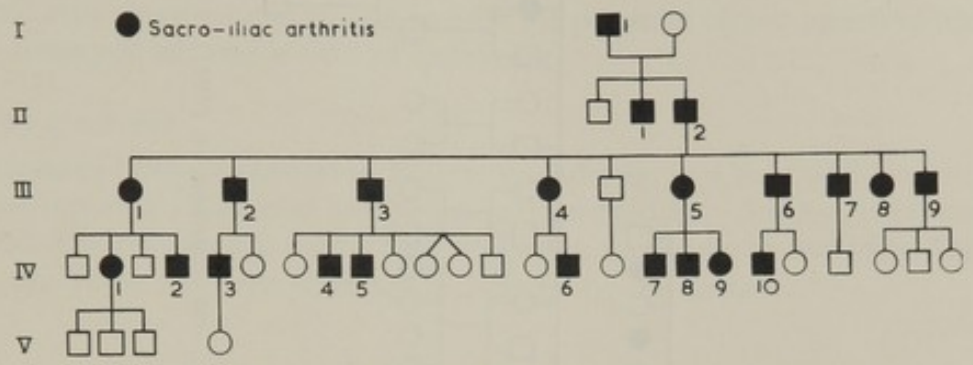


FIG. 154.—Sacro-iliac arthritis. Pedigree showing a dominant autosomal inheritance. There was a possibility of a *forme fruste* of ankylosing spondylitis. (*After Stauffer, J., and Merrihew, N. H. (1944). J. Hered.*, **35**, 112.)

Periodic arthralgia

Reimann (1951) reported periodic arthralgia affecting 23 members in 5 generations (Fig. 156). The transmission was autosomal dominant with excellent penetrance and minimal variability of expression. Blanc (1898), Frenkel-Tissot (1916) and Schlesinger have reported hereditary transmission of periodic arthralgia.

Haemophilic arthritis

This disease entity has for centuries been notoriously recognized as a sex-linked recessive disease and the literature is replete with articles in support of this type of inheritance. There is evidence that heterozygous females occasionally may exhibit mild manifestations. A few families have demonstrated dominant and even recessive forms of the disease.

Non-articular rheumatism

Freyberg (1951) implied that inherited fibrous tissue characteristics may well set the background for the disease entity development. This hereditary factor has

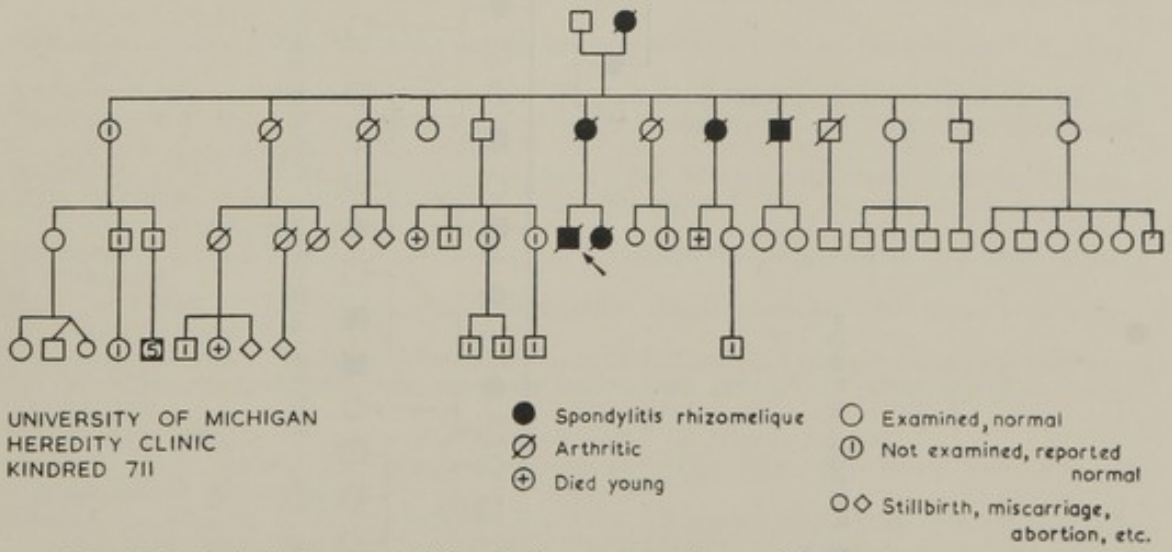


FIG. 155.—Ankylosing spondylitis. Pedigree presenting possible dominant transmission. (*After Riecker, H. H.*, and his colleagues (1950). *Ann. intern. Med.*, **33**, 1254.)

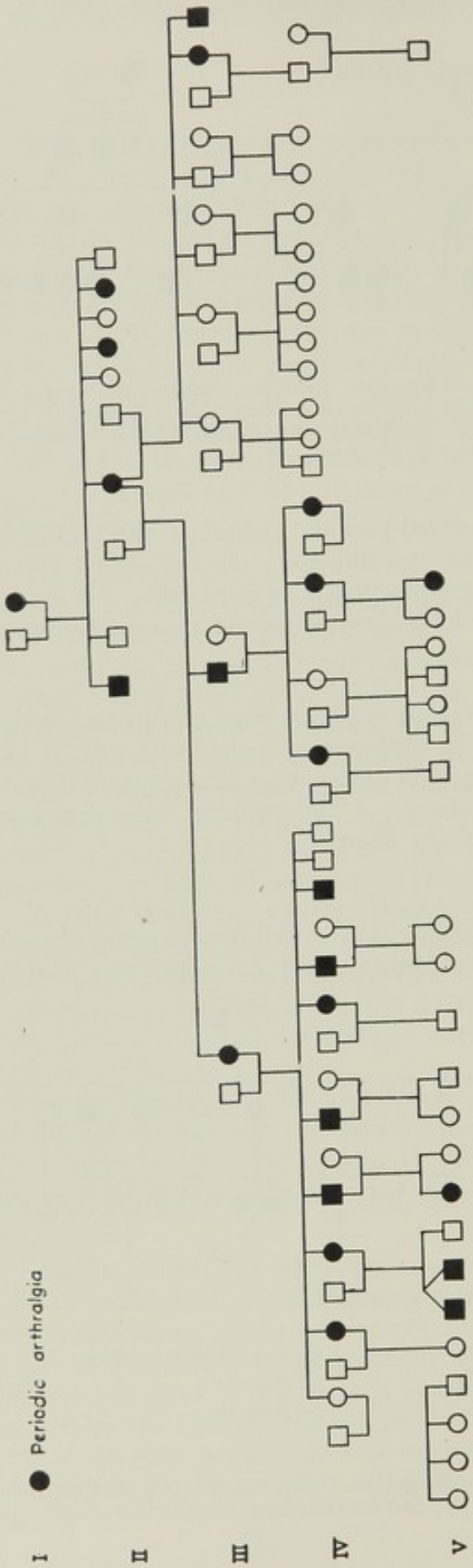


FIG. 156.—Periodic arthralgia. Pedigree showing a dominant autosomal inheritance. (*After Reiman, H. A., and Angelides, A. (1951). J. Amer. med. Ass.*, **146**, 713.)

been but little explored and should provide the prepared clinico-genetical observer with a tremendously fertile field of endeavour.

Sjögren's syndrome

Coverdale (1950) has observed Sjögren's syndrome in a man and his daughter. Lish has reported 12 affected individuals in 3 generations. Sorsby (1951) suggests the syndrome may incorporate Plummer-Vinson syndrome as one of its features.

The syndrome has been observed in 2 sisters by the author.

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CHAPTER 15

MUSCULAR DISORDERS

F. E. STEPHENS

MUSCULAR DYSTROPHIES

THE TERM " muscular dystrophy " is usually applied to those cases of muscular wasting where the primary cause is located in the muscles rather than in the nervous system. The disease progresses over varying periods of time, hence the descriptive title progressive muscular dystrophy. While isolated sporadic cases may arise there is a definite tendency for this defect to occur in more than one member of a kindred and to occur in a certain genetic pattern. The variability of its expression and the similarity of the different genetic types have caused many workers to consider all cases as merely different expressions of one and the same disease. Some investigators have thought that all forms are due to the action of the same gene and that the variability of expression is due to modifying factors. This has led to confusion in the descriptions of the defect since what is true of one genetic type may not in all cases be true of another. For example, the generalization that progressive muscular dystrophy occurs more often in males than in females is true of the sex-linked recessive cases, but, is not true of the dominant type. A recognition of the different forms of expression of the same gene in large groups of individuals makes classification of the types of dystrophy easier and their overlapping better understood. It is, therefore, a decided advantage to study the forms of expression of the same gene in large kindreds.

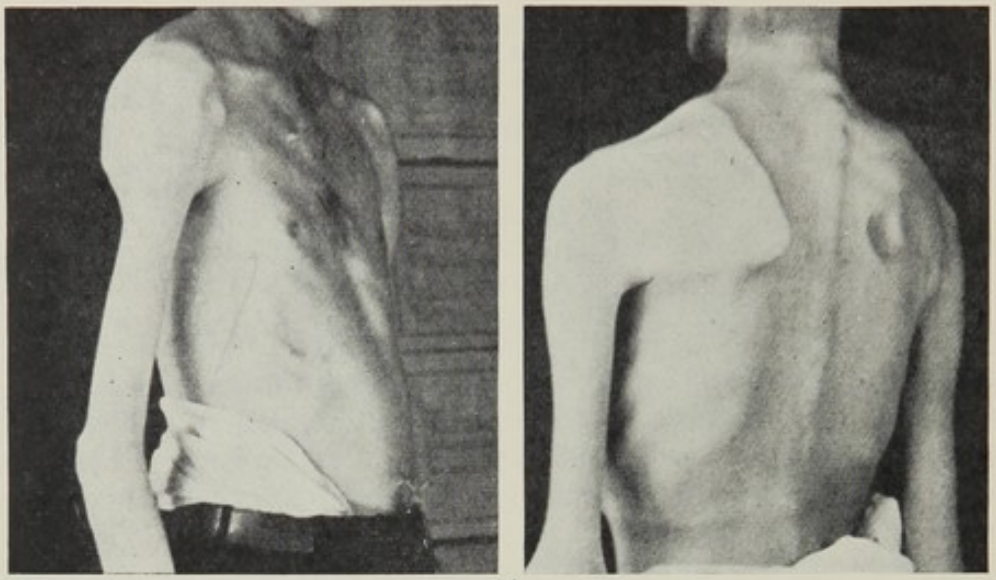
Classification

Different schemes of classification have been proposed from time to time. As a result of studying many cases in large family groups, Tyler and Stephens, 1950, have suggested that most cases of progressive muscular dystrophy can be classified into two general groups according to their type of inheritance as follows: (1) the autosomal dominant (facio-scapulo-humeral progressive muscular dystrophy), which includes Erb's (1884) juvenile dystrophy and the type of Landouzy and Dejerine (1885); and (2) the sex-linked recessive (childhood progressive muscular dystrophy) which comprises most of the patients included in the literature under the headings pseudohypertrophic, simple atrophic, Duchenne and Leyden (1868) and Moebius (1876) types.

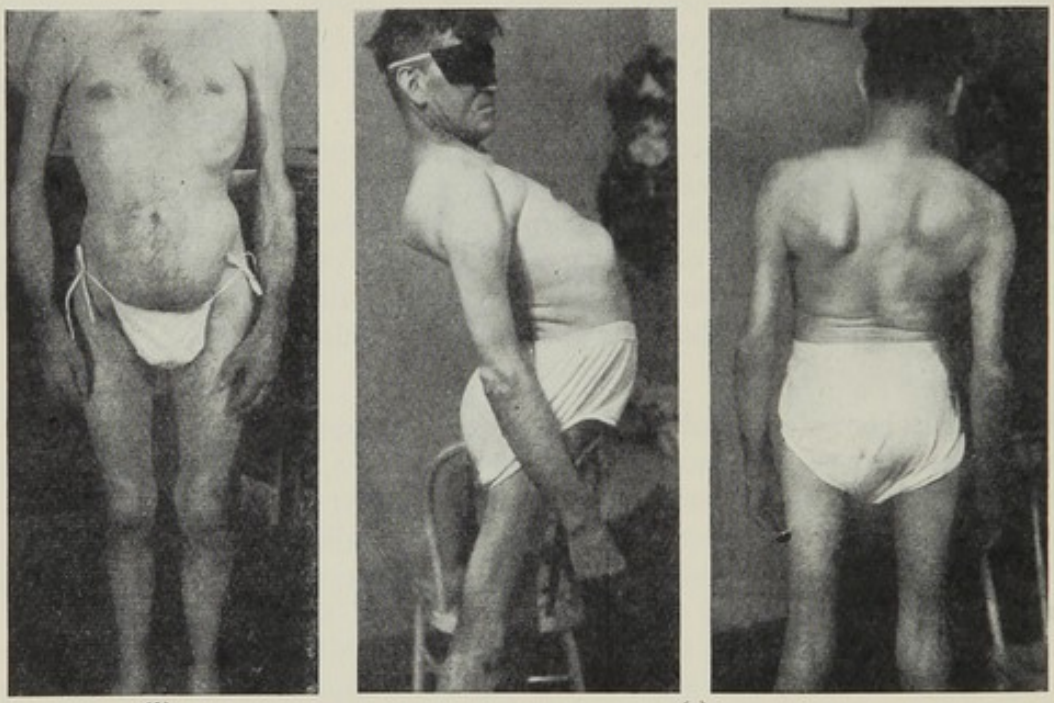
A few individuals do not fit into either of these groups. Eventually, when the inheritance of all the different forms of muscular dystrophy are understood, a complete classification on a genetic basis should be possible.

The autosomal dominant type (facio-scapulo-humeral progressive muscular dystrophy)

Eight kindreds showing facio-scapulo-humeral progressive muscular dystrophy have been studied at the Laboratory for the Study of Hereditary and Metabolic Disorders at the University of Utah. They all show the same general clinical manifestations of the disease and the same type of inheritance. Whether or not



(*a*)



(*b*) (*c*)

FIG. 157.—The autosomal dominant type of muscle dystrophy. (*After Tyler, F. H., and Stephens, F. E. (1950). Ann. intern. Med.*, **32**, 640.) (*a*) Note the nearly complete absence of muscles attached to the scapula except for fibres of the upper trapezius; the high, diagonal and anterior position of the scapula; flattening of anterior chest with atrophy of anterior pectoral girdle muscles and prominences of the clavicles. (*b*) Patient with moderately severe muscle atrophy. Note that the axillary folds slope toward the claviculo-manubrial junction as the result of the atrophy of the sternal head of the pectoralis major. Also contrast the good forearm musculature (except brachioradialis) and the atrophic pectoral girdle and upper arm musculature. The loss in the deltoid in contrast to its lower segment is evident. (*c*) Characteristic lordosis in a patient with moderately severe disease. Note that the pelvis is more anterior than in other common types of lordosis with the result that the line of weight bearing from shoulders to feet passes posteriorly to the sacrum.

the same dominant gene is involved in all of these kindreds is not known.

Clinical aspects.—The disease is characterized by a wasting of the muscles. The wasting generally originates in the muscles of the face, the shoulders, or the arms, hence the name " facio-scapulo-humeral progressive muscular dystrophy ". The age of onset is usually between 7 and 20 years. The dystrophy progresses with the age of the individual. The rate and the extent of the progression varies with different individuals. A small percentage of the cases becomes almost completely incapacitated later in life. A peculiar expression of the mouth, a flattened chest, winged scapulae and the inability to raise the arms above the head are common signs of the disease. Table I (Tyler and Stephens, 1950) shows

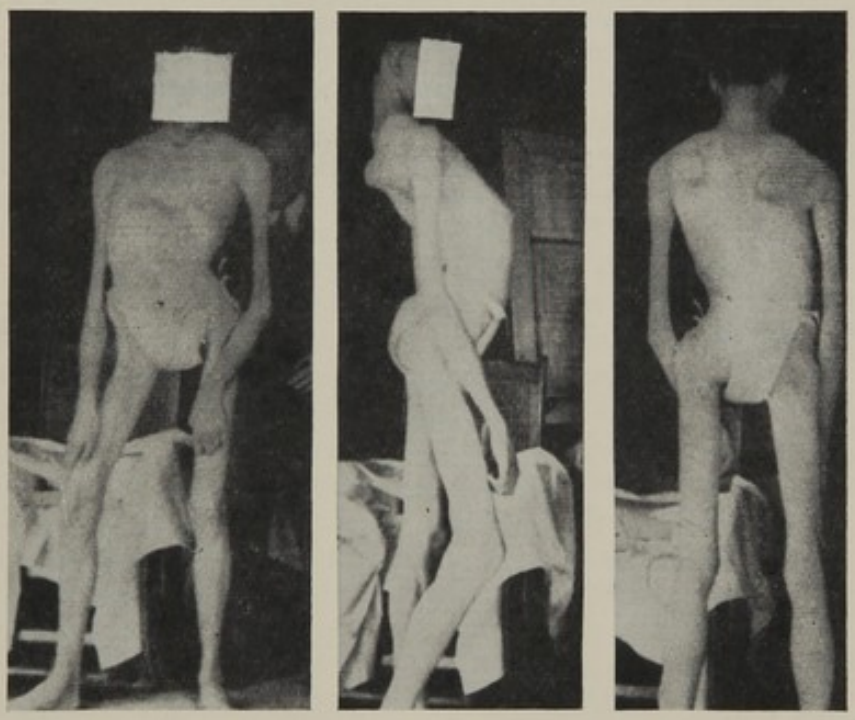


FIG. 157 (*d*).—Severe disability of a young adult. Note the advanced character of the muscular atrophy, but maintenance of the pattern of muscles involved. (*After Tyler, F. H., and Stephens, F. E. (1950). Ann. intern. Med.*, **32**, 640.)

the general pattern of involvement for this type of dystrophy. The muscles which are affected are listed with the number of patients showing different stages of involvement. Fig. 157*a–d* show various expressions of the disease.

Heredity.—The inheritance of this disorder can probably be understood best by examining the pedigree of a large kindred showing the typical expressions of this trait. This will demonstrate the different expressions of the same defective gene and thus aid in showing the nature of its inheritance (*see* Fig. 158). In analysing the data, only those families for which accurate information for nearly all of the members was available were used; also because identification of the trait in children below the age of 12 years is difficult, families with many children below that age were eliminated.

It will be seen that the trait in this kindred is inherited as a typical Mendelian autosomal dominant. In no case does the defect occur unless it also occurs in

one of the parents. If an individual does not develop the trait himself, it never occurs in any of his descendants. While there is a wide variability in expressivity, the penetrance is complete. There is no significant difference in the frequency of expression in males and females. Inasmuch as there is no record of two affected individuals marrying, no opportunity for observing the expression of the trait in the homozygous condition has been made possible and it is not known, therefore, whether or not dominance is complete.

Since all matings involving the trait are between an affected and a normal individual, a 1 : 1 ratio is expected. Table II shows a comparison of observed and expected ratios

TABLE I

PATTERN OF MUSCULAR INVOLVEMENT IN FACIO-SCAPULO-HUMERAL DYSTROPHY IN 58 PATIENTS (TYLER AND STEPHENS, 1950)

	Degree of involvement of certain muscles in typical cases at different stages			
	Minimal	Slight	Moderate	Severe
Facial except orbicularis oris and zygomaticus	0	0	1	2
Orbicularis oris	1	2	3	3
Zygomaticus	2	3	4	4
Sternomastoid, sternal head	0	1	2	3
Pectoralis major, sternal head	1	2	4	4
Pectoralis major, clavicular head	0	1	2	2
Deltoid	0	1	2	3
Triceps and biceps	0	0	2	3
Brachioradialis	1	2	4	4
Trapezius, upper fibres	0	0	1	2
Trapezius, middle and lower fibres	2	2–3	3–4	4
Rhomboids	0	0	3	4
Latissimi	1	3	4	4
Abdominals and recti abdominus	0	0	2	3
Glutei	0	1	2	3
Thigh groups	0	1	2	3
Tibials	1	2	3	4
Peroneals	0	0	2	3
Calf group	0	0	1	2
Hands, fore-arms, feet	0	0	1	2

0 = No change.
1 = Atrophy with significant weakness.
2 = Moderate atrophy and weakness.
3 = Severe disability.
4 = No muscle detectable.

TABLE II

A COMPARISON OF THE NUMBER OF DYSTROPHIC WITH THE NUMBER OF NORMAL OFFSPRING IN FAMILIES WHERE ONE PARENT IS DYSTROPHIC (TYLER AND STEPHENS, 1950)

Phenotypes	Observed	Calculated	Deviation	Standard error	D/SE
Normal (dd)	143	136·5	6·5	8·26	·79
Dystrophic (Dd)	130	136·5	6·5		
Total	273	273·0			

in families of the kindred where data were sufficiently accurate and complete to warrant such a comparison. There is no significant variation from the expected 1 : 1 ratio.

It will be seen from the pedigree that there were several polygamous marriages. II-6, an affected male, married three non-affected wives, two of whom had children by former marriages. Dystrophy occurred in the offspring of all three marriages with the dystrophic father, but no cases occurred in the children nor their descendants of the former marriages of the two wives. The husband of II-10 and III-37, both of whom were affected, had four other wives, none of whom had dystrophy. The disease occurred only in the descendants of the affected wives. This is also true among the descendants of the polygamous husband of III-36.

The sex-linked recessive type (childhood progressive muscular dystrophy)

Clinical aspects.—The name " childhood progressive muscular dystrophy " is used instead of pseudohypertrophic muscular dystrophy because pseudohypertrophy of the muscles may also occur in facio-scapulo-humeral progressive muscular dystrophy, and some individuals afflicted with the childhood type may not show pseudohypertrophy. Childhood dystrophy differs from facio-scapulo-humeral progressive muscular dystrophy in age of onset as well as in type of muscular involvement and it occurs only in males. The age of onset is usually in about the third year of life, and the primary involvement is in the pelvic girdle musculature. The first symptoms are a waddling gait, frequent stumbling and falling, and difficulty in running and climbing stairs. As the disease progresses a characteristic pattern of muscular atrophy and weakness appears. Hypertrophy appears in the calf muscles and occasionally in other muscles as well. The progress of the disease is rapid so that the majority of the affected individuals are bed and wheelchair invalids by the time they reach 9—12 years of age: few live past the age of 25 years. Death does not result from the direct effects of dystrophy but usually comes from respiratory infections in adolescence or early adult life.

Heredity.—Unlike facio-scapulo-humeral progressive muscular dystrophy the childhood type seldom occurs in many individuals in one kindred; frequently only one case is found in a kindred. It is essential, therefore, to study as many different kindreds as possible and to compare their clinical expressions. Polacheck (1941), Arbuse and Sloane (1937), Voshell (1933), and Kostakow (1934) and others have presented pedigrees clearly demonstrating sex-linked recessive inheritance. In the Laboratory at the University of Utah, 33 kindreds of childhood dystrophy have been investigated. They consisted of a total of 1,977 normal and 63 dystrophic individuals. From 1 to 10 affected individuals were found in each kindred. All cases followed a common pattern of clinical expression and were of the same type commonly described in the literature as pseudohypertrophic progressive muscular dystrophy.

For convenience of analysis these kindreds were divided into three groups: (1) those showing good evidence of a sex-linked recessive trait; (2) those having insufficient data to determine whether or not the gene had been transmitted through a line of female carriers; and (3) those showing good evidence that the pathogenic gene had not been passed down through a line of carrier females to the affected individuals.

The fact that many of the kindreds show a good pattern of sex-linked recessive inheritance (Fig. 159*a*) and the fact that the affected individuals in these kindreds

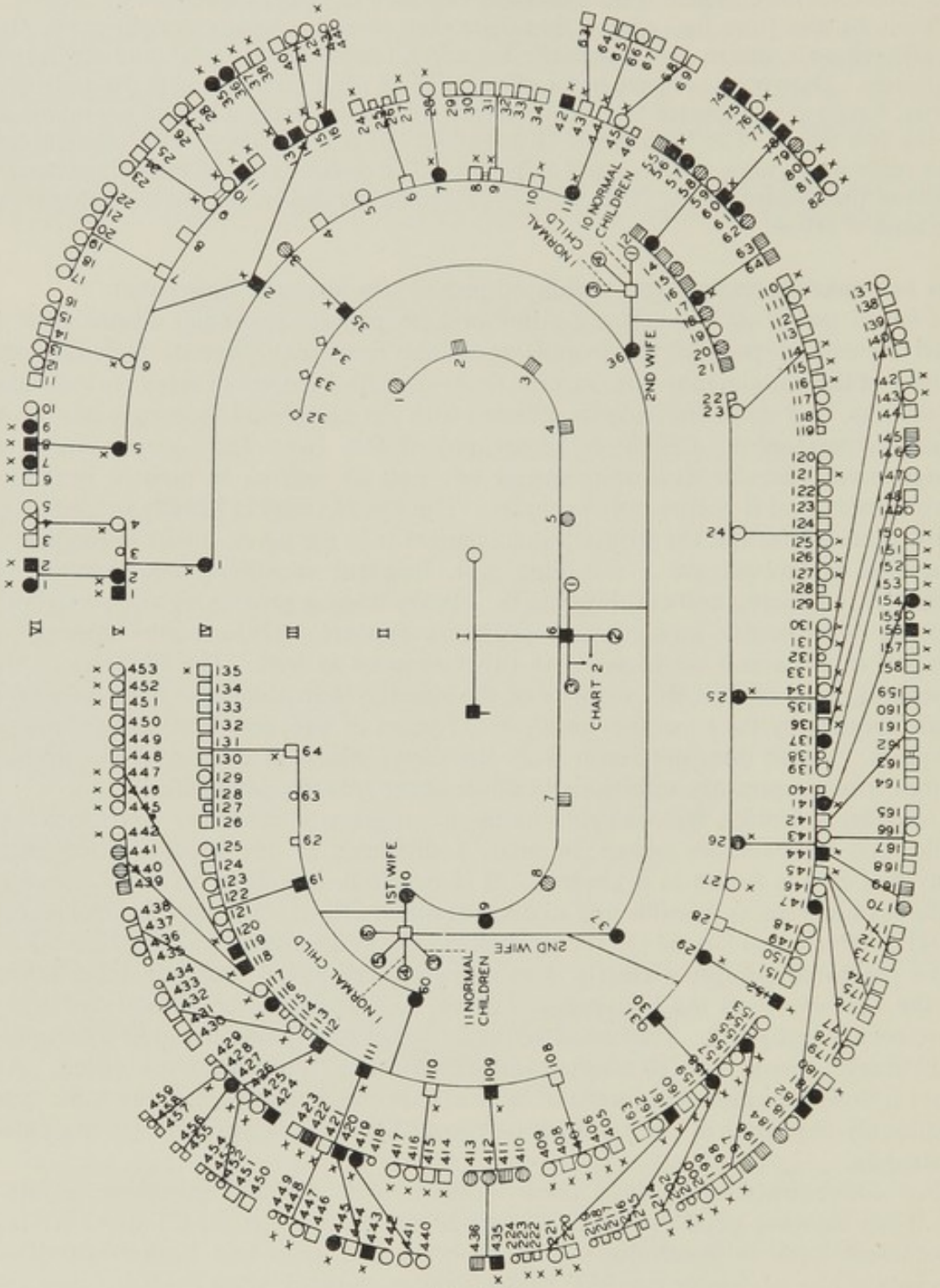


FIG. 158a

FIG. 158.—Pedigree of facio-scapulo-humeral muscular dystrophy. (*a*) The family tree. (*b*) The descendants of II–6 and his second and third wives shown separately. (*After Tyler, F. H., and Stephens, F. E. (1950). Ann. intern. Med.*, **32**, 640.)

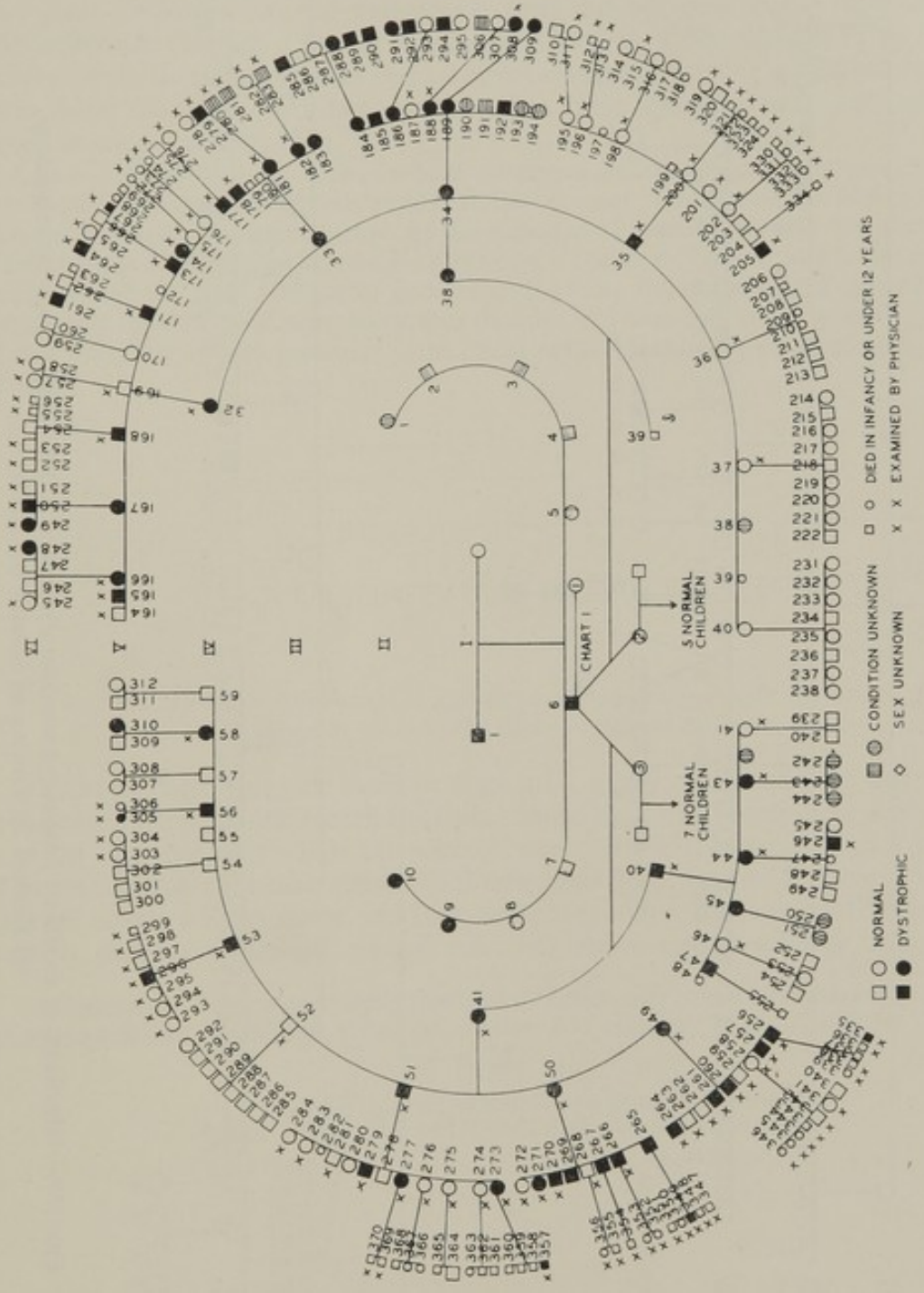
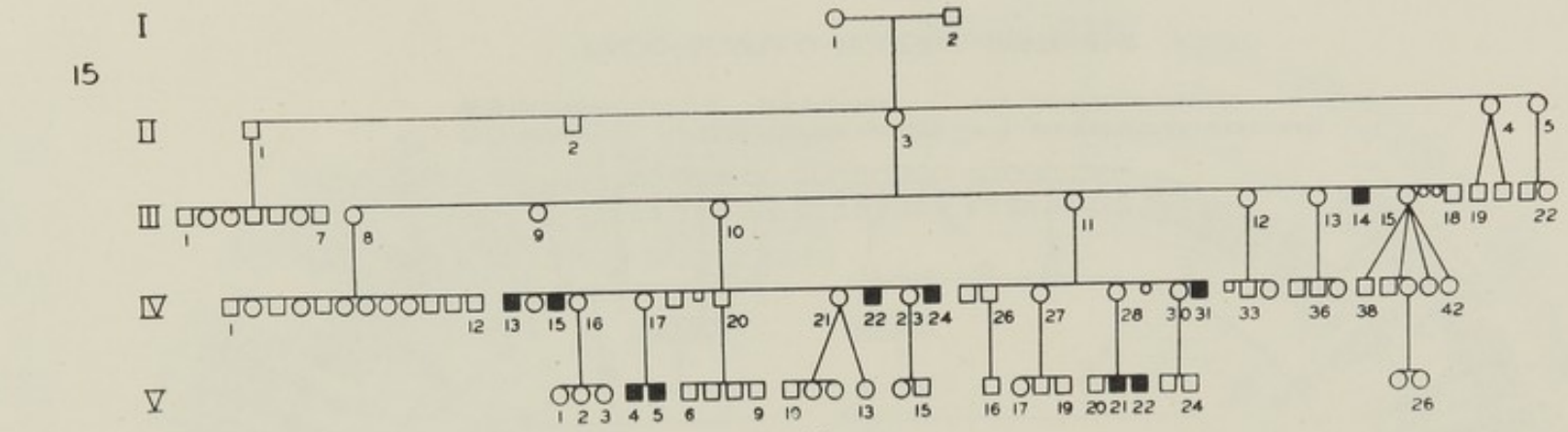
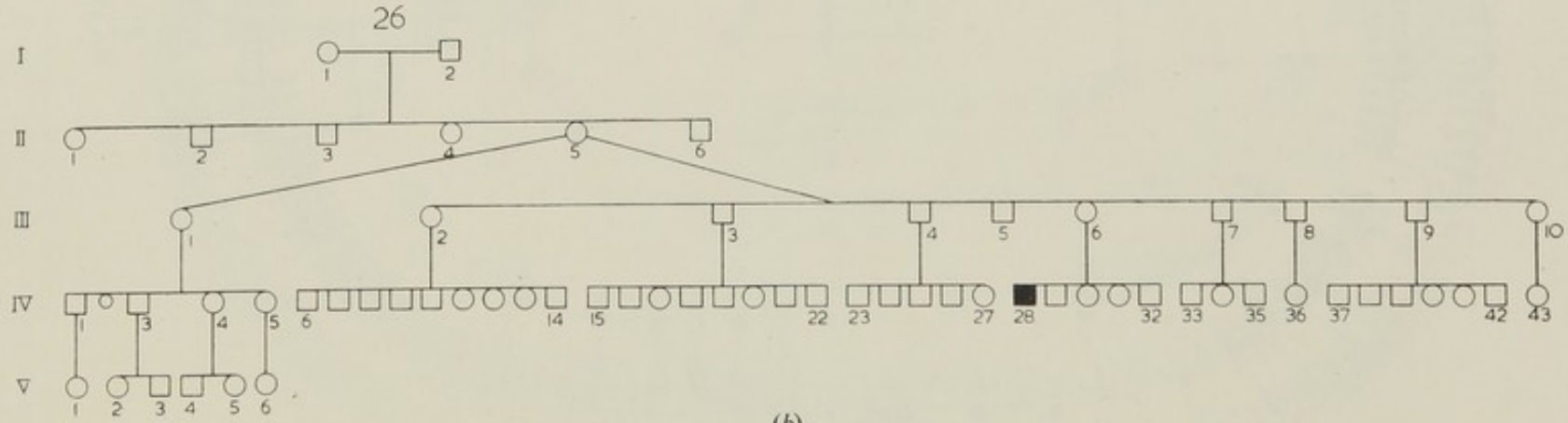

FACIO-SCAPULO-HUMERAL DYSTROPHY
CHART I
5 NORMAL CHILDREN
7 NORMAL CHILDREN
NORMAL
DYSTROPHIC
CONDITION UNKNOWN
SEX UNKNOWN
DIED IN INFANCY OR UNDER 12 YEARS
EXAMINED BY PHYSICIAN

FIG. 158*b*



(*a*)



(*b*)

FIG. 159.—Inheritance of childhood progressive muscular dystrophy. (*a*) Kindred 15 showing sex-linkage. (*b*) Kindred 26 showing an isolated but typical case.

did not differ clinically from cases in the other kindreds suggested that in all instances some pathogenic gene was involved. Even in the kindreds where there was good evidence that the pathogenic gene did not pass down from the first known female through a line of female carriers (Fig. 159*b*) there were no clinical differences in the affected cases and no direct evidence against a sex-linked recessive gene being involved. Further evidence that these sporadic cases are genetic in origin is shown in Fig. 159*c*.

A pair of identical twins both of whom developed childhood dystrophy were born into this family. They ran an entirely similar clinical course. The disease was first recognized at 6 years of age. Complete incapacity developed at 11 years of age and they died within a few months of each other at the age of 25 years. The lack of other cases in this extensive pedigree and the large number of male offspring from the direct line of descent on the female side make it quite improbable that the trait had been previously present. The fact that it occurred in both members of identical twins, however, is evidence of its genetic origin.

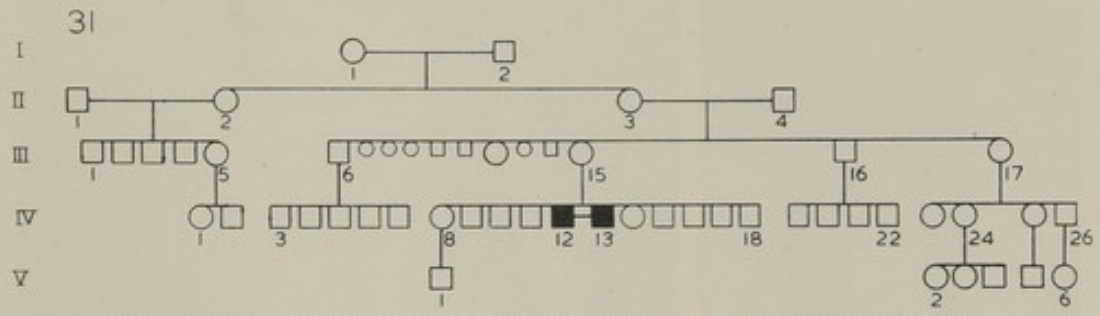


FIG. 159 (*c*).—Inheritance of childhood progressive muscular dystrophy. Kindred 31 showing the affection in identical twins.

The apparently sporadic cases in Group III might conceivably be due to some unknown environmental factor, but their clinical similarity to definitely genetic cases, and the fact that only males are affected, make an environmental factor unlikely. The assumption that they result from new mutations is more feasible. Since the disease occurs only in males and they never reproduce, the trait would in any case rapidly disappear through natural selection unless new mutations occur.

Mutation rate.—A comparatively frequent mutation rate would be necessary to maintain the frequency of the disease in the population at a constant level. Table III shows the

TABLE III

NUMBER OF DYSTROPHICS BORN IN A TEN-YEAR PERIOD (1931–1941) IN UTAH (TYLER AND STEPHENS, 1951)

Year	*Number of dystrophics*
1931	1
1932	1
1933	2
1934	2
1935	0
1936	4
1937	2
1938	2
1939	2
1940	2
Total	18

number of dystrophics born in Utah during the 10-year period 1931–1941. While the numbers are not large there is no indication of any decline in the birth rate. It would seem reasonable, therefore, to conclude that childhood dystrophy is due to the action of a sex-linked recessive gene and that sporadic cases similar to those in Group III are the result of new mutations.

Complete data on the frequency of childhood dystrophy in Utah are not available at the present time. Most of the cases born in the State during recent years have been recorded. The reason for selecting the period 1931–1941 is that some affected individuals born before that date may have died or may not have been recorded, while not all of

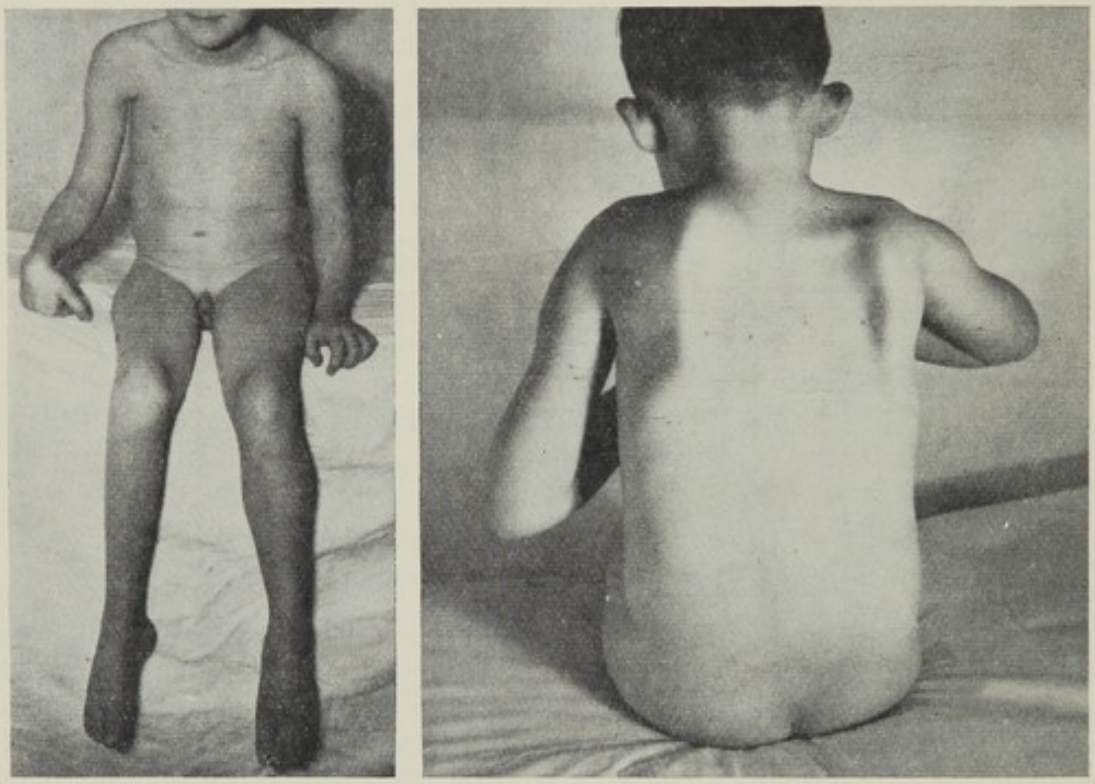


FIG. 160.—Appearances in a boy aged 12 years with childhood progressive muscular dystrophy.

those born since that period may have been identified. If the 6 dystrophic cases in Group III (presumably new mutations) born in Utah during the 10-year period are compared with the number of births during the same period, the minimum mutation rate for this defect can be calculated. Approximately 126,000 children were born in the State during this same time. If we assume one-half of these were males, $\frac{6}{63{,}000}$ should give the approximate mutation rate per X chromosome per generation. This would give a rate of $9{\cdot}5 \times 10^{-5}$ or about 1 mutation in 10,000 male births.

MYOTONIA

Myotonia is a symptom of several different diseases. It is characterized by a delayed relaxation of the muscles after contraction. While the expression of myotonia varies somewhat in each disease, it is a characteristic symptom of Thomsen's disease, paramyotonia and myotonia dystrophica.

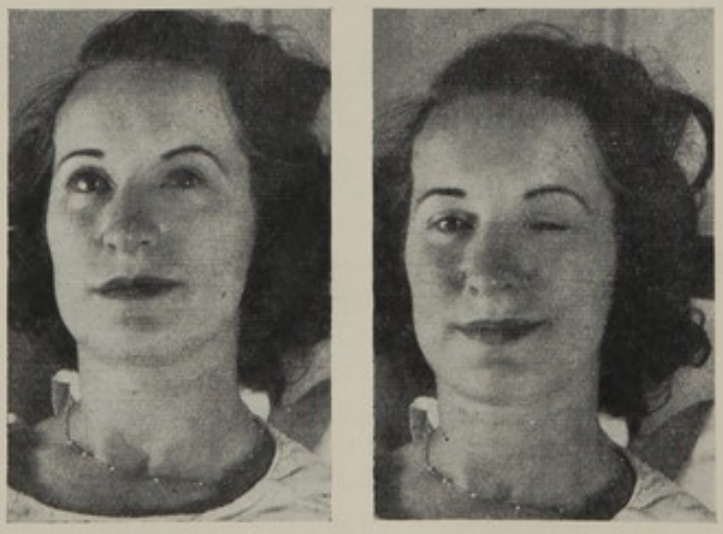
Thomsen's disease

Clinical aspects.—Myotonia congenita is not a common disease; it has been found in the United States of America, some European countries and in Japan. It is characterized by varying degrees of myotonia and, in many cases, by muscular hypertrophy. The degree of myotonia varies in particular cases and with the same individual at different times. Myotonia usually becomes evident in early childhood or it may be congenital. Unlike myotonia dystrophica, myotonia congenita is not accompanied by muscular dystrophy. Sometimes the myotonia is localized in certain muscle groups. Thomasen states that, " localization to the facial muscles and the ocular muscles is an almost specific feature of Thomsen's disease". Localization of myotonia in the hands and legs is also common. The patient often finds difficulty in such activities as climbing stairs or straightening the fingers after clenching the fist. Characteristically, a stiffness occurs which tends to disappear upon repeated contractions of the muscles concerned. Temperature, fright and fatigue may influence the expression of the trait.

Heredity.—The largest and most comprehensive study which has been made on one family showing myotonia congenita is that made on the family of Dr. Thomsen (Thomasen, 1948). It covers seven generations, extends back to 1742, and includes 64 affected individuals. In this family it occurs with equal frequency in males and females and it is inherited as an autosomal dominant. Reports of smaller family units have suggested the possibility of other forms of inheritance but none of these have been well established.

Paramyotonia

In 1886, Eulenberg described a condition in a family over six generations where myotonia had been induced by exposure to cold. The same pedigree was further



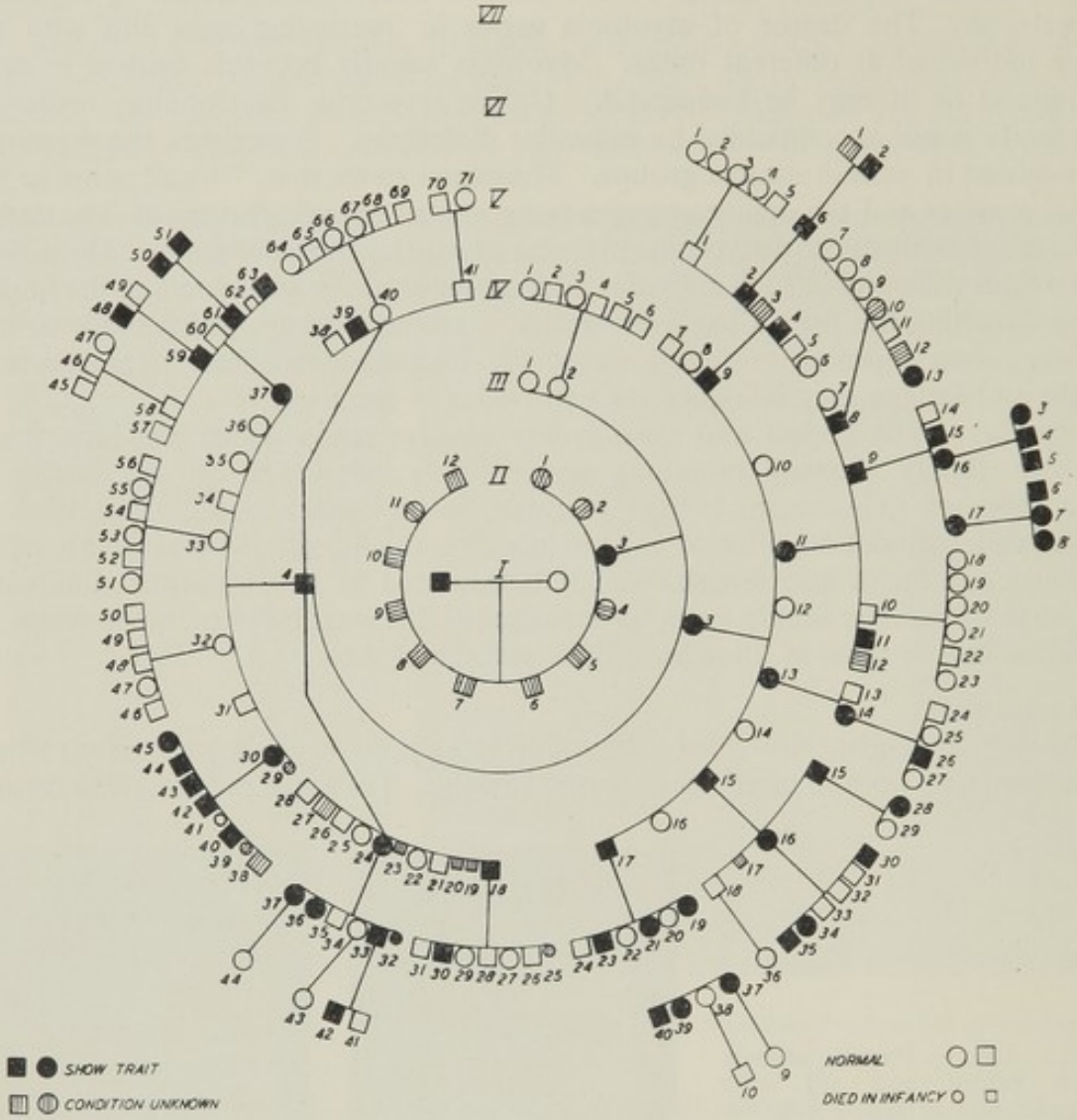
(*a*) (*b*)

FIG. 161. — Paramyotonia, (*a*) before and (*b*) after application of ice-pack to the left side of the face.

investigated in 1916. As a result, paramyotonia was shown to pass, without break, through eight generations as a simple autosomal dominant trait.

In 1894 Rich reported a kindred, similar to Eulenberg's, through which he was able to trace the defect through five generations. In all, 17 members of the kindred

were known to have had the trait. This same kindred has been recently studied at the University of Utah and the pedigree has been brought up to date. In all, 62 individuals in seven generations are known to have been affected.



MYOTONIA DUE TO COLD
(PARAMYATONIA DYSTROPHICA)

FIG. 162.—Pedigree chart of paramyotonia, showing dominant inheritance.

Clinical aspects.—Typically, immobility of the muscles is brought on by cold or sudden changes in temperature. The hands and face or the exposed parts of the body are most apt to be affected. The entire voluntary muscular system, however, may be affected under special conditions. Rich described a case where a young woman after attending a dance retired to her room and went to bed without removing her underclothing which had been saturated with perspiration. There was little covering on the bed and the room was damp. The girl was soon completely paralysed with the exception of her tongue which was kept warm by

her mouth. There was no pain. Recovery in the space of a few hours was brought about by the application of heat. The application of an eye-cup of cold water to the eye or the application of an ice-pack to one side of the face (Fig. 161) produces myotonia in the parts treated while the remainder of the face remains normal. Ice or snow placed in the mouth affects the tongue in the same manner. The myotonia may last from a few minutes to a few hours. The trait becomes evident in the first year of life.

There is a close relationship between paramyotonia and myotonia congenita. Cold temperature increases the likelihood of myotonia congenita and slight myotonia without the stimulation of cold has been detected in at least one case of paramyotonia in the Rich pedigree.

Heredity.—Both Eulenberg and Rich reported their cases several years before the rediscovery of Mendel's paper. Rich in referring to the heredity of the trait states, " I believe the foregoing history of this curious form of motor paralysis establishes its heredity beyond doubt. The peculiarity never skips one generation and appears in the next. The family is aware of the fact, and knows when a child does not inherit the affection it is ended as far as his offspring is concerned." Fig. 162 shows this pedigree brought up to date. It is an excellent example of a simple autosomal dominant trait. Here, as in other cases of myotonia, it is impossible to know the effects of the homozygous condition since there is no case in the kindred where two affected individuals have married. All of the affected cases come from parents, one of whom is affected. The crosses should therefore produce a 1 : 1 ratio of affected to normal individuals. The actual ratio is 61 affected : 60 normal.

Myotonia dystophica

Clinical aspects.—Myotonia dystrophica—a more serious affection than myotonia congenita or paramyotonia—is a disorder commonly characterized by muscular dystrophy and myotonia. The latter is generally, but not always, present and is usually localized in the hands. Dystrophy is found in muscles of the face and neck, the sternomastoid muscles and the muscles of mastication. It may spread to the forearms and to the legs giving the patient a peculiar gait. The voice is often affected so as to produce a low nasal sound, the head droops forward and the mouth may remain partially open due to the weak muscles of mastication. The affected individual has a characteristic " hatchet face " appearance. A characteristic sub-capsular cataract is found in most patients and is common in the otherwise normal parents and relatives of affected individuals as is a characteristic baldness or partial baldness.

Mental changes occur which show a certain amount of intellectual deterioration. Indolence, carelessness and excessive self-esteem, self-satisfaction and cheerfulness are characteristic. The age of manifestation of the disease has been reported to vary from two to over fifty years. Thomasen states that the disease most often manifests itself before the age of 15 years but may set in at a more advanced age. The later the age of onset, the less severe is the degree of expression of the disease. The majority of patients die before the age of 50 years. Lagophthalmos, blepharoconjunctivitis, ptosis of the upper eyelids, and enophthalmos have all been reported in connexion with the disease.

Heredity.—Because of its wide range of expressivity and age of onset, myotonia

dystrophica is difficult to trace in family pedigrees. Most workers report signs of degenerative progression with anticipation in successive generations. Hoffmann (1896), Steinart (1909) and Curshmann (1912) all report a familial incidence and anticipation. Fleischer (1917, 1918) concluded that the disease was inherited latently for several generations, then became evident in families of the following generation. In succeeding generations progression was evident. Particularly so far as cataract was concerned, the disease occurred at a younger age and was more severe in later generations. Maas (1937) reported dominant inheritance with progressive deterioration. Herner (1940) reported dominant inheritance in a Swedish family. Maas and Patterson (1943) concluded that multiple factors are responsible for the myotonic disease (myotonia congenita, paramyotonia, and myotonia dystrophica). These factors might occur singly in normal persons. The absence of single factors might account for cases not showing a complete pathological picture such as the absence of cataract or muscular dystrophy.

Thomasen (1948) studied myotonia dystrophica in 21 families where the disease had occurred. He was able to follow it through three generations in three families, through two generations in 11 families and through only one generation in the remaining 7 families. By supplementing the pedigrees with information regarding the dead family members he was able to follow the disease through four generations in ten families. In all cases where he was able to examine both parents of a patient, one always showed some manifestation of the disease, although in some cases the characteristic cataract was the only expression of the trait. The disease occurs with equal frequency in males and females. Myotonia dystrophica appeared among the descendants of those individuals whose sole lesion was the typical cataract. Thomasen (1948) concluded that myotonia dystrophica is inherited as a dominant trait with varying manifestations, and that it is impossible from the available data to determine definitely whether or not there is progression in the younger generations with anticipation and intensification.

Penrose (1948) proposes a possible genetic explanation for anticipation in myotonia dystrophica. A dominant gene M may cause the disease and its severity may be determined by the alleles m_1 or m_2 which occur in the general population. The genotype Mn_1 produces a severe type with onset at an early age while the genotype Mn_2 produces a milder form of the disease with onset later in life. Whether or not there is progression in the younger generations with anticipation or whether the results are due to natural selection of the milder affected parents cannot be determined until more accurate data on several generations can be secured.

FAMILY PERIODIC PARALYSIS

Clinical aspects.—Family periodic paralysis is a disease which produces periodic attacks of muscular weakness or paralysis. The literature contains case reports of more than 400 affected individuals (Talbott, 1941), and these have shown a great range of severity, extending from a slight recurrent weakness in one limb to a paralysis so severe that nearly the entire body is paralysed; even paralysis so extreme as to cause death has been noted. The length of attacks may range from a few minutes to several days in some families while in others it never lasts more than a few hours. The frequency of attacks may range from a few in a lifetime to several in one day. The age of onset also varies in different families. It may range from a few months to 19 years of age. Attacks may be precipitated by local

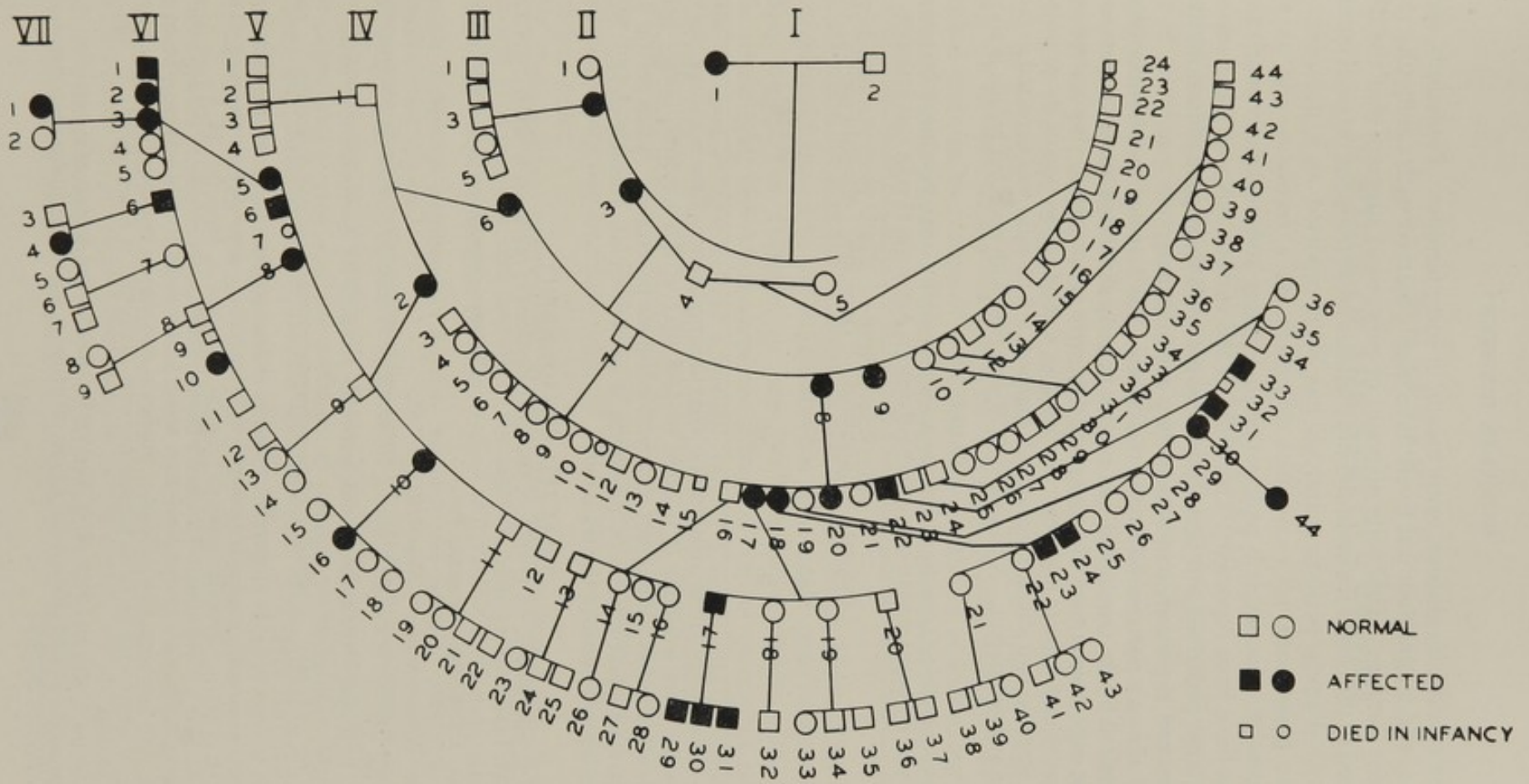


FIG. 163.—Pedigree chart of family periodic paralysis, showing dominant inheritance.
(*After Tyler, F. H., and Stephens, F. E. (1951). J. clin. Invest.*, **30**, 492.)

application of cold, by glucose, or by insulin in some families. Potassium, sodium, phosphate, and magnesium ion levels have been observed with conflicting reports for different families. This wide diversity of expression suggests that the disease as described in the literature undoubtedly includes more than one original mutation.

Heredity.—Family periodic paralysis has been reported as a dominant with incomplete penetrance, as a complete dominant, as a recessive, and as a sex-linked recessive. Incomplete penetrance in females and complete penetrance in both sexes have been reported. The study of the various types of the disease as it occurs in large pedigrees will best show how the individual gene mutations express themselves and the manner in which they are inherited.

Fig. 163 shows a pedigree history of the disease. The fact that the disorder could be readily detected by the family and was evident in early childhood made the nature of its inheritance easy to determine when once the data were accumulated. It occurred equally often in males and females and never occurred in a child unless one of its parents were affected. Since no two affected individuals married, a 1 : 1 ratio was expected in families having one affected parent. A comparison of observed with expected results is shown in

TABLE IV

A Comparison of the Number of Offspring Affected with Family Periodic Paralysis with the Number of Normal Offspring where one Parent is Affected (Tyler and Stephens, 1951)

	Observed	Calculated	Deviation	Standard error	D/SE
Affected – – –	32	34	2	4·123	·485
Normal – – –	36	34			

Table IV. It was not possible to determine what the appearance of the homozygotes would be. From the data available it is quite evident that in this kindred, family periodic paralysis is inherited as a dominant trait with complete penetrance. Each person having the trait has an equal chance of producing a normal or an affected child. Normal individuals do not transmit the trait.

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CHAPTER 16

DISEASES OF THE NERVOUS SYSTEM

R. T. C. PRATT

HEREDITARY ATAXIA

THE CHIEF problem in the genetic study of the large group comprising the various forms of hereditary ataxia rests in the extraction from the whole material of distinct categories of disease. There are many difficulties in assessing the published case reports and allotting them to appropriate categories. In the first place a single clinical picture may result from more than one pathological process; thus, a picture of progressive cerebellar disturbance may be due to any one of several distinct pathological processes involving the cerebellum and its pathways (*see* below). In the second place a single pathological process may lead to a variety of clinical pictures by reason of variables such as the site of lesion, age at onset, and rate of development. Of these two types of classification, on a clinical and on a pathological basis, the first is seen to be inexact, and the second, owing to the rarity of post-mortem studies, often inapplicable.

Classification on a genetic basis does not resolve the problem. The variety of clinical pictures shown in the manifestations of a single gene is sometimes surprisingly wide. For example, in one family affected chiefly with dominant spastic paraplegia, individual members showed a clinical picture of retrobulbar neuritis, of amyotrophic lateral sclerosis, and of a congenital cerebral diplegia (Bickerstaff, 1950). These diverse manifestations are presumably due to the interplay of the main gene with modifying genes and with environmental factors. The reverse may also occur, namely, the production of an identical clinical and pathological picture by two or more different genetic mechanisms; Friedreich's ataxia is a case in point.

With these general reservations in mind the various categories of hereditary ataxia will now be discussed, mainly in the light of observations by Bell and Carmichael (1939) and by Sjögren (1943).

Spino-cerebellar ataxia

Bell and Carmichael collected records of cases published under the titles of " Hereditary ataxia ", " Friedreich's ataxia ", and " Spastic paraplegia ", omitting single cases which provided no evidence of genetic potentiality. They divided the cases into three types: A, ataxia with absence of deep reflexes; B, spastic ataxia with presence or exaggeration of deep reflexes; and C, spastic paraplegia without ataxia. Types A and B did not differ clinically apart from the tendon reflexes, and in 26 out of 182 affected sibships both clinical types were represented. The age of onset of the disease was similar in each type when cases with dominant and recessive modes of inheritance were treated separately. It was therefore concluded that: " types A and B constitute merely slightly differing manifestations of the same source of disease ". In type C scoliosis did not occur, and no affected family contained a member with ataxia: in spite of this Bell and Carmichael were

of the opinion that all three types were " essentially diseases with a common source ". There were three instances of sex-linked inheritance; otherwise in each type both dominant and recessive modes of inheritance were found. The latter, with a raised parental consanguinity rate and the occurrence of the disease in sibships, was somewhat more common in types B and C and considerably more common in type A. The age at onset was found to be significantly higher in the group of cases determined by a dominant mode of inheritance (for type A 20 years as compared with 12 years in the recessive group); this finding is not unexpected, since an early onset would eliminate the patient from the group of potential parents, and so would prevent the disease being handed down to the next generation by direct transmission. To summarize, it appears probable from this investigation that either a dominant or a recessive mode of inheritance may determine the occurrence of spino-cerebellar ataxia, and that the three types are essentially " diseases with a common source ". Haldane (1941) pointed out that in each sibship of recessive spastic paraplegia one sex tends to be predominantly affected, and that in the offspring of cousin marriages relationship through the father's father is associated with affected sons, and through the father's mother with affected daughters. He concluded that recessive spastic paraplegia appears to be partially sex-linked. He also stressed the large size of the correlation coefficient for age of onset within each sibship, and suggested that there were three allelomorphs determining the age of onset at 2, 12 and 30 years. Similar findings suggest that the other forms of hereditary ataxia may be determined either by multiple allelomorphs or by more than one pair of genes.

Sjögren (1943) reached somewhat different conclusions from those of Bell and Carmichael in a study of 188 cases belonging to 118 families in Sweden. He classified his cases into five groups, the two major being Group I, Friedreich's ataxia (84 cases), and Group III, Marie's cerebellar ataxia (64 cases). Marie's cerebellar ataxia was originally a term applied to a heterogeneous group of spino-cerebellar ataxias in which the lesion was postulated to be in the cerebellum (*see* Holmes, 1907). Sjögren uses the term somewhat differently. The cases classified by him as Friedreich's ataxia were characterized by an average age at onset of 13 years, and by a high incidence of loss of tendon reflexes, of pes cavus, and of nystagmus; in those cases classified as Marie's cerebellar ataxia the average age at onset was 34 years, and there was a higher incidence of optic atrophy. Certain cases, however, were allotted with difficulty to the appropriate class, and the clinical distinction was not clear-cut. Genetically, the Friedreich group was determined by a recessive and the Marie group by a dominant mode of inheritance.

From the studies of Bell and Carmichael and of Sjögren it appears that inheritance of spino-cerebellar ataxia may be dominant or recessive, or very rarely sex-linked: there is, however, disagreement on the question of the distinction of two clinical types corresponding to each mode of inheritance (Figs. 164 and 165).

Optic atrophy in hereditary ataxia

The occurrence of ataxia in certain patients with optic atrophy led Behr to describe a separate condition of " complicated " optic atrophy. The association of optic atrophy, leading to progressive diminution of vision, with Friedreich's ataxia and more especially with spastic ataxia is frequent. This feature shows much

interfamilial and little intrafamilial variability. Recently it has been shown that optic atrophy in the hereditary ataxias may be secondary to retrobulbar neuritis, and in these cases the chief visual disability is a central scotoma.

CEREBELLAR ATROPHY

The occurrence of progressive cerebellar dysfunction in late middle age may depend on one of several pathological processes, of which the three best defined are olivo-ponto-cerebellar atrophy, delayed cortical cerebellar atrophy, and

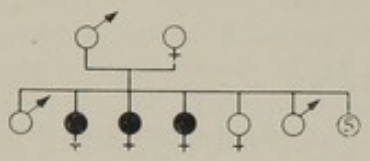


FIG. 164.—Friedreich's ataxia. (*After Friedreich, N. (1876). Virchows Arch.*, **68**, 163.)

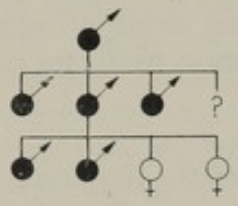


FIG. 165.—Hereditary spastic paraplegia. (*After Strümpell, A. (1904). Dtsch. Z. Nervenheilk.*, **27**, 294.)

cerebello-olivary degeneration. Olivo-ponto-cerebellar atrophy involves the olives, pons, restiform body, middle cerebellar peduncle and the cerebellar cortex; it has occasionally been reported in more than one member of a family. Delayed cortical cerebellar atrophy is characterized by an outfall of Purkinje cells without involvement of the cerebellar peduncles; one type appears to be dependent on the occurrence of carcinoma elsewhere in the body. Familial instances of this type

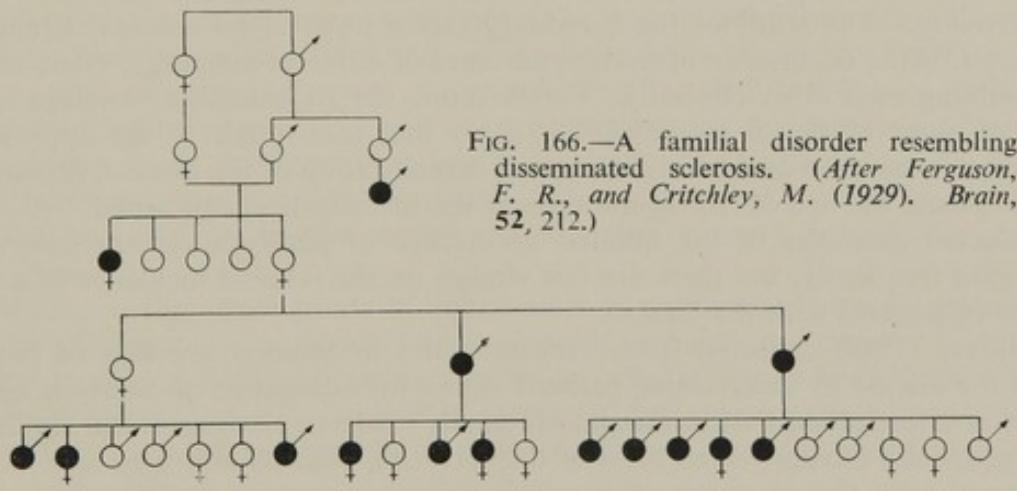


FIG. 166.—A familial disorder resembling disseminated sclerosis. (*After Ferguson, F. R., and Critchley, M. (1929). Brain*, **52**, 212.)

of cerebellar atrophy are rare. The third variety, cerebello-olivary degeneration, consists of cortical cerebellar atrophy with degeneration, apparently secondary to the cerebellar atrophy, of the corresponding parts of the inferior olive. This variety of cerebellar atrophy is predominantly hereditary; it has been observed both in sibs and in two generations of a family. Since the material is very probably not homogeneous no firm conclusions can be made about the mode of inheritance.

Involvement of the spino-cerebellar tracts and of the corpus striatum has been reported both in olivo-ponto-cerebellar atrophy and in cerebello-olivary degeneration. This observation may indicate a link between the cerebellar atrophies and

the dominant condition described by Ferguson and Critchley (1929) as resembling disseminated sclerosis (Fig. 166). In their family there was a variable involvement of the pyramidal, extra-pyramidal, sensory and cerebellar systems, with the production in individual members of clinical pictures as divergent as paralysis agitans and disseminated sclerosis. A related condition, reported by Sanger Brown, was characterized by the high incidence of ocular palsies. There are several other families which can be classified broadly with the hereditary ataxias. Of these pedigrees, Ferguson and Critchley say: " Many of the better-known nosological types remain confined to the family originally recorded ". Although in most instances the mode of inheritance is usually apparent, the classification of the disease in these pedigrees is unsatisfactory.

PARALYSIS AGITANS

Clinical aspects.—Paralysis agitans is a disorder of gradual onset and steady progression: the age of onset in the majority of cases falls between the age of 50 and 60 years. The face is expressionless, movements of the limbs are slow, and muscular rigidity involves flexor and extensor groups. Tremor characteristically involving the thumb and fingers (" pill-rolling ") is most marked at rest, and may disappear temporarily on voluntary movement. The rate varies from four to seven movements a second. Arteriosclerotic Parkinsonism is differentiated by a more sudden onset in an older age-group, by signs of pyramidal involvement, and frequently by bulbar symptoms. Post-encephalitic Parkinsonism possesses additional features such as tics, respiratory disorders, sialorrhoea, oculogyric crises, and paresis of accommodation, and a history of encephalitis lethargica may be elicited.

Heredity.—The study of the hereditary factor in paralysis agitans is rendered difficult by the occurrence of these syndromes of different aetiology, often closely resembling each other clinically. Furthermore, the considerable variation in the age of onset of the disease makes it likely that individuals of the appropriate genotype may have died before the age of manifestation of the disease, or may not have passed the age of risk at the time of the investigation concerned.

Selected examples of the familial occurrence of paralysis agitans have been reported frequently, but there are few studies on the familial incidence in a large series of patients with the disease.

Mjönes (1949) collected from various clinics in Sweden a group of patients with the disease by ascertaining patients with a firm diagnosis of paralysis agitans or of arteriosclerotic Parkinsonism. He finally made an analysis of the families of 250 propositi, having visited most of the surviving patients and their sibs. Those propositi with the diagnosis of paralysis agitans amounted to 194 of the total. In 46 cases (Group 1) one of the parents of the propositus was similarly affected, and a total of 113 secondary cases was found in this group. In 33 cases (Group 2) neither of the parents was similarly affected, and 49 secondary cases were found. In 115 cases (Group 3) the propositus was a solitary case in the family; this latter group was, in the main, excluded from the genetical analysis since it was considered that the aetiology was uncertain and that environmental causation may have played an important part. The conclusion that an autosomal dominant with a manifestation rate of 60 per cent is responsible for the development of paralysis agitans was made in part from the following findings, largely from

Groups 1 and 2: (a) the occurrence of the disease over 3 generations in 9 families; (b) the absence of any increase in the rate of parental consanguinity; (c) the loss in Group 2 of secondary cases amongst parents, who showed a tendency to earlier death than did the parents of patients in Group 1; and (d) the tendency for secondary cases within each family to be found amongst the relatives of one parent only.

In all instances where "juvenile" paralysis agitans was associated with a secondary case, it was found that at least one affected relative fell into the usual group with regard to age at onset; a separate form of juvenile paralysis agitans therefore did not appear to exist. A high incidence of "senile" or "familial" tremor was found in relatives of the propositi; it was held that this condition represents a *forme fruste* of the disease. A further noteworthy observation was the finding that of 32 propositi with arteriosclerotic Parkinsonism, 6 had affected relatives, and of 24 propositi with post-encephalitic Parkinsonism 10 had affected relatives. Thus it appears that a hereditary vulnerability of the extrapyramidal system may determine the development of the Parkinsonian syndrome in patients suffering either from cerebral arteriosclerosis or from encephalitis lethargica.

FAMILIAL TREMOR

Clinical aspects.—The age at onset of familial tremor varies so much that two synonyms for this condition are congenital tremor and senile tremor. The onset is gradual and the rate of progression slow; often after a lapse of time there is no further advance of the disease. The abnormal movements, at a rate varying from 4 to 12 per second, may appear at rest or may take the form of an intention tremor. They are rarely restricted to one limb or to the head. Emotion may lead to an increase in the tremor, while patients often find that alcohol leads to a temporary improvement. Physical examination reveals no neurological abnormality apart from the tremor: in particular there is no increase in tone and no other features suggestive of Parkinsonism. The pathological basis of the condition is probably a lesion in the corpus striatum, but autopsy findings have been inconclusive.

Heredity.—The usual mode of inheritance is dominant; several generations may be affected, with occasional transmission by an unaffected member (Critchley, 1949). In several instances one member of an affected family has shown signs of paralysis agitans or of a cerebellar atrophy, and occasionally a patient with familial tremor may develop one of these conditions; the interpretation of these facts is uncertain.

AMYOTONIA CONGENITA AND PROGRESSIVE INFANTILE MUSCULAR ATROPHY

Clinical aspects.—Amyotonia congenita (Oppenheim) is a condition evident at birth or shortly after; in some instances mothers of affected children have noted diminished or absent foetal movements during the pregnancy. The legs, arms, trunk and face are usually affected in that order of severity. The most characteristic feature is a gross degree of atonia; the affected parts take up the position determined by gravity, and it may be possible to approximate the toes to the shin,

and the dorsum of the hand to the forearm. Muscular weakness varies and may be profound; however, paralysis is never absolute. Localized wasting does not occur, and fasciculation is absent. The tendon reflexes are usually absent. The condition tends to improve although recovery is never complete, and the picture of a non-progressive myopathy may develop. Very few reports, however, have been made of the ultimate progress of patients with the condition.

Progressive infantile muscular atrophy (Werdnig-Hoffman) is characterized by an onset within the first 12 months of life; in about one-third of cases the disorder is noted just after birth. The trunk and girdle muscles are first involved, and the disease process spreads to involve the distal musculature. Muscular weakness leading to paralysis and wasting with loss of reflexes of the affected muscles are the outstanding features, whereas hypotonia is not so marked as in amyotonia congenita. Fasciculation of the affected muscles may be marked. The disease progresses; 50 per cent of the patients die before reaching the end of the first year of life, and 80 per cent within the first four years. Those reaching a later age are invariably severely disabled. In practice it is found that differentiation between this condition and amyotonia congenita is often difficult, since intermediate forms occur, and examples of each condition have been recorded in one pedigree.

Pathology.—Oppenheim in his original description of amyotonia congenita suggested that the disease process primarily affected the musculature rather than the spinal cord. It is now clear that the condition may arise from a primary disorder of muscle or from a primary disorder of the spinal cord. In certain families the clinical picture has been observed to change from one of amyotonia congenita in infancy to one of a non-progressive myopathy in adolescence (Turner, 1949). Histological examination in one of these cases showed histiocytic invasion of individual degenerated muscle fibres, similar to that found in the myopathies, whereas the anterior horn cells were normal in number and in appearance. In the larger number of cases changes are found in the spinal cord. These are of two types; degeneration of anterior horn cells ranging from chromatolysis to shrinking and disappearance of the cell, and a reduction in number of anterior horn cells without evidence of degeneration.

Similar findings obtain in progressive infantile muscular atrophy. In the muscular type degeneration and atrophy affect individual muscle fibres scattered diffusely amongst normal cells, and electromyography shows summated spike potentials; the spinal cord is normal. In the spinal type atrophic fibres are scattered in groups corresponding to a degenerated motor unit amongst groups of normal fibres, and electromyography shows single spikes on maximal contraction. The changes in the anterior horn cells are similar to those found in amyotonia congenita.

It therefore appears that at least two and probably three types of pathological change may be responsible for the clinical picture of progressive infantile muscular atrophy, and that the same types are also found in amyotonia congenita. Clinical differentiation between the two conditions is often difficult, and depends essentially on the age at onset and on the intensity of the pathological process. The problem can only be resolved by a long-term follow-up of a series of cases. Brandt (1949) collected records over a period of 40 years in Denmark of 131 cases diagnosed as amyotonia congenita (73), progressive infantile muscular atrophy (49), and

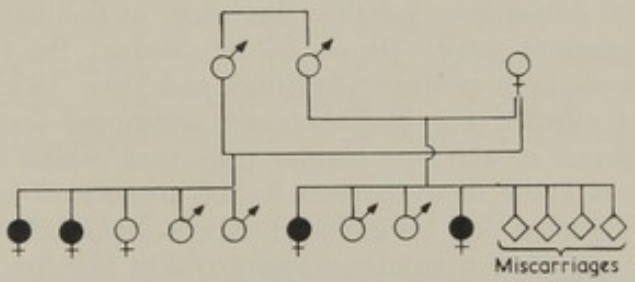
infantile progressive myopathy (9). He reclassified these cases on clinical and pathological grounds and obtained 87 patients in whom he considered the diagnosis of progressive infantile muscular atrophy justified. Of these the great majority were of the spinal type. Twenty-eight patients were diagnosed as symptomatic amyotonia due to a variety of evident underlying disease processes. In 3 cases no diagnosis could be made: in only 13 cases was a diagnosis of amyotonia congenita made. Brandt believed that in these cases the amyotonia was due to some undiscovered cause, and that the diagnosis of amyotonia congenita is only a symptomatic one. His findings, and the case histories he quotes, do not appear to justify his rejection of amyotonia congenita as a primary diagnosis.

Heredity.—The familial incidence of amyotonia congenita has been reported in isolated pedigrees (Fig. 167), but is said to be less marked than in progressive

FIG. 167.–Amyotonia congenita. (*After Turner, J. W. A. (1949). Brain*, **72**, 25.)

infantile muscular atrophy (Fig. 168). Whether this opinion is valid is doubtful, in view of the difficulty in assessing the separate identity of the two conditions. Brandt confined his genetic analysis to those patients in whom he made a diagnosis of progressive infantile muscular atrophy. He believed that he saw all new cases

FIG. 168.—Progressive infantile muscular atrophy. (*After Brandt, S. (1949). Amer. J. Dis. Child.*, **78**, 230.)



in Denmark over a period of 4 years—20 in number in a population of between 4,000,000 and 5,000,000 people. The sex incidence was equal. Of the sibs of the propositi 30 per cent were affected as calculated by Weinberg's proband method, and 38 per cent by Weinberg's sibling method. Parental consanguinity was found in 5·8 per cent of cases, as compared with 0·7 in a control series. In 9 out of 68 families symptoms of progressive paralyses were found in relatives other than sibs, suggesting that, although the disorder is probably due to a recessive mode of inheritance, there may be some degree of manifestation in heterozygotes. Except in one instance there was no intrafamilial variability, whereas there was considerable interfamilial variability.

PERONEAL MUSCULAR ATROPHY

Clinical aspects.—The published pedigrees containing two or more persons affected with peroneal muscular atrophy (Charcot-Marie-Tooth) have been

collected and analysed by Bell (1935). The affection is characterized by the gradual onset and slow progression of atrophic weakness of certain muscle groups. The onset may be so gradual that the patient is unable to determine the first beginnings of his disability. The mean age in years at onset, with neither parent affected, was 10·93 (S.D. 9·65), and with one parent affected, was 18·95 (S.D. 13·59). The muscles of the leg are first affected, and as the name implies it is the peroneal group which is often attacked earliest and most severely. The disease process gradually spreads to involve the muscles of the foot and leg, but does not often advance beyond the knee; in those few instances it stops short at the lower third of the thigh, giving rise to the " inverted champagne-bottle " leg. Some time after the onset of the disease in the legs the hands are affected and a similar process to that in the legs eventually leads to an atrophic weakness of the hands and forearms reaching at times as far as the lower third of the upper arm. Fasciculation and diminution or absence of reflexes accompany the atrophic weakness of the muscles. Sensory changes consist of slight hypo-aesthesia, a minor degree of loss of postural sensibility, and impairment of vibration sense. The pathological basis of the disease is atrophy of the cells in the ventral horn of the spinal cord and in

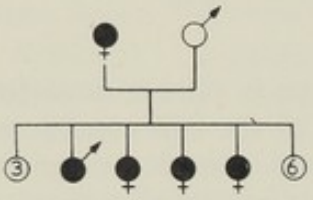


FIG. 169.—Peroneal muscular atrophy. (*After Collier, J. (1908–9). Proc. R. Soc. Med.*, Vol. 2, Pt. 2, Neurol. Sect., 31.)

the dorsal root ganglia. Instances of familial clawfoot with absent reflexes may represent *formes frustes* of the disease; the two conditions have been observed in the same pedigree (Symonds and Shaw, 1926). Occasionally, in certain members of affected families, there are additional features such as nystagmus, defective speech or extensor plantar responses, whilst in other pedigrees certain members may show these features in the absence of any muscular atrophy. It has been suggested that these instances may be a link between the clinical pictures shown in peroneal muscular atrophy and in Friedreich's ataxia.

Heredity.—The most frequent mode of inheritance is dominant (Fig. 169), and the disease has been transmitted through seven generations. Only occasional instances are found of the transmission of the disease by an unaffected carrier, and penetrance is usually high. Sex-linked inheritance undoubtedly occurs, and the evidence for it is on the whole satisfactory, although in certain families placed in this group there are a large number of affected females, and transmission from father to son took place in one pedigree (Herringham, 1888) showing apparently clear-cut sex-linked inheritance in other respects; an alternative interpretation is of an autosomal dominant with low penetrance in the female. In the group considered by Bell to be probable examples of a recessive mode of inheritance there are some features which render the ascription of certain pedigrees to this group uncertain. There is an excess of males over females, which suggests that certain sibships in which males alone are affected may properly belong to the sex-linked group; again the absence of disease in either parent may be due to low penetrance, as is seen in larger pedigrees where a dominant mode of inheritance

is certain: however, the finding of a raised incidence of parental consanguinity supports the hypothesis that inheritance in this group of pedigrees is usually recessive.

PROGRESSIVE HYPERTROPHIC POLYNEURITIS

Clinical aspects.—At a variable age symptoms of a severe progressive polyneuritis (Déjerine and Sottas) occur with shooting pains and numbness in the extremities, and muscular weakness and atrophy in the hands, forearms, and legs. On examination there is meiosis, peripheral anaesthesia of the glove and stocking type, peripheral atrophic weakness with absence of tendon reflexes, and frequently bilateral clawfoot. Kyphoscoliosis, nystagmus and intention tremor are inconstant features. The cardinal finding is of hypertrophy of the peripheral nerves, at

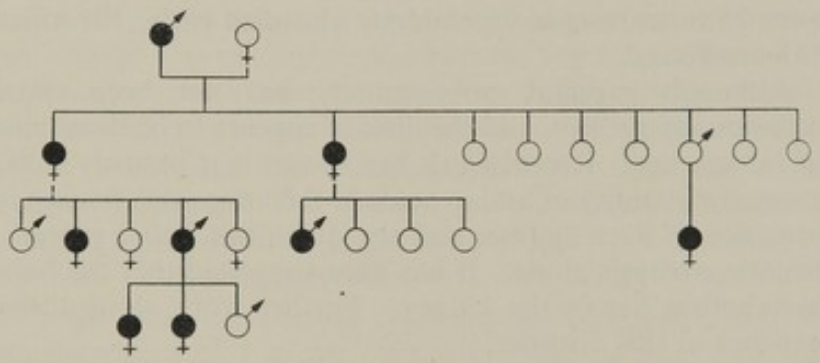


FIG. 170.—Progressive hypertrophic polyneuritis. (*After Russell, W. R., and Garland, H. G. (1930). Brain*, **53**, 381.)

times only discovered at autopsy. The hypertrophy of the nerves depends on an increase in the interstitial tissue and on a proliferation of the sheath of Schwann, resulting in demyelination of the nerve fibres (de Bruyn and Stern, 1929).

Heredity.—The condition has been recorded most often in sibs, but transmission from parent to offspring has also been noted. This finding and the occurrence of the disease in four generations (Fig. 170) point to a dominant mode of inheritance (Russell and Garland, 1930).

HEPATO-LENTICULAR DEGENERATION

Clinical aspects.—The onset of hepato-lenticular degeneration (Wilson's disease) is usually in the second decade, and leads to death in months or a few years. The general picture is of an extrapyramidal disorder. The expression is smiling or

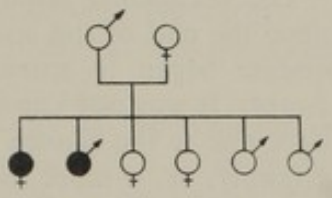


FIG. 171.—Hepato-lenticular degeneration. (*After Wilson, S. A. K. (1912). Brain*, **34**, 333.)

fatuous. Increased lability of affect is accompanied by a moderate degree of intellectual impairment. Tremor, at a rate of four to eight movements a second, consists of alternating contractions of various muscle groups and their antagonists, and involves the head, trunk and limbs. It differs from that of paralysis agitans in that it is commonly increased on voluntary movement. Spasmodic movements of choreiform or athetoid type are less frequent. Hypertonia of the limb muscles is extreme in advanced cases. Dysarthria is severe and may proceed to complete

anarthria. There are, as a rule, no sensory nor reflex changes. An inconstant but unique feature of the disease is the Kayser-Fleischer ring of greenish pigment on the under-surface of the cornea near the limbus. On pathological examination the lenticular nucleus, in particular the putamen, shows changes varying from discoloration to cavitation; the histological picture is of gradual destruction of parenchyma with glial replacement. Multilobular hepatic cirrhosis is a cardinal feature of the disease, but may lead to no symptoms during life.

Heredity.—The familial occurrence of the disease (Fig. 171) is a marked feature, and reported familial cases are eight times more common than isolated cases. In one sibship comprising 14 members, 6 were affected. There is only one instance of the disease appearing in parent and child. It does not occur in any characteristic birth order. In a total of 343 pregnancies of 49 mothers of affected children, there were 25 miscarriages, 76 children who died early, 101 affected (13 doubtful), and 141 unaffected.

Although parental consanguinity has not been consistently studied it is occasionally present, and the disease appears to be determined by a recessive mode of inheritance. Recent work has shown that patients with the disease excrete an excessive quantity of amino acids in the urine; this finding is not dependent on the presence of liver disease, and the quantities found exceed those in patients with hepatic cirrhosis alone. It has been suggested that the basic defect of amino acid metabolism lies in the kidney. Further work along these lines may clarify the genetics of this disorder.

DISSEMINATED SCLEROSIS

When a disease is determined by a fully expressed and manifested gene, the classical Mendelian ratios are expected, and in a single pedigree the mode of inheritance can often be inferred with accuracy. When a disease is determined largely by environmental factors, other methods of analysis are required in order to elucidate the part played by inheritance. Little may be learned from single selected pedigrees, and the study of pooled data is required. An estimate may have to be made of the incidence of the condition in the general population for comparison with the incidence found in relatives of affected patients. Variable factors such as environment and infection require consideration as alternative causes for the occurrence of familial concentration of any disease.

The occasional familial occurrence of disseminated sclerosis has been noted since the end of the last century, when knowledge of the clinical features of the disease began to spread. The significance of these observations remained in doubt. It was not known whether the familial instances of disseminated sclerosis were due to the chance of a common disease affecting more than one member of a family, or, if more frequent than would be expected on the basis of a random distribution of the disease, whether they should be ascribed to genetic, environmental or infective causes.

There have been varying estimates made of the incidence of disseminated sclerosis in the general population. One method is to apply the formula:

$$\frac{\text{Average number of deaths per year from disseminated sclerosis} \times \text{Average duration of disease in years}}{\text{Population}}$$

If an estimate of 18 years is taken as the average duration of the disease, the incidence of disseminated sclerosis in England and Wales is of the order of 1/2,500. An observed incidence of this order has been found in more than one field survey. The incidence of disseminated sclerosis in the living sibs of propositi has been found to be of the order of 1/100, and in the living parents of propositi of the order of 1/200 (Pratt, 1951). The incidence of disseminated sclerosis in similar age-groups of the general population is approximately 1/2,000 and 1/1,600 respectively. There is thus a significantly higher incidence of disseminated sclerosis amongst sibs and parents of propositi, although the actual observed incidence is low. The rarity of conjugal disseminated sclerosis, the lack of evidence of case-to-case transmission of the disease, and the occasional instances of disseminated sclerosis affecting cousins who had never met, all argue against the role of infection in causing the familial occurrence of the disease. The occasional local concentration of the disease has been ascribed to environmental causes; for example, lead in the drinking water: in the absence of further evidence for this hypothesis it would be unwise to ascribe the familial occurrence of the disease to the environment.

The relative incidence in parents and sibs is compatible with a dominant mode of inheritance with low manifestation. The disease has twice been recorded in three generations of a family, and affection of parent and child has occurred in about 25 per cent of families containing more than one case of the disease.

Parental consanguinity has been recorded in three unselected groups, and an incidence of first-cousin marriages of 1·25 per cent was found in a total of 872 patients. This incidence is significantly higher than that of an appropriate control population. The meaning of this finding is obscure: with a recessive disorder of an incidence in the general population of 1/2,500 such a high figure for parental first-cousin marriages would not be expected, even if manifestation were complete. A clinical study of the affected offspring of these first-cousin marriages does not suggest that they suffered from the disease in any unusual degree or form. It is possible however that the material is not homogeneous.

Twin studies reveal that monozygotic twins have both been affected with disseminated sclerosis on six occasions; however, in the majority of instances where one of a pair of monozygotic pairs has disseminated sclerosis the other is unaffected. Birth order and maternal age have a slight influence; there is a deficiency of the first-born and second-born as compared with expectation, and the maternal age at birth is slightly higher than that in the general population. Neuromyelitis optica, a demyelinating disease related to disseminated sclerosis, has been described in identical twins (McAlpine, 1938),

Disseminated sclerosis, therefore, occurs more frequently in the relatives of patients with the disease than would be expected on the basis of a random distribution of the disease. The data however do not allow a simple genetical explanation.

EPILEPSY

The analysis of the heredity of epilepsy is rendered difficult by the lack of homogeneity of the material. The group labelled idiopathic epilepsy may contain patients in whom a local or general cause of the convulsions is present but has

not been revealed; in other words the epilepsy in these patients may be symptomatic rather than idiopathic. Again, as with migraine, variations in the frequency, severity and nature of the attacks in affected persons may lead to faulty classification. These considerations, and the frequency with which information about fits in relatives may be suppressed by interested witnesses, render suspect those investigations in which the incidence of epilepsy in relatives of various classes is contrasted with the incidence in relatives of a control group or with the incidence in the general population. For these reasons the evidence for a genetic factor in epilepsy will here be limited to two investigations of a different type. The matter is more fully described on page 337 in the chapter on Psychiatry.

Lennox (1947) investigated a series of twins with epilepsy. He divided them into groups according to the category of twin (monozygotic or dizygotic) and the presence or absence of cerebral pathology in the propositus. He found that of 24 monozygotic pairs without cerebral pathology, in only 17 per cent was the second twin free from epilepsy; whereas of 19 monozygotic pairs with cerebral pathology in one twin, in 84 per cent the second twin was free from epilepsy. Of 16 dizygotic pairs without cerebral pathology, in 94 per cent the second twin was unaffected, whereas in 7 dizygotic pairs with cerebral pathology in the propositus, in every case the second twin was unaffected. The clinical type of seizure tended to be similar in each when a pair of twins was affected. Furthermore, the appearances of the electro-encephalographic tracings were very similar in identical twins, which suggests that the cerebral rhythm displayed by an epileptic is one step nearer the hypothetical gene involved than is the occurrence of convulsions.

Lennox, Gibbs and Gibbs (1940) studied the records of 13,260 near relatives (parents, sibs and children) of 2,130 patients with epilepsy. The incidence of epilepsy in these relatives was 2·4 per cent, five times that in the general population. Only one epileptic in five gave a history of a relative similarly affected. In an attempt to define more exactly the nature of the inheritance they studied the electro-encephalographic records of 183 relatives (143 parents, 36 sibs, 4 children) of 94 patients with either idiopathic or symptomatic epilepsy. The incidence in these 183 relatives of definite dysrhythmia was 60 per cent, and of questionable dysrhythmia 8 per cent; the corresponding figures for 100 controls were 10 per cent definite and 6 per cent questionable. In 55 instances tracings of both parents were studied, and both were found to be abnormal in 19, or 35 per cent. One or more parents had definite abnormalities of rhythm in 90 per cent of instances. Since the incidence of abnormal electro-encephalographic tracings is 10 per cent of the general population, from random matings in only 1 per cent of marriages would both parents show abnormal tracings, whereas in the above series 35 per cent of marriages showed this feature. Electro-encephalographic abnormality in both parents thus increases greatly the likelihood of the offspring being affected.

These studies failed to establish a sharp cleavage between idiopathic epilepsy and symptomatic epilepsy. In the first place the incidence of dysrhythmia in relatives of patients with symptomatic epilepsy is the same as that in relatives of patients with idiopathic epilepsy. The incidence of overt seizures was almost as high in the relatives of the symptomatic group with age of onset in childhood (three times the general population) as in the idiopathic group (five times the general population). When the age of onset of symptomatic epilepsy was in

adult life, the incidence of epilepsy in the relatives of these patients was no higher than in the general population. From these findings it appears that inherited cerebral dysrhythmia plays an important part in determining the appearance of clinical epilepsy, whether of the symptomatic or idiopathic type. Williams (1950) has suggested that two factors may be involved, one a tendency to the state of epilepsy, and the second a tendency preventing spread of the epileptic state.

Myoclonic epilepsy

Clinical aspects.—Myoclonic jerks, brief contractions of muscles or of part of a muscle, occur frequently in idiopathic epilepsy and are known colloquially as " the jumps ". Myoclonic epilepsy is a term applied to the condition originally described by Unverricht. The onset of the disease is around puberty, with typical epileptic attacks, often at night, increasing in frequency. After a few years the second stage appears, characterized by myoclonic contractions. Symmetrical muscles of the limbs, trunk and face are involved; the contractions interfere with voluntary movement, and speech, swallowing and use of the limbs are all affected. During this stage the epileptic attacks diminish in frequency. In the third stage of the disease a progressive dementia appears, and death results from complications due to involvement of the bulbar musculature. Electro-encephalographic studies have shown that bursts of spikes are associated with the myoclonic jerks. Degenerative changes are found in cortical ganglion cells at autopsy.

Heredity.—The most extensive pedigree of this condition was published by Lundborg (1913). In this family group intermarriage was very frequent, and the condition appears to be determined by a recessive mode of inheritance.

SPECIFIC DYSLEXIA (CONGENITAL WORD-BLINDNESS)

Clinical aspects.—Specific dyslexia, first recognized at the end of the last century, was soon found to have a familial incidence, but a formal genetical analysis has only recently been made. Hallgren has made an extensive analysis of 116 propositi and of 160 secondary cases in Stockholm; he personally examined 270 of these cases. The diagnosis was made on the grounds of difficulty in learning to read and write, with an impairment of the proficiency in reading and writing disproportionate to the proficiency in other school subjects and the child's general intelligence. The severity of the disability varies; some children have difficulty in reading the simplest words after several years' schooling, whereas in others the difficulty may completely disappear. In the majority of cases individual letters can be identified, but the word is not recognized correctly as a whole. The mistakes made do not differ qualitatively from those made by beginners. Spontaneous writing and writing to dictation are more severely affected than is copying. Certain patients with the disability have considerable facility in mirror reading and writing. Hallgren found that the prevalence in an unselected group of schoolchildren was about 10 per cent; boys were more frequently affected than girls. Other estimates of the prevalence of this condition have been 0·05 per cent and even lower; the boundaries limiting the diagnosis vary widely with different observers.

Heredity.—Hallgren found that only 12 of his 116 propositi were solitary cases. The offspring of the parent mating affected × affected yielded 2 affected children

out of 5. The mating affected × unaffected gave the following Mendelian ratios: 45·7 per cent by Weinberg's proband method, 55·2 per cent by Weinberg's sibling method, and 58·9 per cent by Haldane's method. The parent mating unaffected × unaffected occurred in the families of 19 propositi—in 7 of these secondary cases were ascertained. From these figures it was concluded that the mode of inheritance was autosomal dominant with almost complete manifestation. With regard to the solitary cases it was not possible to exclude the occurrence of secondary dyslexia, and the aetiology could not be demonstrated. Of three monozygotic pairs of twins, all were concordant. Of three dizygotic pairs of twins, one was concordant and two discordant.

SOME OTHER AFFECTIONS

Congenital malformations

One-tenth of all foetuses reaching viable age are born dead or die within the first year of life, and one-tenth of these deaths are due to congenital malformations, of which more than half involve the central nervous system. An extensive investigation into factors determining these malformations has recently been made by McKeown and Record (1951). They studied, from the records of the Maternity and Child Welfare Department of the City of Birmingham, all malformations of the central nervous system which resulted in stillbirth or death in the first year of life in the years 1940–1947. A control group of approximately the same size was selected by taking every two-hundredth name in the registers of live-birth and stillbirths for the same years.

The 930 consecutive malformations were classified into four categories: anencephalus 366, spina bifida 389, hydrocephalus 150 and " others " 25. There was some overlap between the categories; of the most frequent types of combined malformation, those with coexisting anencephalus and spina bifida were classified as anencephalus, and those with coexisting spina bifida and hydrocephalus as spina bifida. The percentage of males in the three main categories was: anencephalus 32 per cent, spina bifida 43 per cent and hydrocephalus 43 per cent. The influence of birth-rank and maternal age at birth was investigated. The risk of anencephalus and spina bifida was considerably increased at the first parity and above the sixth; a similar but less marked trend was found in the case of hydrocephalus, where the risk was markedly increased with raised maternal age. The incidence of anencephalus was significantly higher in births in the first and fourth quarters of the year than in the second and third.

The incidence of all malformations of the central nervous system among the 1,534 sibs of 742 propositi of the malformation group was 1·89 per cent, and among the 1,374 sibs of 742 propositi of the control group was 0·29 per cent. The incidence was higher for the sibs of the cases of spina bifida (2·75 per cent) than for anencephalus (1·03 per cent) and for hydrocephalus (1·15 per cent). The incidence of the same malformation was greater than the incidence of a different one, and the incidence of a different neurological malformation was greater than the incidence in the control population. The incidence of malformation in sibs born after the birth of a malformation rose to 2·77 per cent compared with 0·45 per cent, the risk in the control population. Other major

malformations outside the central nervous system were not found more frequently than in the control group.

All three groups of malformation therefore show a significant familial incidence, and all are affected by a variety of environmental factors. Analysis is difficult because the groups may not be homogeneous. Hydrocephalus resulting in death before the age of one year may be due to a variety of pathological lesions, including stenosis or forking of the aqueduct of Sylvius, obstruction at the foramina of Luschka or Magendie, the Arnold-Chiari malformation, and obstruction following meningitis. In certain families the incidence of hydrocephalus has been high. In one such family (Bickers and Adams, 1949) the mother of 3 affected sons had 4 affected brothers out of 9 sibs. Autopsy on one of the sons revealed a stenosis of the aqueduct of Sylvius. Apart from this instance the contribution of the various pathological types to the familial incidence of hydrocephalus is not known. With the evidence at present available it is not possible to determine the homogeneity of the various types of malformation of the central nervous system. Hypotheses that could account for the observed biology of these malformations are autosomal genes with low manifestation rates, chromosomal abnormalities, fresh mutations, antigenic incompatibility, and unfavourable maternal environment (Penrose, 1949).

Congenital cerebral diplegia

Congenital cerebral diplegia is characterized by the presence at birth, with a tendency to improvement, of spastic weakness of the legs, associated at times with involuntary movements, ataxia, and mental defect. The underlying pathological basis varies: during parturition haemorrhage or asphyxia may lead to permanent neurological damage. Other cases undoubtedly have a genetic basis; the condition has been reported in sibs and in identical twins, and parental consanguinity has frequently been reported. It appears that one or more recessive genes may determine the appearance of this disorder.

Encephalitis periaxialis diffusa

The clinical picture of encephalitis periaxialis diffusa (Schilder) is of a progressive dementia, with cortical blindness, fits, and increasing spastic quadriplegia. At autopsy there is massive degeneration of the subcortical white matter, dependent on a demyelination of the affected parts. The disease often appears in more than one member of a family, more especially in the cases where the age at onset is in childhood. Parental consanguinity has been reported, and the disease appears to be determined by a recessive mode of inheritance.

Pelizaeus-Merzbacher disease

The onset of Pelizaeus-Merzbacher disease, a rare condition, is in infancy, with nystagmus, tremor of the head, and spastic paralysis spreading from the trunk muscles to involve the extremities. Mental deterioration is progressive. The disease process tends eventually to become stationary, and death follows in the third and fourth decades. Pathological examination reveals extensive degeneration of the subcortical white matter. The disease is transmitted by healthy females, and is considerably more frequent in males. The disease has been considered to be inherited as a sex-linked recessive, and the occasional instances of cases in

females ascribed to manifestation in the heterozygotes. An alternative mode of inheritance is by an autosomal dominant gene with diminished penetrance in the female. Since affected males have no offspring it is not possible to decide which of these two modes of inheritance is operative.

Bilateral acoustic neuroma

Bilateral acoustic neuroma differs pathologically from the unilateral variety, and is regarded by some as a manifestation of neurofibromatosis. Within each affected family the manifestations of neurofibromatosis tend to be similar, often to a remarkable degree; for example, instances have been recorded of two brothers with an isolated tumour of the left upper eyelid, and of a man and his son with an isolated tumour of the buttock. Gardner and Frazier (1930) recorded a family in which bilateral acoustic neuroma, with other manifestations of neurofibromatosis almost completely lacking, was transmitted as a dominant trait through five generations, 38 being affected of 217 members of the family. The average age at death decreased from the second to the fifth generations (72, 63, 42, and 28 years).

Haemangioma of the cerebellum and retina (Lindau's disease)

Certain cysts of the cerebellum contain in their walls nodules which histologically have the characteristics of a haemangioblastoma, a mass of capillaries usually filled with blood and sharply demarcated from the nervous tissue. These cysts are frequently associated with angiomatosis of the retina (von Hippel's disease), and at times with cystic pancreas and kidneys, and with hypernephroma. Symptoms of the cerebellar cyst arise chiefly between the ages of 30 and 45 years.

In 20 per cent of patients with haemangioma of the cerebellum there is a further member of the family similarly affected. Since the disorder has twice been reported in three generations of one family it appears that it is transmitted by a dominant mode of inheritance.

Heredopathia atactica polyneuritiformis

In 1946 Refsum reported the occurrence of a new syndrome in five members of two families. In every case parental consanguinity was noted, and the disorder was considered to be inherited by a recessive mode of inheritance. The onset was in the second to the fourth decades; night-blindness and concentric limitation of the visual fields were associated with atypical retinitis pigmentosa. Later a form of polyneuritis with complaints of paraesthesiae and muscular weakness developed, and pupillary meiosis, muscular atrophy, cerebellar ataxia, posterior column loss, and a raised protein in the cerebrospinal fluid were found on examination. The disorder tended to be terminated by sudden death.

Torsion dystonia

Torsion dystonia is characterized by turning and twisting movements of the trunk and proximal parts of the limbs, with alterations in muscle tone. It has been observed following encephalitis lethargica and in hepato-lenticular degeneration. It has on occasion been recorded in sibs and these cases probably depend on an abiotrophic lesion of the basal ganglia. A recessive mode of inheritance is the most likely in those cases determined genetically.

Syndrome of Hallervorden and Spatz

The original description of the syndrome of Hallervorden and Spatz was based on five sisters in a sibship of twelve; increasing rigidity of the limbs with dysarthria was accompanied by progressive dementia. At autopsy the globus pallidus and the substantia nigra were found to have a brown discoloration, due to pigment accumulation in ganglion cells. This and related syndromes are probably determined by a recessive mode of inheritance.

Progressive ophthalmoplegia

The age of onset of progressive ophthalmoplegia may be in childhood or in adult life. The first symptom is usually ptosis, followed by a progressive restriction of ocular movements. Eventually there may be no independent movement of the eyeballs, but ptosis is usually incomplete and the intrinsic muscles often escape. The prognosis with respect to life is good, since it is rare for extra-ocular muscles to be affected. The pathological basis in some cases has been shown to be a degeneration of the brain stem in the region of the oculomotor nuclei, whereas in others it depends on a myopathy of the extrinsic muscles of the eye. In one pedigree the condition was transmitted through four generations (Beaumont, 1900), and in most instances a dominant mode of inheritance is operative (Fig. 172).

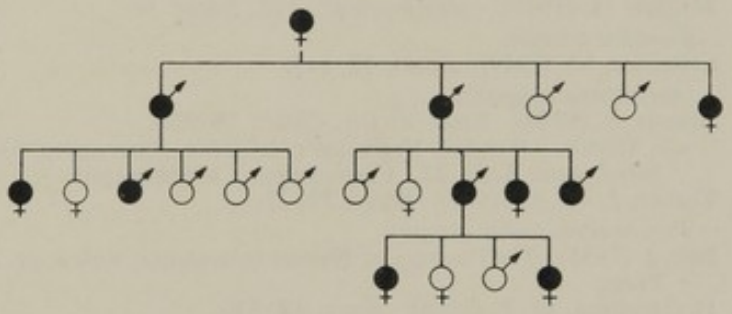


FIG. 172.—Progressive ophthalmoplegia. (*After Beaumont, W. M. (1900). Trans. ophthal. Soc. U.K.*, **20**, 259.)

Migraine

The characteristic features of an attack of migraine are visual hallucinations followed by unilateral headache and vomiting. Genetic inquiry into this condition is severely limited in its accuracy by wide variations in the frequency of the attacks and in the nature of the symptoms, and by the necessity of making the diagnosis on the history given by the patient. Allan (1928) has carried out a most extensive genetic investigation on the inheritance of migraine. He did not find it associated with any general neuropathic trait, nor did he find a raised incidence in brain-workers. The prevalence in the offspring of the matings affected × affected was 83·3 per cent, affected × unaffected 61 per cent, and unaffected × unaffected 3·7 per cent. Parental migraine was found in 91 per cent of migrainous subjects. He concluded that the disorder was transmitted by a dominant mode of inheritance. Since he found the prevalence of migraine to be 60 per cent, or possibly higher, in the general population, it is probable that his diagnostic criteria were somewhat loose, and the applicability of his genetic conclusions to the more restricted connotation of the term migraine is in doubt.

Congenital auditory imperception

In congenital auditory imperception there is an inability to understand the

meaning of sounds, without affection of hearing. The child does not respond to spoken words, and does not speak; later a personal vocabulary may be built up, with only slight resemblance to normal words. This disorder appears to be inherited by a dominant mode of inheritance.

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CHAPTER 17

OLIGOPHRENIA

J. A. Böök

Classification

It is customary to distinguish at least three gradations of mental defect, namely *idiocy* (approximate IQ range 0–19), *imbecility* (IQ 20–49) and *debility* (corresponding to the British feeble-minded and the American moron with an IQ range of 50–69). These limits are of course arbitrary as is the grouping together of all individuals of an IQ level below 70 under the heading *oligophrenia*, a term which is preferable to the British " mental deficiency " or the American " feeble-mindedness ". From the IQ level of 70 and upwards other designations are used from mentally retarded, poorly gifted, to physiological stupidity.

With the exception of some well differentiated disorders, the neuropathology of mental deficiency has not attracted many workers, and the available findings are too meagre to serve as a basis for pathological or aetiological differentiation. The study of Berry and Norman (1934) showed an unspecific under-development and shortage of cortical neurons. Cell counts of supragranular and granular elements are below normal in almost every instance. So far only some 50 odd brains of " undifferentiated mental defectives of unknown aetiology " have been examined by competent neuropathologists, and the findings suggest that psychological explanations are not necessary to account for the clinical conditions of these patients (Benda, 1947; and Christensen and Vestergaard, 1949).

An outstanding symptom which is commonly associated with mental deficiency is convulsive disorder (" epilepsy "). *Grand mal*, only, occurs in 9 per cent of higher grade defectives, in 16 per cent of imbeciles and 21 per cent of idiots (Yannet, 1945; observations on 1,330 patients). To what extent *petit mal* and other types of seizures occur is difficult to ascertain, due to the mentality of the patients; but *petit mal* especially was fairly common in my own experience of over 1,000 institutionalized defectives. As these convulsive disorders occur in all types of cases irrespective of aetiology it is possible that they are a feature of all varieties of brain lesions.

It is noteworthy that electro-encephalographic studies indicate an unusually high incidence of moderately abnormal tracings as reported by Yannet (1950). In unpublished studies of undifferentiated imbeciles and idiots of probable genetic aetiology abnormal tracings were observed in 19 out of 39 cases. These abnormalities were mostly dysrythmias and of non-focal type, indicating diffuse lesions (Böök, Schut, Reed, and Rossen).

Neurological signs are also prominent. Gordon, Norman and Berry (1933) after routine neurological examinations of 500 certified defectives of all grades emphasized that the lower the grade the more symptoms. The general diversity of the signs suggest diffuse lesions in most of the cases. Most impressive are the objective signs of the pyramidal system varying from simple release phenomenon (hyperactive reflexes) to positive toe signs. These pyramidal signs which are

especially obvious in most imbeciles and idiots irrespective of aetiology carry no significance of localized pathology but follow from the fact that the pyramidal system is wide-spread and easier to cover with objective neurology than any other system. Furthermore, the signs are compatible with the neuropathologic observations of a general paucity of cortical neurons which in many cases is characteristic also of areas 4 and 6 of the cerebral cortex.

Where psychiatry, psychology, neurology and pathology have failed to differentiate oligophrenia there still remains the hope that biochemistry might do so. Basically the genes participate in metabolic processes which control not only development but also function, so that every genetic disorder is primarily a biochemical disturbance. The discovery of phenylketonuria, formerly one of the " undifferentiated mental defects of unknown aetiology ", is instructive, for the biochemical test established a clinical genetical entity caused by one single gene difference.

At present it is therefore not possible to give an adequate classification of mental deficiency.

A useful framework is supplied by the following classification which could be elaborated when more facts have accumulated.

(1) Genetic diseases or defects with mental defect as essential symptom,
(2) Genetic diseases or defects with mental defect as occasional symptom.
(3) Environmental affections group, in which mental defect occurs as a symptom caused by either physical lesions (such as injuries, prematurity, infections) or by adverse psychic mechanisms.

The incidence of mental deficiency

The estimates of the frequency of mental deficiency in the general population vary with the diagnostic requirements of different authors. Differences of evaluation will be found mostly concerning the debiles and borderline cases whereas by and large a better agreement exists concerning the group idiocy and imbecility. With allowance for the shorter average duration of life for the latter, especially pronounced for low-grade idiots, a conservative estimate of the morbidity risk is 5–10 per one thousand live births. These are individuals who have to be taken care of in special institutions or at the best cannot follow simple-grade school teaching. Dahlberg (1951) gives the figure of 5 per thousand for Sweden. There was a slight preponderance of men which is a consistent feature in most surveys. Sjögren (1948), using the same criteria, found 6·8 per thousand in a West Swedish island population of 8,736 and Böök (1951) 11·9 per thousand in a North Swedish population of 8,651.

American estimates of the incidence of all grades of mental defect vary between 2 and 3 per cent.

Dahlberg (1937) estimated the incidence of children who, due to mental defect, have to be educated in special classes at public schools in Sweden at 1·7 per cent among the girls and 3 per cent among the boys.

A representative survey in Finland covering a population of 418,472 gave an average incidence of idiocy and imbecility of 4·43 per thousand (Kaila, 1942). These figures for the low-grade defectives (with the exception for the smaller samples where differences may be due to special factors as isolation and inbreeding)

seem to agree well with previous estimates (Luxenburger, 1928—5·7; Schulz, 1927—5·4; Berlit, 1935—6·2; and Brugger, 1930—5·9 per thousand; Kaila, 1942).

The British survey of 1929 (Penrose, 1949) which was undertaken in a number of communities in England and Wales had social and legal purposes mainly. The aim was to discover all cases of mental deficiency which were potentially certifiable. The figure arrived at was an average for all age-groups of 8·6 per thousand.

The incidence of mental defect as reported in the official statistics of different countries is based on a very incomplete registration and furthermore depends on the number of beds available in the institutions for the mental defectives. Thus they have no great interest for the present review.

It would seem that a conservative estimate would give 5 per thousand of idiocy and imbecility and 20–30 per thousand of the higher grades.

GENETIC FACTORS IN MENTAL DEFICIENCY

Birth injuries, prematurity, postnatal skull injuries and a number of different infections of the central nervous system occurring before or after birth, are amongst the recognized causes of mental deficiency due to environmental factors, whilst recently brain lesions, which may occur after maternal rubella during the early months of pregnancy, and by toxoplasmosis infection have come to be appreciated.

The aetiology of many clinically differentiated entities such as diplegia, microcephaly, mongolian idiocy is not known. It is hardly warranted to assume a genetic origin because further cases of mental deficiency are found among near relatives. None the less, in any large sample of mentally deficient index cases there is such a high and statistically significant frequency of secondary cases among parents, sibs and other relatives that this distribution could not have occurred by mere chance (*see* Table I). If the index cases are exclusively those of unknown aetiology this becomes even more marked (*see* Table II).

The available figures of the incidence of mental deficiency among relatives of affected propositi may serve as empirical risk figures, and as such they are valuable for certain practical purposes. However, as they are based upon highly heterogeneous data, any attempt to discuss their meaning in a Mendelian sense is futile. It has been suggested that the low-grade defects (especially idiocy) should preferably be recessive and the higher grades dominant, but the more impressive accumulation of higher grade defectives in certain family groups might equally well be due to intra-familial environmental factors.

There is, however, no doubt that an appreciable fraction of the mental defects are caused by specific genes which taken together are very common in any population. This fraction has been estimated at anything from 80 to a few per cent. It can be said with certainty that no less than 20 per cent of the cases have a recognized environmental aetiology and that the majority of the remaining 80 per cent are highly suspicious of a basic genetic aetiology. None the less, those genetic diseases which have mental deficiency as an essential symptom and which are completely analysed from a genetical point of view account for only a small percentage of all defectives.

Suggestive findings in large series.—(*a*) *Twin studies* show a greater similarity

between monozygotic siblings than between dizygotic. In the series reported by Smith (1929) 14 out of 16 monozygotic pairs were concordant whereas among 50 dizygotic pairs 4 only had both siblings affected. Another large series was presented by Juda (1939). Whereas Smith's propositi were unselected mental defectives of all the different kinds, Juda had selected cases of unknown aetiology only. All of her 60 monozygotic pairs were concordant and of 168 dizygotic pairs 76 were concordant. In both series the differences between monozygotic and dizygotic pairs are highly significant statistically. The relatively high concordance figure of the dizygotic pairs in Juda's data is consistent with the high risk of being affected which is characteristic for ordinary sibs of mental defectives.

TABLE I

INCIDENCE OF DIFFERENT GRADES OF MENTAL DEFECTS IN PARENTS AND SIBS OF 1,280 DEFECTIVES IRRESPECTIVE OF AETIOLOGY (FROM THE COLCHESTER SURVEY, PENROSE, 1938)

Propositus grade	Parents			Sibs		
	Number ascertained	Idiot or imbecile	Debile or borderline	Number ascertained	Idiot or imbecile	Debile or borderline
Idiot or imbecile (653 cases)	1,277	1 0·08%	196 15·3%	2,429	109 4·5%	312 12·8%
Debile or borderline (627 cases)	1,188	3 0·3%	346 29·1%	2,216	58 2·6%	453 20·4%

TABLE II

INCIDENCE OF MENTAL DEFICIENCY AMONG THE SIBS OF PROPOSITI WITH "MENTAL DEFICIENCY OF UNKNOWN AETIOLOGY" (BRUGGER, 1939).

Author	Both parents normal		One parent defective		Both parents defective	
	Number of sibs	Per cent defectives	Number of sibs	Per cent defectives	Number of sibs	Per cent defectives
Lokay – –	123	13·0	36	33·0	5	100·0
Brugger – –	310	17·8	124	41·3	41	93·2
Wildenskov –	94	13·8	72	40·3	78	93·6
Kreyenberg –	753	15·9	280	33·9	23	82·5
Frede – –	278	17·3	82	48·8	81	90·1

(*b*) *Consanguinity*.—The incidence of cousin marriages among the parents of mental defectives is somewhat higher than the average figure. According to Penrose (1949) 3 per cent among the parents of low-grade cases and 2·2 per cent for the high-grade cases were first cousins. As Penrose's cases probably included a relatively large number of different genetic disorders, one would expect higher rates of consanguinity if most of these disorders were due to single recessive gene differences. It is therefore likely that some of these genetic disorders were caused by common recessive genes, dominant genes, or by polyhybridism. As Penrose pointed out, the data are heterogeneous and another, though less probable, explanation could be that a large group of non-genetic cases have been included.

(*c*) *Birth rank*.—Another test which is sometimes valuable is the examination of the distribution of affected on different birth ranks. If the main aetiology is

genetic one will expect a random distribution. This was confirmed in a study of 819 mental defectives (Brugger, 1939).

SPECIFIC GENETIC DISORDERS ASSOCIATED WITH OLIGOPHRENIA

Most of the specific genetic disorders associated with oligophrenia are rare, but taken together, they are not insignificant.

As most of them are also due to single recessive gene differences, the number of heterozygous carriers in the population may be considerable (as is seen from the fact that a recessive condition with a frequency of 1 : 50,000 would make approximately 1 per cent of the population carriers). The detection of such carriers who may show some slight clinical or biochemical deviation is of considerable importance, and some studies carried out under the supervision of the author suggest that a diagnosis of the heterozygotes of juvenile amaurotic idiocy may become possible for these carriers, at least in some families, show a peculiar vacuolization of the lymphocytes.

Affections discussed elsewhere

Several of the differentiated disorders in which oligophrenia is a constant feature are discussed elsewhere in the text. They are: infantile amaurotic idiocy (page 196); juvenile amaurotic idiocy (page 196); gargoylism (page 201); phenylketonuria (page 177); the Laurence-Biedl syndrome (page 248); and tuberose sclerosis (page 231).

Congenital cataract with oligophrenia

The most extensive study was reported by Sjögren (1935).

Clinical aspects.—Congenital bilateral cataract is combined with low-grade mental deficiency, in most cases idiocy. A few cases may have microphthalmus or megalo-cornea. More or less pronounced skeletal malformations are common. The condition is stationary and the neurology unspecific. Like most idiots, the patients are of small stature. Nine out of Sjögren's 44 cases had *grand mal* seizures. A slight, though not significant, preponderance of affected males was observed (26 ♂ : 18 ♀).

Heredity.—The incidence in the Swedish population was estimated at about 1 : 50,000 live births. No accumulation to particular geographical regions was noted. The risk for sibs of those affected was about 16 per cent. The parents of affected were first cousins in one out of 30 families only, but in 16 families details could not be obtained. A recalculation of the data, testing the theory of simple recessive inheritance, gave a P-value of between 0·30 and 0·50 that the deviation may be due to chance only; thus this type of transmission is likely. Until further confirmation, however, it seems better to use the empiric risk figure for practical purposes.

Franceschetti and Brugger (1944) studied 35 cases of congenital cataract associated with mental deficiency. Among 127 siblings 14 showed the same condition, but 10 had oligophrenia and 3 cataracts only. They questioned Sjögren's conception of a clinical and genetical entity—a criticism that is hardly valid.

Congenital spastic diplegia with oligophrenia

The separation of this condition from the heterogeneous group " cerebral palsies " seems justified although a symptomatological clear-cut diagnosis cannot yet be secured. This disorder was suggested as a separate clinical and genetical entity by Hanhart (1936) and Böök (1951). The findings seem so similar that the following clinical description should be valid for both series of observations.

Clinical aspects.—Though the condition is undoubtedly congenital the parents do not note that something is wrong with the child until the end of the first year. The main finding is a symmetrical spastic diplegia of varying severity. No indications of birth injuries or other exogeneous lesions are found. The mentality of the patients (7 observations by Hanhart and 24 by Böök) varies from low-grade idiocy to imbecility. The condition is practically stationary though complicated by increasing muscular contractures which may make walking impossible. Pathological and biochemical data are not available as yet.

Heredity.—The incidence in a special geographic isolated area in North Sweden was estimated at 1–2 per one thousand births. A high incidence of consanguinity among the parents of the affected was observed by both authors and the genetical analysis suggests a simple recessive gene difference. It is as yet not possible to tell what part of the " cerebral palsies " might be due to this gene or other genes.

Microcephaly

Microcephaly may occur in a great number of conditions with purely enviromental aetiology such as prenatal or postnatal infections or x-ray damage of the foetus. There is, however, also a genetic condition, usually referred to as *microcephalia vera.*

Clinical aspects.—There is a typical " pin-point " skull form, symmetrical hypoplasia mainly of the membrane bones, and dysplasia mainly of the basal and facial bones of the skull. General nanosomia and pyramidal hypofunction

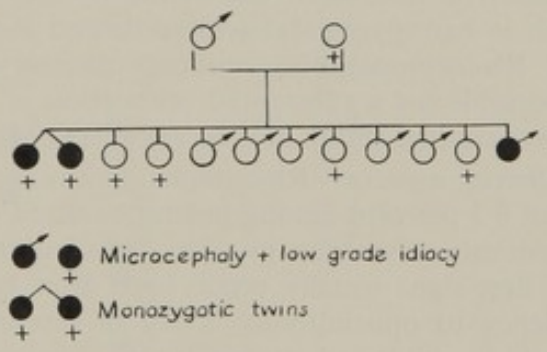

FIG. 173.—Pedigree of microcephaly.

are almost constant. Electro-encephalographic studies of three cases by the author showed distinct abnormalities with low-voltage random waves in one case. No indications of focal lesions or convulsive disorders were found in any case. Seizures have, however, been reported to occur occasionally in other cases. Most patients are low-grade idiots. No special pathological studies of the genetic type appear to have been undertaken, though there are a number of reports on micrencephalic brains in the literature. The brain is, of course, always underweight and may show general hypoplasia, micro-gyria and porencephaly. It is,

however, at present impossible to tell what pathology is connected with the genetic type, and no biochemical studies have been undertaken so far.

Heredity.—The incidence of genetic microcephaly (micrencephaly might be a better term) is probably somewhere between 1: 25,000 and 1: 50,000 births. The consanguinity rate in the pooled literature is about 10 per cent. The meagre data available suggest a simple recessive gene difference as the primary cause (Fig. 173).

Microphthalmus with oligophrenia

On a study which covered practically all cases in Sweden (35♂ and 23♀) Sjögren and Larsson (1949) estimated the frequency of this type at 2·5: 100,000. The risk figure for the sibs of affected (both parents unaffected) was 9 ± 3 per cent. Observations on a smaller number of cases apparently displaying a sex-linked recessive mode of inheritance had been reported earlier, both in Great Britain and in the United States of America.

Muscular weakness, atrophy and oligophrenia

One large pedigree with 22 cases of this apparently clinical and genetic entity was described by Allan and co-workers (1944) (Fig. 174).

Clinical aspects.—The outstanding features were muscular weakness and moderate generalized atrophy and low-grade mental deficiency. The reflexes were hypo-active and some ataxia was noted. The condition is stationary.

Heredity.—Affected males only were found. The theory of a simple recessive sex-linked gene difference as primary cause seems well founded.

Rh-encephalopathy

Rh-incompatibility which is the genetic mechanism behind erythroblastosis (haemolytic disease of the newborn) may sometimes cause brain lesions which result in extrapyramidal symptoms and mental deficiency. An earlier statement that Rh-incompatibility without obvious haemolytic disease or kernicterus is responsible for a substantial proportion of " undifferentiated mental defectives " is unwarranted (Böök and co-workers (1949) and Gilmour (1950)).

Clinical aspects.—Rh-encephalopathy seems to occur with a frequency of about 0·5 per cent among institutionalized defectives. Mental defect, however, is an inconstant symptom as many cases with normal intelligence have been reported. The first signs usually occur soon after birth. They consist of convulsions, a tendency to opisthotonus, a cry of cerebral type, or tonic alterations. Later, usually in childhood, more pronounced signs become apparent as rigidity, spasms, athetotic or choreic movements and general inco-ordinations. All of these signs are due to extra-pyramidal lesions. Eventually other parts of the brain become involved. Rh-tests of mother and child and a complete history of icterus neonatorum should be required for diagnosis.

Pathological aspects.—Kernicterus, that is, an icteric discoloration of chiefly the caudate and lentiform nuclei is conspicuous. Occasionally other nuclei and the cerebral or cerebellar cortex may be involved. Demyelinization, degeneration and pigmentations of the ganglion cells and proliferation of the glial tissue has

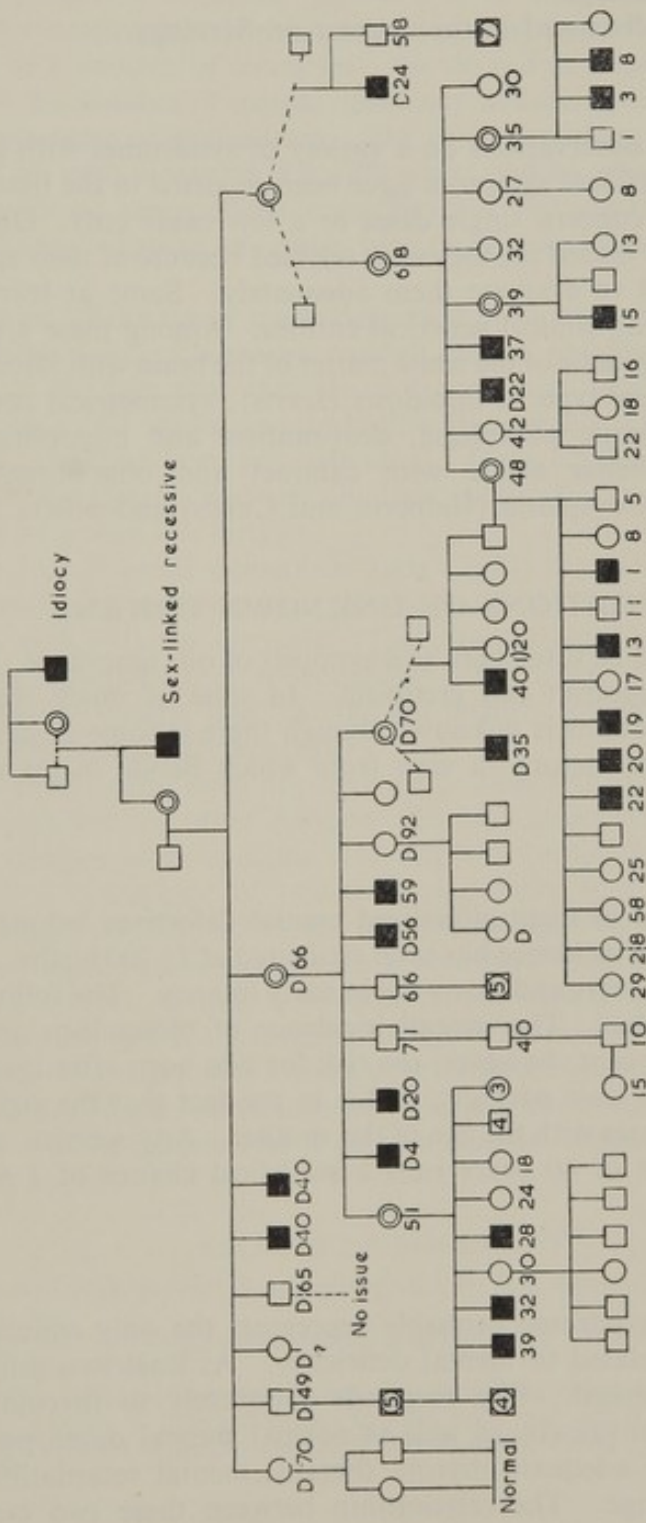

FIG. 174.—Pedigree of an apparently sex-linked syndrome, muscular weakness, atrophy and oligophrenia. (*After Allan, W., and his co-workers (1944). Amer. J. ment. Def.*, **48**, 325.)

been observed. Biochemically a positive thymol turbidity test in at least some cases indicates liver damage.

Heredity.—This is discussed in the chapter on Serology.

Other affections

A large number of observations on a variety of syndromes with mental defect as an essential or occasional symptom have been reported in the literature. Most of these publications concern single cases or a few cases only. Obviously, data of this kind are heavily biased for they were selected because of their special interest and it is thus difficult to evaluate them adequately. Some at least suggest the possibility of their being clinical genetical entities. Among these are: xeroderma (Ruud's syndrome); agenesis of the white matter of the brain with idiocy (Waggoner and co-workers); a new type of lipoidosis (Jervis); symmetrical cerebral calcifications (Fritsche); spastic paraplegia, deaf-mutism and oligophrenia (Jakob); congenital spino-cerebellar ataxia with cataract and oligophrenia (Sjögren); anhidrotic ectodermal dysplasia (Halperin and Curtis) and others.

CONDITIONS OF UNKNOWN ORIGIN

Many conditions could be listed here as a synopsis of our ignorance. Outstanding among these are mongolism and cretinism. In spite of much work the basic aetiology of these affections is unknown though there is some evidence in favour of participating genetic factors—a view from which Benda in his recent monograph (1949) dissents.

Mongolism

Five to ten per cent of institutionalized mental defectives belong to this well known syndrome. The incidence has been estimated at 1 : 700 births. The average expectation of life is 9 years and many die in early infancy. The following empiric risk figures are of value. The overall incidence of mongolism among sibs of affected is about 1 per cent; however, the risk for sibs born after the first affected is 4 per cent. This, at least partially, is due to the fact that the risk of having a mongoloid child increases with the age of the mother. Any woman who becomes pregnant after the age of 40 years runs a statistical chance of 1–6 per cent of having such a child.

Cretinism

This characteristic syndrome probably represents the only endocrine disorder which is specifically related to mental deficiency. At least two different clinical types can be distinguished. One responds completely to thyroid substitution therapy, giving normal growth as well as normal mental development. In the other type, in spite of adequate thyroid therapy, mental retardation will persist with little or no change. The relationship between these two types is as yet unknown. Studies of so-called endemic cretinism in Switzerland failed to show any appreciable genetic factors. In contrast, families with sporadic cases not responsive to therapy suggest a genetic basis.

SOME SOCIAL ASPECTS

Oligophrenia has attracted much ignorant, or at best uncritical, attention from eugenists. Sterilization laws, which take a special interest in mental deficiency, are operative in a number of countries. We do not at present have the necessary knowledge on the genetics of mental deficiency to assess precisely the future effect of a rigid programme of sterilization. The belief that these disorders could easily be eradicated by such measures is hardly warranted by what we know at present.

The advocates of more effective sterilization frequently stress that mentally defective individuals display an unduly high fertility and thus threaten to upset our present culture.

Actually, most of the lower grade defectives do not propagate at all. In many cases the profound defect is reason enough even if physical possibilities exist; in others there is the fact that they do not constitute acceptable sexual objects. In a survey of 1,650 idiots and imbeciles in Sweden, Dahlberg (1951) found altogether 0·11 children born per individual. Only 1·5 per cent of the males and 9·3 per cent of the females had any children at all. The group as a whole is thus characterized by a very low fertility.

As for the higher grade defectives, Juda (1934) examined the fertility of 220 individuals belonging to this group. She found 3·91 children per female defective as compared with 3·01 for normals. The infant mortality, however, was much higher for the defectives thus reducing the net fertility to 1·93 against 2·50. A somewhat peculiar finding was that the net fertility for male defectives was 2·93 or somewhat higher than for normals.

But whilst sterilization does not need to be imposed to avoid a catastrophy it may still be justified for other reasons. Mental defectives are not able to care properly for their children and this may warrant sterilization. There is a genetic indication for it in the case of two normal parents who have a child with an apparently genetic condition and the risk for subsequent children is substantial. Naturally such sterilizations can be on a voluntary basis only.

The serious import of this symptomatologic variety of the human mind is obvious. However, it is not justifiable to equate all mental deficients and consider them a burden on society which should be removed in any way which could be legally defended. Many individuals carrying the socio-legal diagnosis of mental deficiency are well adaptable and if given a suitable education are able to play a useful part in society.

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CHAPTER 18

PSYCHIATRY

ELIOT SLATER

WHILST it is unlikely that psychiatry will provide any noteworthy contribution to the science of genetics, the solution of many fundamental psychiatric problems may depend on help from the genetical side. The causes of mental illness are still very obscure; but as we know that heredity plays a material part in many cases, the unravelling of the extent and mode of genetical causation will help to clarify the vexed problems of aetiology in general. Classification in psychiatry is still in its infancy. Many authorities reject classification of the forms of illness on an aetiological basis, preferring a purely descriptive delimitation between one form of illness and another. This would seem to be a counsel of despair, as only an aetiological classification has the potentiality of permanence and of providing the firm foundation on which advances are made. Further research in psychiatric genetics may enable the clinician to distinguish syndromes in a less subjective and disputable way than is possible at present.

This modest statement of the present relationship between psychiatry and genetics would be over-optimistic without further modification. Psychiatrists are divided into schools, some of which reject even the most fundamental theses which are accepted by others. The attitude which is adopted in debate on these issues is often emotionally toned to a degree which is exceptional in scientific circles. The belief in some system of dogmas may transcend the purely provisional acceptance which is appropriate to a scientific approach, and take on the form of an adherence to articles of religious faith. To find a parallel in general medicine we have to go back a century or so to the days of debate between "allopaths" and "homoeopaths". Such a state of affairs is only possible when the total body of proved and accepted factual data is very small in proportion to the needs of practical medicine.

Difficulties in psychiatry

There is much evidence that mental potentialities and susceptibilities are inherent aspects of physical qualities of the same order, and that attributes of both kinds are, in part at least, determined by hereditary factors. Yet there are schools of psychiatry basing themselves on a dualistic philosophy in which mental attributes are regarded as without a physical basis, and mental illness is treated as if it existed on a supraphysical level, in the world of ideas. The schools of psychiatry which are based on psycho-analysis attempt to describe mental abnormalities in this way, and while they retain a strictly causative mode of approach, derive all the causes of mental illness from disturbances within the individual, and of mutual relations between individuals, on emotional and psychological planes. Clearly, the data provided by genetical research are almost meaningless for adherents of these schools.

The worker in psychiatric genetics is therefore practically bound to take his stand on ground that is still being contested, and his position is thereby weakened. As it is unthinkable that all forms of mental disorder are genetically equivalent

he is equally compelled to adopt some system of classification. It is still possible to withdraw to some extent from an arena of unprofitable dispute. Penrose, for instance, regards all psychiatric diagnosis as insufficiently certain, and has produced interesting studies in which the classification of mental illnesses is based solely on the age of onset. The cost that is thereby paid is the loss of much valuable information—information which, for at least most European psychiatrists, is invaluable for prognostic and therapeutic purposes. There is also some strong evidence that the usually accepted clinical syndromes, insufficiently restricted and precise though they are, do correspond to some extent to different genotypes.

Psychiatry differs from general medicine in a number of ways which are important for the geneticist. Psychiatric findings are not as readily verifiable as are physical observations. As further clinical advances are made we learn that the schizophrenic, for instance, differs from the normal individual in glucose and oxygen metabolism and in various other biochemical modes. These differences are not very marked, and do not suffice for diagnosis. For diagnostic purpose we are reduced to psychological findings, such as the observation of a disturbance of formal thought processes which it is often easy to recognize but always difficult to describe and practically impossible to define. In borderline cases, therefore, there is more difference of opinion than is generally the case in medicine; and what is even more important the evaluation of observations made by others, such as those which are contained in case records, is particularly difficult. Standards of normality are much vaguer in the psychological than in the physical field, and the allocation of a particular individual to the category of the abnormal is correspondingly more liable to doubt. Yet it is on the basis of these arbitrary designations that attempts have been, and have to be, made to fit observational data to genetical expectations.

One might suppose that with so many difficulties in the way, the attempt to apply genetics to psychiatry was premature. This is, however, not the case. Although all the work the geneticist does is provisional and will probably have to be discarded at a later time when the clinical concepts he had to apply have been replaced by ones more sure and precise, meanwhile his work is helping to provide the needed precision. Even on the information already available we can be sure that heredity supplies the specific cause of a number of mental disorders.

" Exogenous " and " endogenous " mental disease

In general medicine the heredo-familial diseases are much less important than diseases due to external noxae, trauma and infections. In psychiatry a converse relationship holds; the disorders due to trauma, intoxications, vitamin deficiencies and so on are numerically less well represented than the so-called endogenous psychoses. This difference is no doubt due to the fact that the brain, though better protected against damage from outside than any other organ, has undergone a great expansion and development quite recently on the evolutionary time-scale, so that spontaneous break-downs are more likely.

This relationship between the endogenous and exogenous forms of mental illness is reflected in the calculations which have been made of the expectations of different forms of mental illness. In England and Wales it can be estimated that 2·65 per cent of males and 2·93 per cent of females born can expect to be

admitted to a mental hospital during the course of their lives. These figures are probably an under-estimate. The expectation of a schizophrenic illness has been calculated in different countries as lying between 0·8 and 0·9 per cent, the expectation of an affective psychosis as 0·4 per cent, and of epilepsy as 0·5 per cent. All these are mainly endogenous illnesses. The expectation of general paresis, which is the commonest mental illness caused by an external agent (syphilis) was, in Great Britain in 1935, 0·28 per cent for men and 0·07 per cent for women.

GENETIC INVESTIGATIONS

Early difficulties

In its earliest stages psychiatric genetics depended on the application of methods of research which were being used with profit in other branches of medicine, and especially on the collection of pedigrees. In psychiatry these methods proved less successful, and though they have thrown some illumination here and there, they also led to a good deal of mental confusion. It was found that though insanity ran in families, the several insane members of one family often showed rather different forms of mental disorder, and there would also be other members who were mentally defective or abnormal personalities, such as tramps, prostitutes, criminals, or social misfits. Some families were so overloaded with mental abnormality that they hardly contained a single normal member; and in general the proportions of the normal and abnormal varied very greatly between the findings of one investigator and another and in no case indicated any recognizable mode of inheritance.

Theory was governed by metaphysical preconceptions, such as that of a mythical degeneration which would attack some family, affecting more and more members at increasingly early ages until the stock died out. The so-called law of " anticipation " was widely accepted. (The present writer remembers being instructed by a famous neurologist that the disease myotonia dystrophica first appeared in a family as senile cataract and in later generations in progressively earlier and more malignant forms until in the youngest generations there would be mental deficiency.)

At this stage in the history of psychiatric research all forms of mental disorder were confused together, and much unreliable observation and ill-based theorizing resulted. A typical example is the literature on the Kallikak family with its two stems, one of defectives, criminals and psychopaths resulting from an ancestor's union with a prostitute, the other of men and women of ability and good character descending from the same ancestor's marriage to a Quakeress of good family. Much of the literature on the " Social Problem Group " has been greatly influenced by the same basically unscientific notions.

Later developments

A necessary break with tradition was made by Rüdin and his followers at Munich, by instituting two parallel methods of inquiry, both of which relied on making the most accurate clinical assessment possible (Kraepelin's system of classification was used, enabling a number of forms of mental disorder to be distinguished), and keeping the insanities, the mental deficiencies and the psychopathies distinct from one another.

Frequency rates in the general population

In the first place a series of investigations into the frequency of all these kinds of abnormality in the general population was made. The first to be done (Luxenburger) started from the consorts of general paretics, there being no reason to think that these persons were other than a random sample of the general population. A great number of other inquiries have followed, with improved methods of sampling, so that now there are fairly reliable figures for the frequency of various mental abnormalities, both in Germany and to a lesser extent in other lands. The incidences are usually and most conveniently expressed in the form of expectations; and to cope with the statistical problems involved there has been a corresponding improvement in statistical technique. One of the effects of this line of work has been to emphasize the importance of accurate knowledge of the distribution of ages of onset of the several mental disorders.

An offshoot of the interest in the incidence of mental abnormality in the general population has been a series of psychiatric censuses. The first of these was carried out by Brugger in Switzerland, and a valuable survey of all the work in this field has been provided by Strömgren (1950). The psychiatric census is of course of great social importance, so much so in fact that its genetical significance is overshadowed. The data that emerge are different in quality from those obtained by other methods of studying incidences in the general population; for clearly, if a disorder is of a type which may be followed by either death or recovery its frequency will be under-represented in a census of living persons.

All the work of this kind has brought out the great frequency of mental illness and has helped to explain some of the confusion seen in earlier pedigree investigations. Clearly, if 0·9 per cent of persons born can expect to become schizophrenic, then in any large family, however selected, the appearance of one or more schizophrenics (depending on the size of the group investigated) can be expected. The same is true of mental deficiency, and still truer of such even more common conditions as neurosis and psychopathy.

Set studies

The second main line of research emanating from the Rüdin school was the investigation of the relatives of persons suffering from some specific and named mental disorder. Instead of taking a dozen families and following them up and down the ancestral tree into cousins and second cousins, a restricted group, such as the sibs of schizophrenics would be taken. The incidence of the various mental disorders within this group could then be compared with the corresponding incidence in the general population. The type of genetically important result which emerged would be, to continue with the example taken, that the incidence of schizophrenia in the sibs of schizophrenics was much higher but the incidence of manic-depressive psychoses no higher than in the general population.

Some results

Delineation of symptoms

In this way, little by little, a picture has emerged of a number of different clinical syndromes to which genetic specificity must be allowed. The clinically much disputed question of paranoia was settled in this way. Paranoia was at one time singled out by Kraepelin as a distinct clinical syndrome, a chronic insidious mental

disorder which left the main features of the personality intact but involved it in a system of delusional ideas of growing complexity. However, cases were often observed showing features intermediate between this state and the more malignant admittedly schizophrenic ones in which the personality was more or less severely damaged. Kolle, by following up the actual cases which Kraepelin had selected as ones of " paranoia ", and then by investigating the incidence of all forms of insanity among their relatives, was able to show that, from the genetical viewpoint, paranoia was not to be distinguished from schizophrenia itself. This was shown, among other things, by the high incidence of ordinary forms of schizophrenia among the relatives. A problem of great clinical interest had been solved by genetical research.

Another example of the way in which family investigations may aid classification is provided by involutional melancholia. The name signifies no more than a state of depression of spirits, coming on in the later years of life, say after the age of forty years. This illness was at first included in the same group with the manic-depressive disorders, simply because they both shared some important clinical features—a depression of mood of spontaneous origin and not adequately accounted for by environmental circumstances, which persisted despite efforts at treatment or distraction until it eventually passed off of its own accord, as a rule leaving the personality undamaged. Nevertheless, when family investigations were instituted it was found that the syndrome was heterogeneous. If those cases were separated out who had had previous attacks of depression, familial relations were those typical of manic-depressive families; if those cases were separately studied in which paranoid symptoms, such as delusions of persecution, were prominent, a high incidence of schizophrenia among the relatives was found. Even the cases that remain probably represent aetiologically different conditions, as some involutional depressive states are found in conjunction with organic cerebral disease (for example, arteriosclerosis), and others with a make-up of personality of a peculiar (obsessional) stamp. The analysis, which has already gone a little way, can profitably go a great deal further.

Assessment of risk

The great advantage of the line of investigation started by Rüdin was that it led to results of immediate practical importance. The relatives of persons suffering from mental disorder often wish to know to what extent the condition is hereditary, and what is their own personal risk of developing the disease, or the risk of their actual or potential children. The results of investigation enabled a precise answer to be given. The chance of the child of an epileptic developing epilepsy is about 5 per cent, the chance of the child of a manic-depressive developing a recognizable manic-depressive state is about 15 per cent, and the risk of schizophrenia for the child of a schizophrenic lies between 9 per cent for some forms of the illness and 20 per cent for others. Similar estimates were obtained for grandchildren, nephews and nieces, in these and other clinical groupings.

Residual difficulties

It is at once obvious that these figures correspond to no recognizable mendelian ratio, and in the early days efforts were made to evolve theories to fit the facts.

Complex hypotheses were proposed, involving two or more genes, all of which now seem premature and forced.

There is no reason to suppose that complex and improbable genetic mechanisms will ever prove theoretically necessary. The discrepancy between observation and mendelian expectations can be readily explained in a number of ways. It is, in the first place, exceedingly difficult to be quite sure of one's facts and of interpreting them correctly. It is not possible for the field worker to visit every member of a family under investigation, and he will have to depend a good deal on hearsay evidence. Secondly, people suppress facts relating to their own or their relatives' mental abnormalities more than they do with facts relating to most other matters. Furthermore, members of the same family lose touch with one another, and even forget each other's existence. Thirdly, it is often exceedingly difficult to be sure of interpretations, whether the " fits " in one case are epileptic or not, whether another man's suspicious temperament and eccentric ways are or are not due to a schizophrenic illness which passed unnoticed and never led to admission to hospital. It is therefore no surprise that the findings of different workers agree in only a very rough way, the expectations calculated by one being sometimes perhaps only half of what another has calculated.

However, when full allowance is made for all these sources of error, it is still true that observations are lower than theoretical expectations. There is only one reasonable explanation, that manifestation of the hypothetical genes is incomplete. When this idea dawned on the psychiatric geneticist it led to a feverish effort to calculate manifestation rates, and some rather bizarre statistical methods were used. Nowadays there seems little purpose in continuing this sport as other lines of investigation are likely to prove more profitable.

The newer trends

Further breakdown of genetically heterogeneous groups into smaller entities is an obvious development. Equally significant are studies of the conditions themselves and an understanding of the basic physiological disturbances they involve. Both these trends are well exemplified by the developments in epilepsy.

The investigation of epilepsy

The ability to respond to some kinds of stimuli with an epileptic fit is a normal human potentiality. Although the occurrence of a fit has always been looked on as abnormal, the ability to react in this way is probably no accidental by-product of cerebral physiology but an adaptive mechanism. This is especially suggested by the successful use of artificially induced electrical fits to benefit patients suffering from melancholia. The epileptic patient, however, suffers from fits through something having gone wrong. Epilepsy may be caused by organic disease of the brain, such as cerebral tumour, or the scar of past trauma. A proportion of epilepsies are attributable to causes of this kind but there is also a proportion of cases in which no such cause can be found. The two kinds of epilepsy have been called symptomatic and idiopathic, and at one time it was thought possible that the progress of research would successively enlarge the field of the symptomatic and restrict the field of the idiopathic epilepsies until the latter ceased to exist. The death blow to these hopes was given by Conrad's investigation of epileptic twins.

Uniovular twins, and the very remarkable resemblances they may show, have been of interest to medical men at least since the days of Galton. It was the service of Luxenburger to put twin work in pyschiatry on a satisfactory scientific basis. He showed that casuistic

data obtainable from the literature had an extreme selective bias in favour of uniovular, as compared with binovular, twins, and in favour of similarity rather than the opposite ; he pointed out that if an investigation were to provide statistically reliable results the principles of unbiased selection would have to be rigidly followed. Conrad carried out his investigation on these lines, and took as the basic material all the epileptics in hospitals and institutions in the whole of Germany. The ascertainment of twinship was made on each case separately, by an inquiry directed to the register office where the patient's birth had been registered, as it was a matter of public record whether births were single or multiple.

Starting from 17,030 epileptics, Conrad discovered 258 who had come from a multiple birth. They had 149 same-sexed and 105 opposite-sexed twin partners, and 4 partners of sex unknown. By Weinberg's differential method, therefore, only 17 per cent of the twin pairs were uniovular, which is a remarkably low figure. Conrad was so impressed by this fact that he proposed a theory associating the genetical predisposition to epilepsy with a genetical predisposition to binovular twinning. The same high incidence of binovular twinning has been found in mental deficiency (Juda), and in each of these two cases the cause of the association is unknown. In fact the biological basis of twinning is still a very obscure problem.

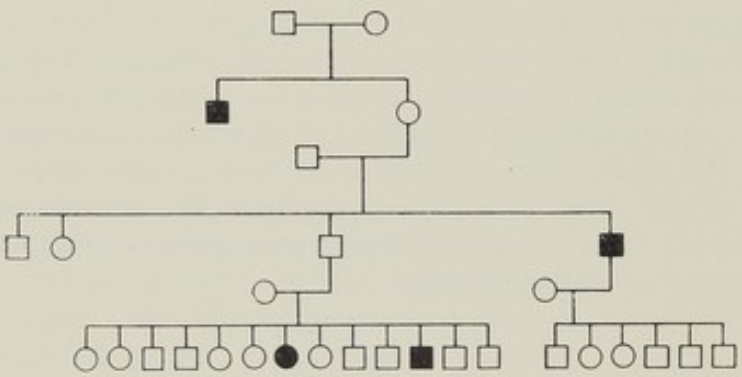

FIG. 175.—An epileptic family; the pedigree suggests an irregularly manifested autosomal dominant.

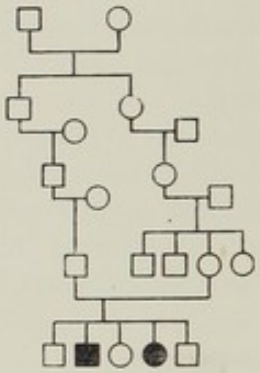

FIG. 176.—Another epileptic family pedigree suggestive of an autosomal recessive mode of inheritance.

(After Alström, C. H. (1950). A Study of Epilepsy in its Clinical, Social and Genetic Aspects. Copenhagen; Munksgaard.)

After omitting pairs in which the twin partner died under the age of 5 years, Conrad was left with 131 binovular pairs, 3 pairs of doubtful ovularity, and 30 uniovular pairs. The diagnosis of ovularity was made by a large and sufficient range of anthropometric measurements. In the binovular twin-partners there were 4 epileptics and in the uniovular partners 20. The incidence of epilepsy in the binovular twins was in fact no higher than the incidence in ordinary sibs. Conrad made an exact clinical study of the epileptics and subclassified the propositi into cases of symptomatic and idiopathic epilepsy. In the former group the incidence of epilepsy in binovular and uniovular partners was 0 : 34 and 1 : 8 ; in the latter 4 : 97 and 19 : 22.

Several conclusions of considerable importance could be drawn from this work. One of them was that the clinical subdivision of epileptics into symptomatic and idiopathic was aetiologically justified. Although hereditary factors seemed to play some part even in the symptomatic epilepsies it was, as might have been expected, a comparatively minor one. The very high degree of concordance of the idiopathic uniovular twins, on the other hand, showed that there certainly are epilepsies which are preponderantly caused by the hereditary make-up. A detailed clinical study of the uniovular twins and of the

concordant binovular twins showed that the clinical resemblance between members of concordant pairs extended into details—the age of onset, the neurological pattern of the convulsion, the course and prognosis, and psychiatric concomitants. Some of those cases which would be most likely to impress the clinician as symptomatic, because of the existence of a gross brain lesion, were found themselves to be hereditarily caused.

On the other hand the problem of mode of inheritance was left even more mysterious than before. The " manifestation rate " of 86 per cent, calculated on the ratio of 19 : 22 was not a very meaningful figure. Obviously it was at best an expression for the possible latitude which would have to be allowed for environmental differences. As uniovular twins must be held to be identical not only in their common possession of any single mutant gene but in respect of total genetic constitution, the high degree of similarity of uniovular twins might be in large part caused by this general similarity of constitution, and not to great regularity of expression of the hypothetical " epileptic gene " itself. No estimate of the latter could be made without examining material in which there was genetical as well as environmental variation.

A contribution on the point was made by Conrad's next study, which was his investigation of the children of epileptics. This showed that about 6 per cent of the children of idiopathic epileptics themselves became epileptic, but other sorts of pyschiatric abnormality were also shown to great excess. The most important of these other abnormalities was a form of abnormality of personality (" psychopathic personality ") which led its possessor into such deviations as violent changes of mood, suicide, crimes of violence, and impulsive acts of other kinds. Among the children of epileptics there was also a large excess of mental defectives. The suggestion arises, therefore, that any gene or genes which can in some circumstances bring about the development of epilepsy, can in other circumstances cause abnormalities of a rather less easily recognizable kind. These temperamental qualities may, in fact, be a form of masked epilepsy.

The next shaft of light to be thrown on the subject came from electro-physiological work. The development of the electro-encephalograph has contributed to advancement in many fields, but nowhere more than in epilepsy. It has been found that actual epileptic attacks are accompanied by a highly specific alteration of the electrical rhythms of the brain. Even when the epileptic patient is not having what is clinically recognizable as a fit, and superficially seems to be in quite a normal state, these specific electrical changes may be taking place. Even if they are not, there may be changes in rhythm of a less specific but still suggestive kind. And finally, even when no abnormalities can be seen in the patient at rest, they may appear if he is subjected to some form of physiological stress, such as overbreathing. The electro-physiological concept of epilepsy is wider than the clinical one, and includes a larger number of individuals. It has, for instance, been found that psychopaths of the kind that Conrad found among the children of epileptics very frequently show electro-encephalographic abnormalities which are highly suggestive of epilepsy. The notion that such temperamental qualities might be a masked epilepsy receives support.

The latest link in the chain of evidence has been provided by the work of Lennox and his co-workers on the electro-encephalograms of twins and of the near relatives of epileptics. This is discussed fully elsewhere (page 314). They have shown that the general qualities of the electro-encephalographic rhythms are so alike in uniovular twins that the EEG may even be used to diagnose ovularity. The salient features of the pattern must be determined by hereditary factors in a rather direct way, probably to about the same extent as the main features of fingerprint patterns are caused genetically. When they investigated the first-degree relatives of epileptics, regardless of their psychiatric normality or abnormality, Lennox and his co-workers found that 62 per cent of the parents showed a general non-specific abnormality of the EEG. It was therefore open to them to make the suggestion that the genetical basis of epilepsy is to be seen in an

autosomal dominant gene which in the heterozygote causes "cerebral dysrhythmia"—the non-specific EEG abnormality already mentioned. If someone of this type suffers in addition from some environmental trauma, perhaps a quite minor head injury, then epilepsy will very likely result. An alternative form of this theory, which has been suggested by Whitteridge, is that the gene in question causes dysrhythmia in the heterozygote, epilepsy in the homozygote.

There are objections to both theories into which it is not now necessary to enter. From what has been said, however, it will be seen that it is quite possible that confused and unintelligible genetical relationships may be clarified by advances in other fields which allow of a closer approximation of genotype and phenotype.

SOME DOMINANT AFFECTIONS

Whilst the collection of pedigrees has not proved a generally very useful technique in psychiatric genetics, it has had some outstanding successes.

Huntington's chorea

One of the earliest hereditary maladies to be recognized, Huntington's chorea, which is a form of progressive dementia, was identified in this way. Huntington's cases (in families also observed by his father and grandfather) were traced to passengers from Bures in Suffolk who had arrived by ship in Boston Bay in 1630. One line of descent was followed unbroken through 12 generations and over 300 years from the Bures original (Wilson). The condition has since been identified in most other civilized countries of the world, and excellent recent studies have been published by Sjögren.

There is no doubt that the disease is due to a dominant autosomal gene. There is no suggestion of heterogeneity and no reason to think that more than one gene capable of causing the condition exists. Huntington's chorea is of the order of rarity that one expects for pathogenic genes. The age of onset of the disease is distributed over a wide range from childhood to old age, with a mode at 34 years (Bell). According to Penrose the mean age of onset is lower for females than for males, and this fits in with genetical expectations. Clearly in the balance which is reached between mutation pressure on one side and negative selective processes on the other, the persistence of the gene in the population is aided by an onset which is sufficiently delayed for children to be born before incapacity is severe. As the reproductive life of woman ends earlier than that of man, the accumulation of modifying genes which exercise a longer protective influence in the male than in the female is encouraged.

Attempts have been made to estimate the manifestation rate of the mutant gene in Huntington's chorea. Pedigrees are observed in which there is overlapping, that is, families in which grandparent and grandchild were both affected by the disorder while the intervening parent lived to an advanced age and remained normal. Such cases are very rare. Sjögren, making use of an entirely statistical argument based on relation between the expectation of abnormality in a sibship and actual observation, with allowance made for the age distribution, reached the conclusion that observation showed 35 per cent affected when 50 per cent should have been. The manifestation rate, therefore, could be taken as 70 per cent. Entres, working along slightly different lines, concluded that the manifestation rate was little below 100 per cent.

Pick's and Alzheimer's diseases

Huntington's chorea is not the only presenile dementia which can be clinically recognized as a distinct syndrome. Pick's and Alzheimer's diseases have long been known as pathological curiosities, and have sometimes been diagnosed in life. Evidence is accumulating that each of them is, like Huntington's chorea, caused by a dominant autosomal gene. Recent developments in neurological diagnostic methods, especially the use of air encephalography enabling the early recognition of cortical atrophy in the brain, already make the diagnosis of these conditions during life much easier. There are certainly yet other presenile dementias in which there is none of the focal signs accompanying the three diseases mentioned; and while some cases of this kind can be attributed to general constitutional disorders, such as arteriosclerosis, others will probably prove to be genetically determined abiotrophies. A form of Parkinsonism, due to a dominant autosomal gene, has been identified by Mjönes.

The senile dementias

There are *a priori* reasons for thinking that among the welter of degenerative disorders of later life, such as the senile dementias, hereditary conditions due to dominant genes lie concealed. It is possible that a large amount of the disabilities of old age may be explained this way: for if the manifestation of a mutant gene is entirely suppressed until after the end of reproductive life, the gene itself is immune to natural selection. The new balance which will be reached will not be between mutation and selection, but between mutation and back-mutation. From this point of view it would appear that the social forces which tend to postpone marriage and reproduction in modern cultures are exercising a eugenic effect in favouring stocks which will be long-lived.

The clinical evidence of the involvement of genetical factors in senility is rather scanty. Nevertheless, Pearson observed a positive correlation between the life spans of blood-related individuals, and similar data have been supplied by Pearl. Recently, Kallmann and Sander have published twin data showing a greater correspondence in life span between uniovular than between binovular twins.

Manic-depressive psychosis

A great deal more variability of expression is to be expected with dominant than with recessive genes; and it would be surprising to find any large number of dominant disorders in psychiatry with very high manifestation rates, at least if the age of onset was at all early life. It is, however, probable that there are dominant genes with low manifestation rates which can, perhaps with the aid of environmental or other constitutional factors, cause mental illness. A case in point in which the data though not conclusive are suggestive is manic-depressive psychosis.

Although many clinicians prefer to consider all forms of affective mental illness together, without attempting any subclassification of an aetiological kind, the most typical manic-depressive state is a highly distinctive illness. The illness itself comes on endogenously, without any adequate cause in the form of an environmental upset, and it persists with or without treatment for a time lasting from days to months. The length of the phase is to a considerable extent peculiar

to the individual, for the illness is a recurrent one, and both the attacks and the remissions to which any one patient is liable tend to resemble each other in length. Recovery, barring accidents such as suicide, is almost invariable. Many of these patients are liable to both manic and depressive attacks, mania and depression appearing to be merely opposite phases of the same functional disturbance. The illness is commoner in women than in men, and is correlated with mental and physical traits of temperament and bodily build. In clinical experience typical manic-depressive psychoses are far from common and probably constitute but a small fraction of the total amount of affective psychotic illnesses, though this is obscured by the considerable liberties taken by clinicians in the use of the term. Family investigations show strong indications of dominant inheritance (Fig. 177), as up to 20 per cent of parents, of sibs and of children of manic-depressive propositi have been found to suffer from similar conditions. However it is not the illness as such which is inherited but the tendency to show throughout life not, as is the case in the normal individual, an equable mood varying appropriately with the circumstances of the time, but a state of mood which fluctuates between elation and depression in phases which seem to be determined by deeper-lying biological causes. These spontaneous variations do not by any means have to be so severe

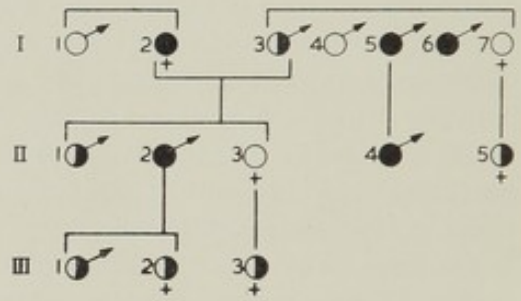

FIG. 177.—Pedigree of a manic-depressive family. (*After Lange, J. (1928). "Die endogenen und reaktiven Gemütserkrankungen", Handbuch der Geisteskrankheiten, Ed. by O. Bumke, Vol. VI, Special Part II, p.* 19, *Berlin; Springer.*)

Generation I: 1, diabetes. 2, melancholia. 3, alcoholism. 5, manic-paranoid psychosis. 6, "in his last years not normal".

Generation II: 1, imbecile. 2, manic-paranoid psychosis. 4, manic-paranoid psychosis. 5, epileptic imbecile.

Generation III: 1, hypomanic. 2, depressive temperament. 3, suicide.

that the subject is recognizably ill and in need of treatment, and in fact only exceptionally and in a minority of the hypothetical gene-carriers do they ever become so. Although possession of a hypothetical manic-depressive gene may lead to a pathological state of mind, there is no reason to consider the gene itself or the manic-depressive constitution as a pathological variant. Personalities of this type are often exceptionally sociable and well-adjusted, apart from the occurrence of phases of ill-health, and there is evidence that as a class their attainments and achievements are above average. This fact, as well as the difficulty in distinguishing cyclothymics from normals and from other types of affectively unstable persons, leads some authorities to the view that a multifactorial type of inheritance is more probable than inheritance *via* a single dominant gene.

Clinical Variability and Identity in Dominant Inheritance

Some of the most interesting work along the lines of pedigree study has been carried out by Leonhard (1934). He collected a series of families in which there were indications of dominant inheritance, and the psychotic illnesses were not only in themselves atypical and with an individual stamp but kept this peculiar quality throughout the affected family.

Fig. 178 shows the simplified pedigree of one of these families and gives a strong impression of simple autosomal dominance. We note also that there were two cousin marriages between trait-bearers ; one of these resulted in six stillbirths or early infantile deaths, the other in a stillbirth and a girl who had only reached the age of 13 years at the time the investigation closed. On the individuals numbered 1, 2, 4, 5, 9, 13 and 16 the details available are scanty, though they all seem to have been psychotic at one time and to have made partial or complete recoveries; in the cases of 2, 9 and 13 the main symptoms seem to have been depressive, in 5 and 16 more on the paranoid side. Case 3 had two depressive illnesses from both of which she recovered though in one of them she thrust her arms into the oven to be burnt. Case 6 first fell ill at 31 years of age with an acute agitated depression with marked confusion, he recovered, relapsed again at 37 years of age and this time took nearly seven years to recover, but did so fully apart from a slight change of personality leaving him shy and touchy. Case 7 had a very similar psychosis at the age of 40 years which killed him in two months. Case 8 was never in a mental hospital but was an irritable psychopath liable to depressive phases. Case 10 had two depressive illnesses for one of which she was in a private mental hospital. Case 11 had depressions at the ages of 15, 18, 24 and 38 years, and on the later occasions had psychoses

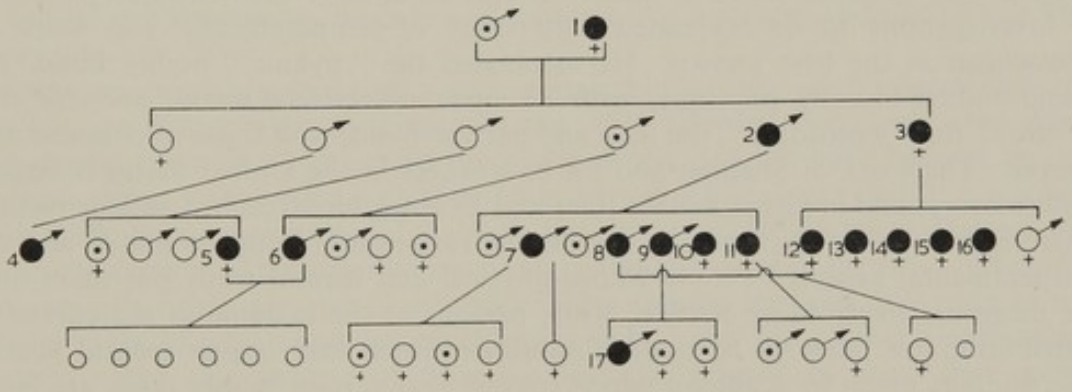

FIG. 178.—Pedigree showing the incidence of anomalous " schizo-affective " psychoses in the same family, suggesting an autosomal dominant. (*After Leonhard, K. (1934). Z. ges. Neurol. Psychiat.*, **149**, 520.)

of very much the same rather atypical quality as the other members of the family, that is to say, acutely agitated depressed confused states which eventually passed off into almost complete recovery but leaving behind some permanent slight change of personality. Case 12 fell ill at 34 years of age with a similar depression, she recovered, relapsed again and though mental changes were very slight after the second recovery, they were marked enough to render return home impossible. Case 14 had her agitated melancholic state for the first time at 45 years of age but after recovery (which was eventually complete) maintained for a long time delusional ideas of a markedly schizophrenic stamp. Case 15 again had a very similar psychosis at 40 years of age, she recovered completely and relapsed again at 53 and died. Case 17 is the only one which does not fit the family picture, going into a mental hospital at the age of 20 years for abnormal behaviour which suggests a combination of psychopathy and mental deficiency rather than an affective or schizo-affective psychosis.

All these psychotic illnesses caused the clinicians diagnostic difficulties in their time, being sometimes regarded as schizophrenic, at other times as manic-depressive, yet they nearly all fall into the same general picture, and once the family is

regarded as a family instead of as a collection of individuals, the diagnostic difficulties disappear as the pathological state assumes a new meaning.

If several such families can be found by one investigator, it seems probable that they are not infrequent. Were it possible to follow families affected by mental illnesses over a number of generations, the problems of psychiatric classification might fall into an entirely new pattern.

MULTIFACTORIAL INHERITANCE

In so far as genetical factors are called on to explain normal variation, especially in continuously variable qualities, they have for a long time been regarded as multifactorial. " Modifying genes ", " genes of small effect " and the " genotypic milieu " are terms frequently used which express the same idea. The question whether inheritance of this type plays any large part in psychiatric genetics is clearly important.

There can be little doubt that it does. Qualities of physique, which are known to have their genetical basis in factors of this kind, have been shown by a series of investigations to be correlated with traits of temperament. The work of Kretschmer is the best known. He associated the " pyknic " bodily build, the round-bodied chubby physique, with an open, affectively warm, sociable disposition; the " leptosome ", the long and narrow build, with traits of coldness and reserve. The work of Sheldon and his co-workers in the United States is largely confirmatory, and in Great Britain Rees and Eysenck have reached similar results. There is little doubt that there is continuous variation in both the bodily and the temperamental aspects. People whose physical and mental traits put them near the mean are likely to be normal, while persons at the extreme of the curves of distribution are likely to be under disabilities which may impair mental health. The findings made by Kallman which suggest that certain bodily types are more and others less resistant to schizophrenia have already been mentioned.

The neurotic temperament

Apart from the frank psychoses, the psychiatrist has to deal with a great deal of ill-health which is called neurosis. Whereas the schizophrenic patient is likely to impress the observer as totally mad, with ideas which cannot be understood and feelings into which others cannot enter, this is not the case with the neurotic. His symptoms are likely to strike a chord of sympathy, and the observer is likely to feel that he, too, might feel like that if things became bad enough. This purely subjective impression is likely to be based on an underlying reality. Qualitative differences between neurotic patients and normal individuals have not been found in either the mental or the physical realms. Although they differ from normal people, it is only in degree. The conception that the neurotic is a normal variant, although an extreme one, has found a great deal of recent support, especially with the work which has been done in psychiatry and in psychology during the last war. If genetical factors lie at the foundation of temperamental variation, they are most unlikely to be of a single factor type, to be genes of large effect, most likely to be of a multifactorial kind.

The genetics of personality

There is a great deal of evidence that the main outlines of the personality are

determined by genetical factors. Large-scale studies on the uniovular and binovular twins of criminals have shown this, though they have not confirmed the original idea of Lange (1931) that crime itself was attributable to heredity. The investigation of the blood relatives of various classes of abnormal personalities, such as psychopathic swindlers (von Baeyer), hysterics (Kraulis), anxiety neurotics, obsessionals (Brown) shows that tendencies to abnormal forms of reaction are inheritable, and that relatives tend to resemble one another in these respects. The mode of inheritance shows that there are some elements of specificity, but also a good deal of non-specificity. Thus, Brown found that obsessional states were commoner among the relatives of obsessional patients than they were among the relatives of anxiety neurotics, but were commoner among the latter than among the relatives of a control group. It seems that we must indeed think of continuous variation in constitutional tendencies of these kinds, but not solely along one dimension. The man who breaks down with a neurotic illness is likely to be handicapped not by one constitutional weakness of severe degree, but with a number of minor weaknesses. And in his illness he is likely to show a mixture of symptoms, depression, anxiety and hysteria, for instance, and not of one kind only.

There are persons so constitutionally abnormal that they are burdened throughout life, no matter what the circumstances, with neurotic symptoms; but this is not the general rule. The greater part of neurotic patients have become so only because things went wrong with them in some way. The illness itself is a reaction, and apart from constitutional liability the factor of environmental stress also enters the picture. The writer knows of no systematic study of the twins of neurotic patients other than his own small series. This showed that out of 9 pairs of uniovular twins of which one was neurotic, in only 2 was the partner also similarly affected. The examination of their life histories seemed to show that critical deviations in a man's career might be caused by relatively chance occurrences, such as the personality of the chosen partner in marriage. In a pair of persons of almost identical personality, one might suffer a mischance which would lead to a vicious circle of ill-health, social failure, hardship, discouragement and increased ill-health, while the other totally escaped. And yet after years in which their careers had progressively diverged, the fundamental personalities of the twins might remain very much the same.

The genetics of personality are perhaps the vaguest and the most subtle of all the fields in which genetics has been applied in psychiatry, but the rules by which they may be investigated may still be the simplest. When we are dealing with continuously variable qualities we may hope to develop methods of measurement, and with them to apply the statistical techniques of analysis of variance which have proved so powerful in other fields. On the other hand the more precise problems of inheritance in schizophrenia and other pathological aspects of psychiatry may well defy elucidation for many years to come, and require entirely new methods of inquiry.

THE PROBLEM OF SCHIZOPHRENIA

Since Rüdin first showed that among the sibs of schizophrenics there was an excess of schizophrenic illness, the question of the mode of inheritance has been debated

with a vigour and enthusiasm unmatched elsewhere in psychiatric genetics. Weinberg, the statistician who handled Rüdin's data, proposed a complex theory involving more than one gene. A later expert, Luxenburger, who carried out the first systematic twin survey in psychiatry, on schizophrenic propositi, was inclined to support a hypothesis attributing the disorder to a recessive autosomal gene. Lenz, whose interests embraced the whole range of human genetics, supported the notion of dominance. The latest in the field to take a definite standpoint is Kallmann, and he bases his opinion on the widest experience of actual investigation. He is strongly in favour of the hypothesis of recessivity.

Kallmann's data for monofactorial recessive inheritance

Kallmann's contributions of a major kind are twofold. He made a very extensive family survey (1938) covering the sibs, half-sibs, children and grandchildren of 1,087 schizophrenic propositi, the study differing in a significant particular from similar studies which had been made before. In earlier studies of the children of schizophrenics, families were almost automatically taken in which there were known to be one or more children. This involved a degree of biased selection of the parents, parents being automatically over-represented whose illness came on late or was so mild that reproduction could still occur after the illness had begun. Kallmann started from a hospital population, without selection, and without knowledge whether there were children or not. His material contained a fairer selection of the graver forms of psychosis than had been obtained before. His second major contribution has been the collection and examination of a very large series of twins from the New York State mental hospitals. This series includes 953 schizophrenic propositi, as well as much smaller numbers of manic-depressive, involutional and senile psychoses. A detailed statistical study of the first 794 schizophrenic pairs appeared in 1946, when 2,741 sibs as well as parents, consorts and other relatives had been investigated. The material was gathered by a systematic attempt to discover all the twins in a total mental hospital population of some 85,000 persons. From these studies the following percentage figures relating to the incidence of schizophrenia among various classes of relatives are of interest: (1) unrelated: general population, 0·85; step-sibs, 1·8; husbands and wives, 2·1: (2) relatives: first cousins, 2·6; nephews and nieces, 3·9; grandchildren, 4·3; half-sibs, 7·0–7·6; parents, 9·2–10·3; full sibs 11·5–14·3; dizygotic co-twins, 12·5; children 16·4; children of two schizophrenic parents, 68·1; same-sexed dizygotic twins, 17·6; monozygotic twins who have been separated for five years or more, 77·6; monozygotic twins who have not been so separated, 91·5. The increasing likelihood of schizophrenia with increasing nearness of blood relationship to a schizophrenic is very striking.

Kallmann considers that his findings and the findings that have been made by others support the hypothesis of single-factor inheritance of a recessive type, but with a lower than 100 per cent rate of manifestation, that is, some homozygotes never develop schizophrenia but will nearly always be schizoid personalities. Manifestation in the heterozygotic state is not entirely suppressed, but may also be shown in some schizoid traits of personality. Non-specific genetical factors are postulated to account for variation in the clinical form of the disease and its degree of malignancy. Kallman and his co-workers have found that a robust

bodily physique tends to mitigate the severity of the disease, or to protect against it, while loss of weight and an asthenic physique have the opposite tendency.

Some difficulties

The hypothesis of recessivity has been criticized by Koller, and his argument is an important one. Although in the detail in which he presented it, it is complex, it can be quite simply presented. If the schizophrenic is homozygous for gene s, he will only produce schizophrenic children by mating with a heterozygote, or with another individual homozygous like himself. Schizophrenics compose approximately 1 per cent of the population, so that the frequency of s in the population is approximately 0·1, and the frequency of heterozygotes approximately 0·18, if one assumes that mating is at random. The frequency of persons homozygotic for s among the children of schizophrenics should be, accordingly, and again assuming random mating, $0{\cdot}5 \times 0{\cdot}18 + 0{\cdot}01 = 0{\cdot}10$. The frequency of homozygotes among the sibs of schizophrenics, which is not affected to the same degree by the gene frequency, may be taken as 0·25. If s is recessive the frequency of homozygosity for s, and therefore the frequency of schizophrenia, should be higher among the sibs of schizophrenics than among their children. Assortative mating would only equalize the two frequencies, or lead one to expect a higher frequency of schizophrenia in the children than in the sibs, if it was of a very extreme degree, if in fact a very large proportion of schizophrenics married others also homozygotic for s. Several studies of the consorts of schizophrenics and their families have been published and it is clear that in them the incidence of schizophrenia is only very slightly greater than in the general population. The incidence of schizophrenia in the consorts themselves has, for instance, been found to be 2 per cent. Assortative mating therefore can be neglected for this purpose.

The actual observations, however, do not fit these expectations. The incidence of schizophrenia has been found by Kallmann to be higher in the children than in the sibs. This is therefore a strong indication of dominance. On the dominance hypothesis one would of course expect an equal incidence in children and sibs, but a difference of the extent which actually exists would not be a serious objection to the theory as it may result from a sampling error or be explicable in other ways.

One of the findings which Kallmann has adduced as evidence in favour of recessivity is that approximately 5·7 per cent of schizophrenics have been found to be the children of consanguineous matings. The relation between gene frequency (p), the incidence of cousin-marriage in the general population (a) and the incidence of cousin-marriage between the parents of recessive homozygotes (c) is given by Dahlberg's formula, which may be written $p = a(1 - c)/16c$. If for a we write 0·006, which is Bell's estimate of the frequency of cousin-marriage in England and Wales (the incidence in the United States of America is unknown to the writer), and if we assume that about two-thirds of Kallmann's consanguineous matings were first-cousin marriages and give the value of 0·042 for c, the value of p proves to be 0·008554, and the value of p^2 0·000073. However, the expectation of schizophrenia for a member of the general population, and the frequency of hypothetical homozygotes is about 0·009. The theory therefore leads us to the supposition that some 125 distinct autosomal recessive genes are involved.

This number is not, perhaps, quite such an unlikely one as it would seem to be at a first glance. There might well be a large number of different genotypes in schizophrenia, just as there almost certainly are in the hodge-podge of clinically inadequately differentiated imbecilities and idiocies. There are, however, factual grounds for considering this consequence of the recessivity hypothesis improbable. A fair number of families have now been collected in which two schizophrenic parents produced children. The incidence of schizophrenia among these children has been estimated by Schulz as 38 per cent, or 45 per cent if doubtful cases were included. An earlier estimate made by Luxenburger was 66 per cent, and Kallmann's estimate is 68 per cent. Whatever the true figure, it is quite a high one: but if there are 125 different genes involved, it would be extremely unlikely for any two schizophrenic parents to be of the same genotype, and the incidence of schizophrenia in their children should be little higher than the incidence of schizophrenia in the children of one schizophrenic and one normal parent.

The incidence of schizophrenia in the children of schizophrenics is rather more easy to reconcile with the dominance hypothesis. If dominant genes are involved, we must calculate their manifestation rates as approximating to 0·3. The children of two parents both of whom carry a dominant gene, but at different loci, should contain equal proportions of persons carrying one gene, carrying the other, carrying both, and carrying neither. The expectation of normality should therefore be $(0{\cdot}7 + 0{\cdot}7 + 0{\cdot}49 + 1)/4 = 0{\cdot}72$, and we should expect an incidence of schizophrenia of 0·28. If, however, the genes were at the same loci, the homozygous dominant would almost certainly be abnormal and, unless the double dose proved lethal, the incidence of schizophrenia would be 0·40.

The possibility of heterogeneity

None the less, Kallmann's finding of a greatly increased rate of consanguineous marriage among the parents of schizophrenics would seem to be a direct proof of the operation of recessive genes. The only reasonable way in which to reconcile all the conflicting evidence is on the supposition of heterogeneity. In view of the fact that schizophrenia is a great deal more common than any single genetically determined disorder is otherwise known to be, heterogeneity is inherently probable. As far as the writer is aware, there is no evidence to the contrary which should be allowed great weight. The principal objection to the hypothesis of heterogeneity is that so far it has proved impossible to identify genetically distinct forms of the disorder. A brief glance at the work which has been done on this aspect may be allowed.

If schizophrenia is genetically heterogeneous, we may expect to find some forms which are not genetically determined at all. There is some evidence that they exist. It is an accepted finding of clinical psychiatry, since the work of Kretschmer, that schizophreniform reactions may occur, that is, states of mental disturbance clinically resembling schizophrenia, but produced by some form of physical or mental stress, accessible to treatment by psychological means and by adjustment of the environment, and likely to recover without, as in the great majority of cases of schizophrenia, leaving some sequelae behind. Schulz found in his investigation into the sibs of schizophrenics that if he singled out a group of propositi whose illness came on after a head injury, the incidence of schizophrenia in their sibs

was much lower than in the families of the remaining propositi. The work of Leonhard, showing that in some rare families a clinically distinct form of psychosis, with many schizophrenic-like features, may be identified with possession of a dominant gene, has already been mentioned. Leonhard, following Kleist, believes that it is possible to distinguish between " typical " forms of schizophrenia, which take a progressive and malignant course, and " atypical " forms with a better prognosis. An experiment was staged in which the clinical differentiation was done by Leonhard, without knowledge of family relationships, and the familial investigation was done by Schulz without knowledge of the clinical findings in the propositi. One of the interesting findings that emerged was that the incidence of schizophrenia in the parents of the propositi was in the typical group 1 per cent, in the parents of the atypical group 6 per cent. This does suggest a preponderance of recessive types in the former, and a proportion of disorders due to a dominant gene in the latter.

On the other hand the attempt to identify the clinically recognized subforms of schizophrenia—catatonia, hebephrenia, paranoid schizophrenia and schizophrenia simplex—with distinct genotypes has failed. Some suggestive points have emerged, but do not take us far. Kallmann's figures, derived from his investigation of the children of schizophrenics, show, though he did not observe the point himself, a noteworthy correlation between the form taken by the illness in the propositus and in the relative. Furthermore, he found that the incidence of schizophrenia was more than twice as high in the children of catatonic and hebephrenic propositi than in the children of paranoid and simplex cases.

The matter must be left here, with the important questions still all unanswered, although the available evidence has been far from exhaustively discussed.

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Atypical psychoses

Leonhard, K. (1934). " Atypische endogene Psychosen im Lichte der Familienforschung." *Ztsch. ges. Neurol. Psychiat.*, **149**, 520.

Schizophrenia

Kallmann, F. J. (1938). *The Genetics of Schizophrenia.* New York; Augustin.

Psychopathy and neurosis

Lange, J. (1931). *Crime as Destiny.* London; Allen and Unwin.

Slater, E., and Slater, P. (1944). " A heuristic theory of neurosis." *J. Neurol. Psychiat.*, **7**, 49.

CHAPTER 19

SENSE ORGANS

I.—The Eye

Arnold Sorsby

In highly developed countries even in recent years infectious diseases were the main cause of blindness and of eye disease in general—as they still are today in the greater part of the world. In 1922 some 30 per cent of all children admitted to blind schools in England and Wales had been blinded by ophthalmia neonatorum. Today children blinded by ophthalmia neonatorum, or other infectious diseases, are seen only exceptionally, and in the greatly reduced numbers at blind schools congenital malformations and genetic disease now predominate. A similar decline in the infectious causes of blindness, and a consequent relative increase in the significance of congenital and genetic anomalies, has been observed in the United States of America.

Nearly 80 per cent of those registered as blind in England and Wales are over the age of 50 years, and the leading causes of blindness are cataract, glaucoma, and the senile degenerations of the fundus. Each of these affections may well have more than one cause, and there is at least strong presumptive evidence that hereditary tendencies play a not inconsiderable part. Genetics has greatly helped accurate diagnosis, and ophthalmology in turn has contributed to the study of human genetics to such an extent that examples from ophthalmology are readily available to illustrate the main tenets of human heredity.

GENETIC PRINCIPLES EVIDENT IN OPHTHALMOLOGY

Modes of inheritance

Almost every known mode of inheritance is exemplified by pedigrees in ophthalmology. In addition there are two modes of inheritance which are not readily explicable by present-day genetic theory—the transmission of Leber's disease and the occurrence of colour-blindness exclusively in women.

Autosomal inheritance

Dominant autosomal inheritance.—This is well exemplified by the famous Cunier-Truc-Nettleship pedigree of congenital night-blindness (Fig. 179). Admittedly much of this pedigree is based on documentary matter rather than on observations. A striking pedigree of dominant transmission of congenital optic atrophy over four observed generations and two antecedent generations reputed affected is shown in Fig. 180.

Recessive inheritance.—Many of the numerous pedigrees on albinism are good illustrations of recessive inheritance, as can be seen from Figs. 181, 182 and 183 which bring out both common and uncommon situations.

Intermediate inheritance.—It is likely that albinism illustrates intermediate rather than recessive inheritance, for the pathogenic gene is not altogether unexpressed in the simplex state. The parents of albino children have irides that are translucent to light. There is no known example of intermediate inheritance with pathological manifestations.

X-chromosomal linkage

Recessive X-chromosomal linkage.—A typical pedigree, concerning red-green blindness, is shown in Fig. 184. Unusual situations, including apparent dominance and manifestation in women, are shown in Figs. 185–188.

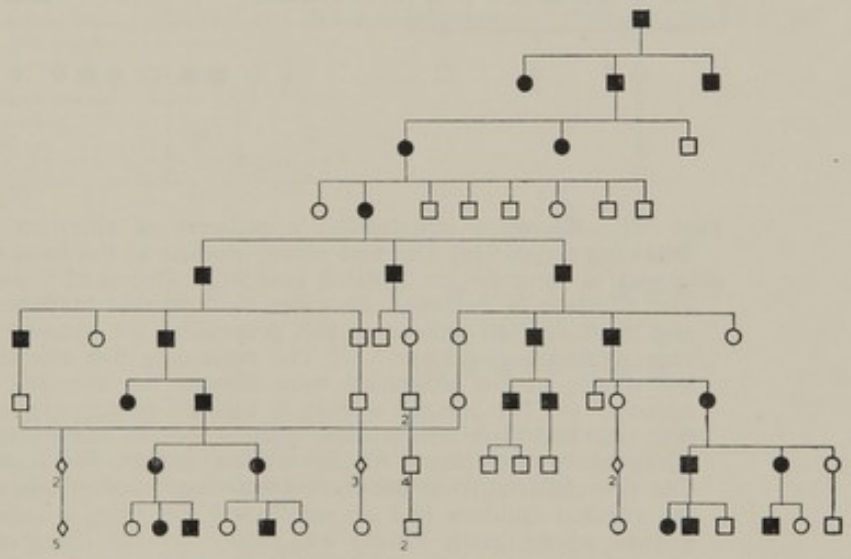


FIG. 179.—Dominant inheritance. Part of the Cunier-Truc-Nettleship pedigree of congenital stationary night-blindness. (*After Nettleship, E. (1907). Trans. Ophthal. Soc., U.K.*, **27**, 269; *and in Treasury of Human Inheritance (1933). Ed. by K. Pearson, Vol.* 2 *(by Julia Bell). Pedigree No.* 317. *London; Cambridge University Press*).

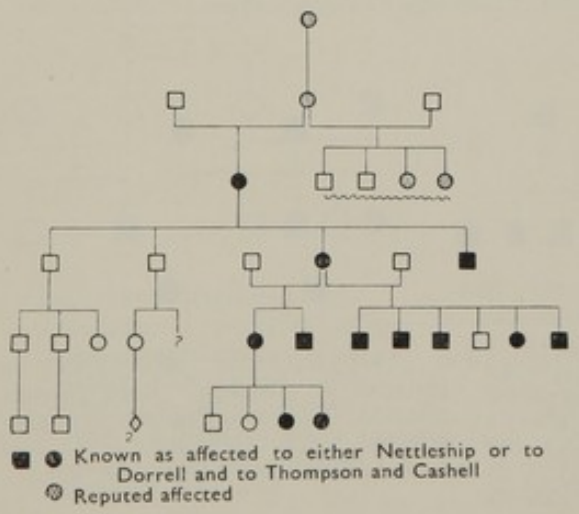


FIG. 180.—Dominant congenital optic atrophy. Pedigree chart combining the findings of Nettleship with those of Dorrell and of Thompson and Cashell. (*After Nettleship, E. (1909). Trans. Ophthal. Soc., U.K.*, **29**, 116 and 149; *Dorrell, E. A. (1932). Roy. Berks. Hosp. Rep.*, 122; *Thompson, A. H. and Cashell, W. G. T. (1935). Proc. R. Soc. Med.*, **28**, 1415.)

Intermediate.—This is well illustrated by Fig. 189 which shows inheritance of choroideraemia. Here the women carriers can be readily picked out by non-pathological ophthalmoscopic anomalies.

Dominant.—There is no adequate example in opthalmology of dominant X-chromosomal inheritance, unless congenital sex-linked nystagmus shows recessive and dominant allelomorphic forms (*see* Figs. 202 and 203).

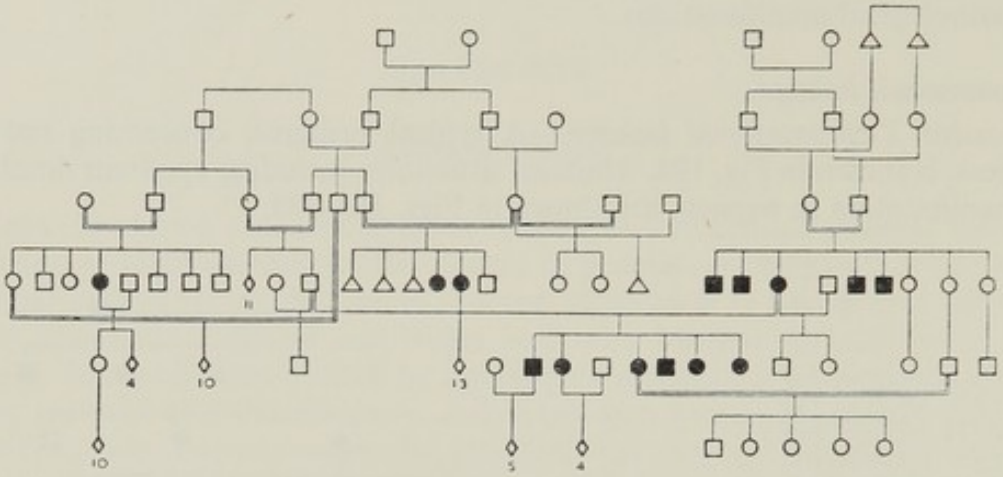


FIG. 181.—Recessive inheritance; a pedigree of albinism illustrative of the following points: (*a*) The first albino woman in the fourth generation would appear to represent an isolated case in a sibship of consanguineous origin. The affection is, however, also seen in collateral branches. (*b*) The second and third affected women in this generation are likewise the offspring of a consanguineous marriage. (*c*) The remaining five affected members in the last sibship in this generation were likewise the offspring of consanguineous parents. (*d*) The affected woman in this last sibship married twice, once to a man who had three affected first cousins and the second time to a man whose family history was clear. All six children from the first marriage were affected. The two children from the second marriage were unaffected. The father of the affected children had an unaffected son from a second marriage to a woman whose family history was clear. (*e*) The many offspring of albinos married to normal individuals are themselves normal. (*After Marlow, F. W., and Faxon, W. L. (1913). A Monograph on Albinism in Man, by Pearson, K., Nettleship, E., and Usher, C. H. London; Cambridge University Press.*)

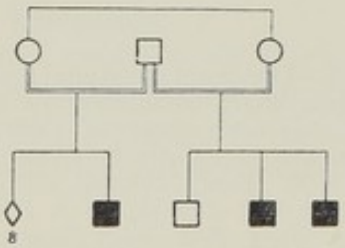


FIG. 182.—Recessive inheritance; a pedigree of albinism. A man marries successively two sisters, his first cousins. They must all be presumed to have been carriers. (*After Heidenreich (1913). A Monograph on Albinism in Man, by Pearson, K., Nettleship, E., and Usher, C. H. London; Cambridge University Press.*)

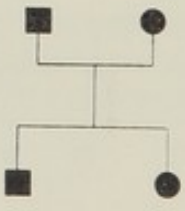


FIG. 183.—Recessive inheritance; a pedigree of albinism. Both parents affected. Their two children were also affected. (*After Davenport, G. C., and C. B. (1910). Amer. Nat.*, **44**, 705.)

Y-chromosomal linkage

There is no well-established example of this mode of inheritance in ophthalmology. A suggestive pedigree is shown in Fig. 190.

Partial X-chromosomal linkage

Haldane regards the pedigrees shown in Figs. 191 and 192 as illustrative of recessive and of dominant partial sex-linkage respectively.

Obscure modes of inheritance

Fig. 193 is a pedigree illustrative of inheritance of Leber's disease. Transmission in Leber's disease does not fit in with recessive sex-linkage as there is no known case of an affected man passing on the optic atrophy; moreover, more than 50 per cent of the sons in affected sibships tend to suffer, and more than 50 per cent of the women are carriers.

A pedigree of colour-blindness transmitted exclusively in the female line is shown in Fig. 194. It can be explained on the assumption of non-disjunction of the X chromosomes.

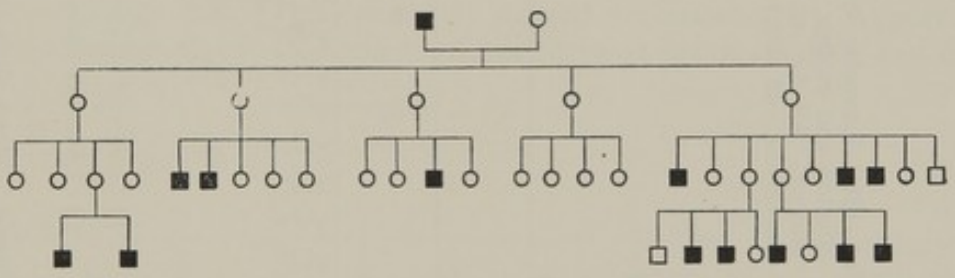


FIG. 184.—Recessive sex-linkage; a pedigree of red-green blindness. (*After Horner, W. D. (1876) quoted in Treasury of Human Inheritance (1933). Ed. by Pearson, K., Vol. 2 (by Julia Bell). London; Cambridge University Press.*)

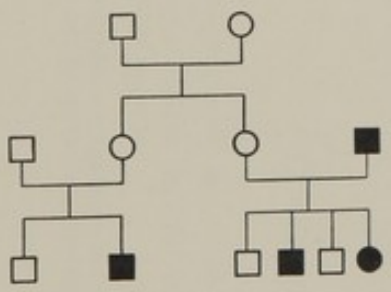


FIG. 185.—Recessive sex-linkage; a pedigree of red-green blindness. The father affected and the mother a carrier. (*After Vogt, A., and Klainguti (1922). Arch. Rass-u. GesBiol.*, **14**, 129.)

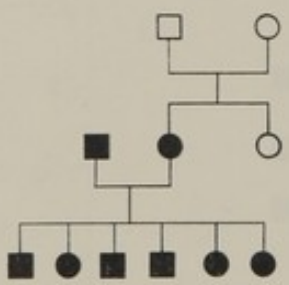


FIG. 186.—Recessive sex-linkage; a pedigree of deutranopia (green-blindness). Both parents and all children affected. (*After Göthlin, G. F. (1925). Acta Ophthal.*, **2**, 15.)

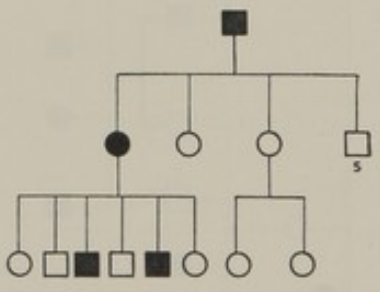


FIG. 187.—Recessive sex-linkage; manifestation in a heterozygous woman. A pedigree of colour-blindness. (*After Bell, Julia (1933) in Treasury of Human Inheritance. Ed. by Pearson, K. Vol. 2. London; Cambridge University Press.*)

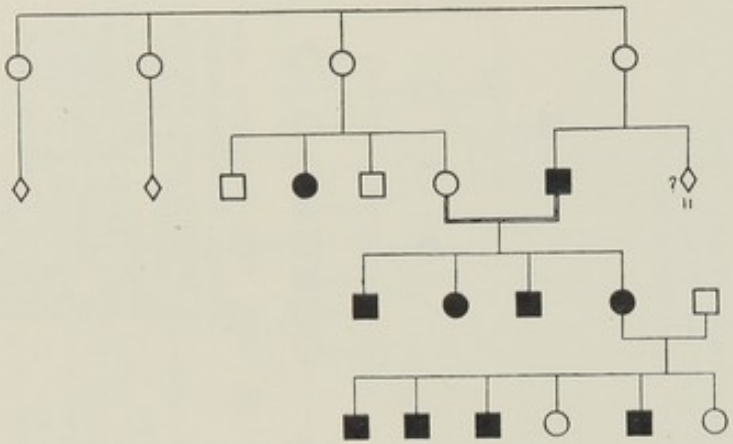


FIG. 188.—Recessive sex-linkage; a pedigree of colour-blindness. (*a*) Father affected and mother presumed a carrier. (*b*) Mother affected and father normal. All the sons are affected. (*After Schiötz, I.* (*1922*). *Klin. Mbl. Augenheilk.*, **48**, 498.)

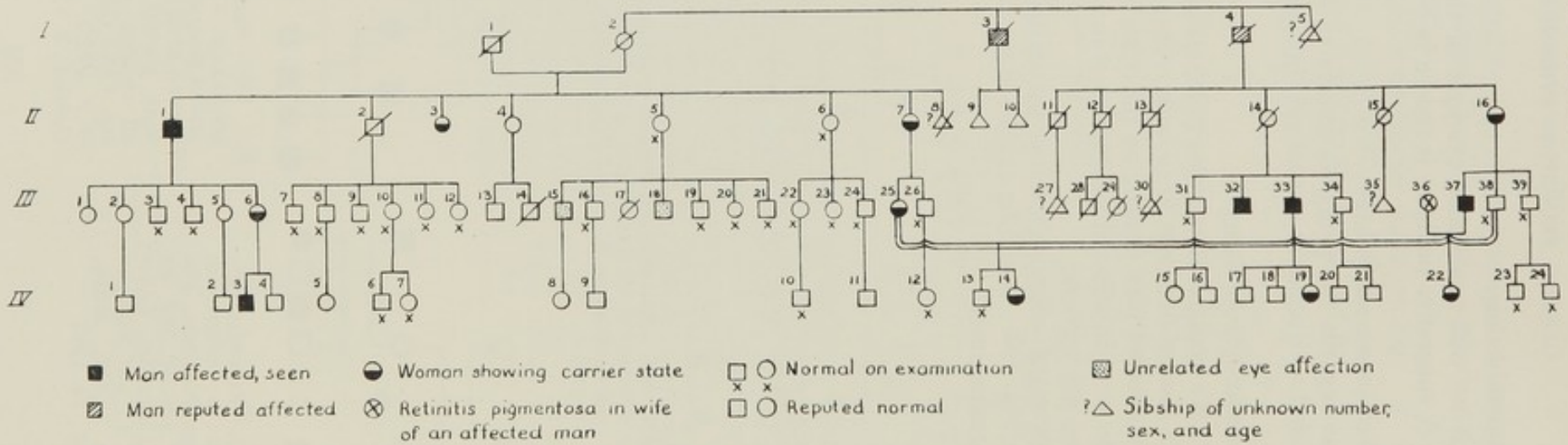


FIG. 189.—Intermediate sex-linkage; a pedigree of choroideraemia. Males show the full affection, whilst women show characteristic non-pathological fundus lesions indicative of the carrier state. (*After Sorsby, A., Franceschetti, A., Joseph, R., and Davey, J. B.* (*1952*). *Brit. J. Ophthal.*, **36**, 547.)

Penetrance

The statistical concept of penetrance applied to a single family explains irregularly dominant pedigrees. Figs. 195 and 196 are illustrative. Isolated pedigrees merge of course on those illustrative of variable expression, as it is always possible that some minimal manifestation of the anomaly, or of a non-pathogenic pleiotropic effect of the gene, may have been overlooked.

Expression; sex limitation

Figs. 197, 198 and 199 illustrate a wide range of expression in a dominant affection. Fig. 200 illustrates partial expression in a pleiotropic gene responsible for the recessively inherited Laurence-Moon-Biedl syndrome, whilst Fig. 201 shows similar features for the dominantly inherited arachnodactyly. The Laurence-Moon-Biedl syndrome also illustrates sex-limitation, for there is a considerable male excess.

Multiple allelomorphs

The pedigrees of colour-blindness contain examples illustrative of multiple allelomorphs. In a pedigree of Wolfflin the daughter of a deuteranope married a deuteranomalous man. Their daughter showed deuteranomaly. Apparently she received from her father an X chromosome carrying deuteranomaly and from her

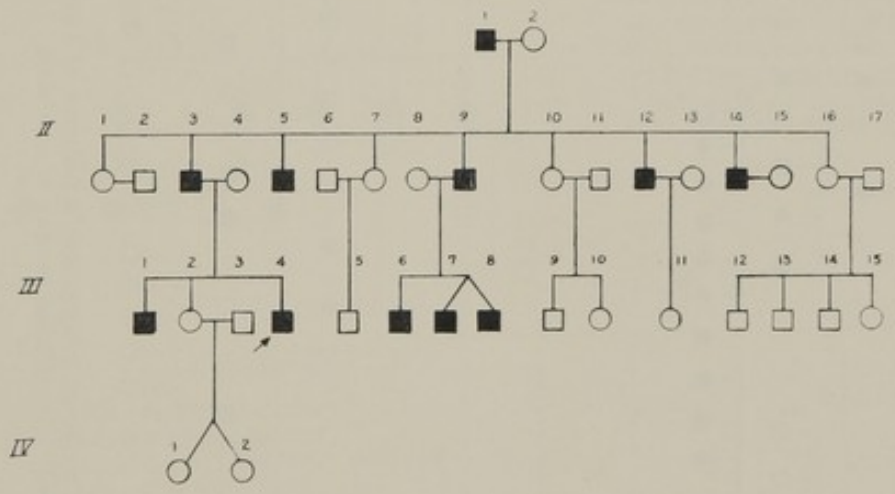


FIG. 190.—Y-chromosomal inheritance; a unique pedigree of colour defect. (*After Reed, S. C., Cambier, R. K., and Applen, J. E. (1951). Amer. J. hum. Genet.* **3**, 282.)

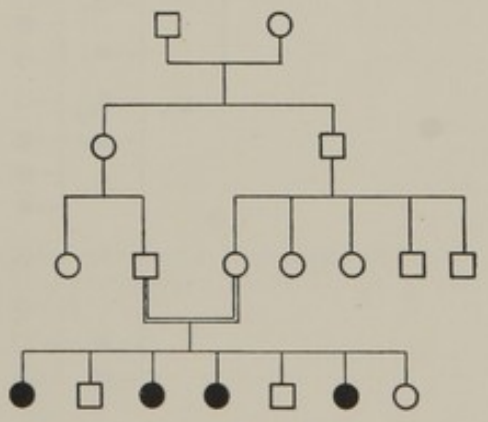


FIG. 191.—Presumed recessive partial sex-linkage; a pedigree of total colour-blindness. The sons should all be normal and 50 per cent of the daughters should be affected on theoretical expectations. By itself the pedigree is inconclusive. (*After Komai from Haldane, J. B. S. (1940). New Paths in Genetics. London; Allen and Unwin.*)

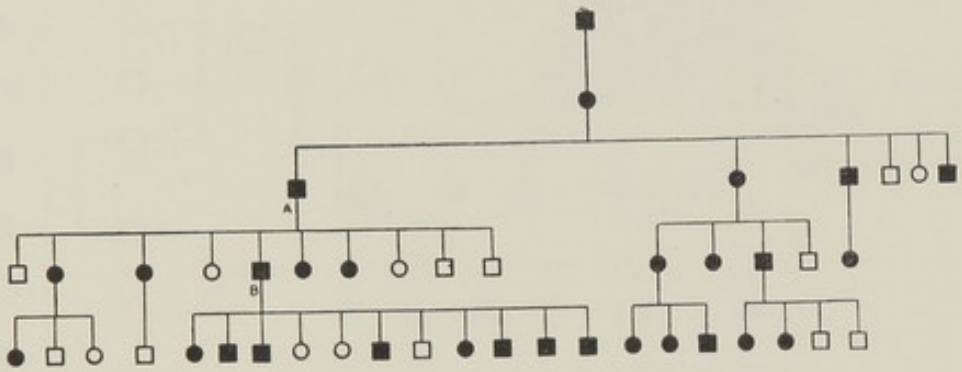


FIG. 192.—Presumed dominant partial sex-linkage; a pedigree of reitiniter pigmentosa. Haldane assumes dominant partial sex-linkage. If the affected man in the first generation carried the dominant gene on his X chromosome he could have only affected daughters. Such daughters in turn could contribute their abnormal X chromosomes to either sons or daughters. The man marked A in the third generation would again transmit it to all his daughters and to none of his sons. Actually, two of his daughters are unaffected, and one son is affected. This can be explained on three cross-overs occurring in this generation. The affected son B in the fourth generation now carries the pathogenic gene on his Y chromosome and would therefore transmit the affection to his sons only. Actually, one of his sons is normal and two of his daughters are affected. This, too, could have occurred as the result of cross-over. (*After Snell, S. (1903). Trans. Ophthal. Soc., U.K.*, **23**, 68.)

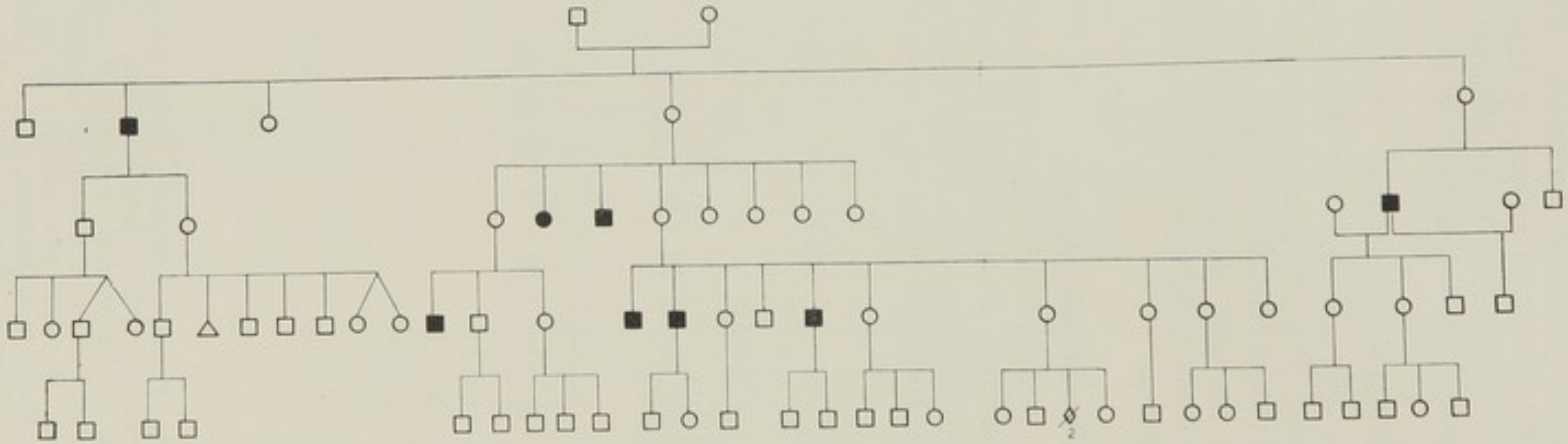


FIG. 193.—An unexplained mode of inheritance; a pedigree of Leber's disease showing affected sons of unaffected women whose brothers are affected. An affected woman is also seen. (*After Usher, C. H. (1927). Brit. J. Ophthal.*, **11**, 417.)

mother an X chromosome carrying deuteranopia. On the assumption that the two genes are allelomorphs, deuteranomaly is dominant over deuteranopia. Similar relationships have been established between protanomaly and protanopia. The different forms of dichromatism appear to be caused by different genes on the X chromosome, and the different degrees of a particular form of dichromatism are determined by alleles. The order of relative dominance of these alleles in formula:

Normal > deuteranomaly > deuteranopia
Normal > protanomaly > protanopia

In nystagmus recessive sex-linkage is the common mode of inheritance (Fig. 202), but some pedigrees suggest dominance (Fig. 203). It is, however, possible that one and the same gene with alleles which are either recessive or dominant are responsible, and that the counterpart for the occasional manifestation in women in recessive sex-linkage is met in dominant sex-linkage by suppression of the manifestation in some one-third to one-half of the women carrying the gene.

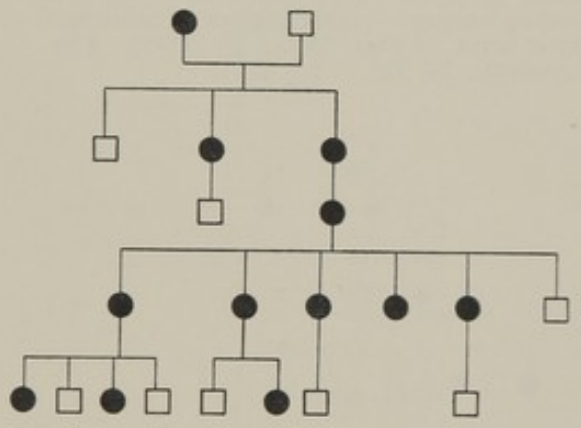


FIG. 194.—Direct transmission through women only; a pedigree of colour-blindness. The normal mechanism of sex chromosomal inheritance does not explain this mode of inheritance. Theoretically, it can be explained by the assumption of non-disjunction of XX chromosomes. (*After Cunier, F. (1839)* in *Treasury of Human Inheritance (1933). Ed. by Pearson, K., Vol.* 2 (*by Julia Bell*). *London; Cambridge University Press.*)

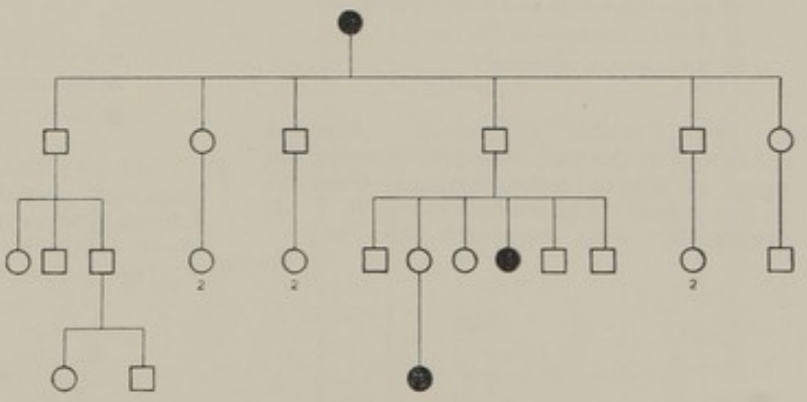


FIG. 195.—Irregular dominance; a pedigree of epicanthus. (*After Usher, C. H. (1935). Biometrika*, **27**, 24.)

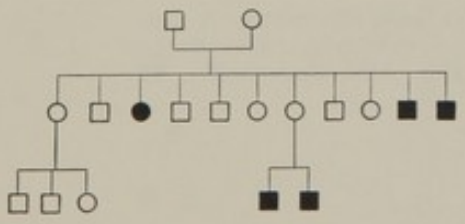


FIG. 196.—Irregular dominance; a pedigree of retinoblastoma. (*After Purtscher, O. (1915). Zbl. prakt. Augenheilk.*, **39**, 193.)

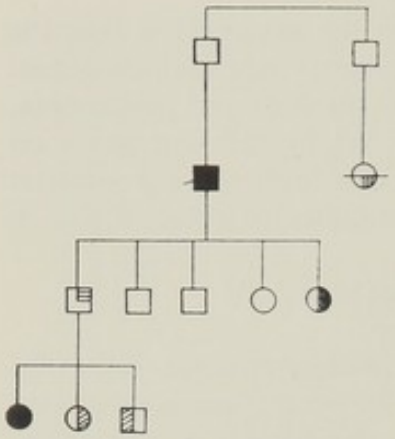


FIG. 197.—Variable expression. Pedigree of a family showing anomalies extending from coloboma of the iris and of the lens microphthalmos. (*After Sebz, E. (1900). Eine Colobom-Familie. Jena Thesis. Modified from Fleischer, B. (1938). In Handbuch der Erbrankheiten, Ed. by Gütt, A. Vol. 5, p. 13. Leipzig; Thieme.*)

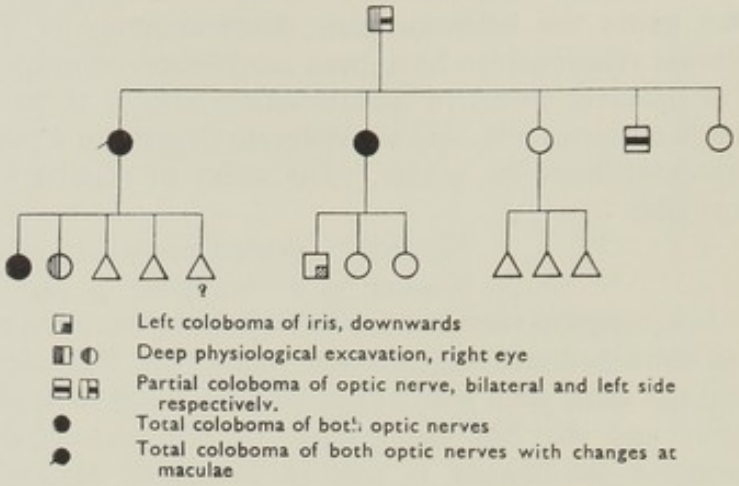


FIG. 198.—Variable expression. Pedigree of a family, one member of which shows coloboma of the iris and the other members various degrees of coloboma of the optic nerve. (*After Weyert, F. (1890). Klin. Mbl. Augenheilk.*, **28**, 325.)

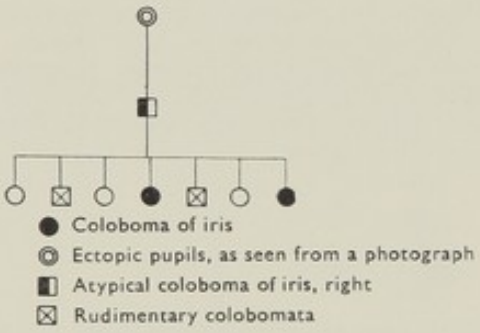


FIG. 199.—Variable expression. Atypical coloboma of the iris. Pedigree showing the range of defects—some minimal—observed in one family. (*After Halbertsma, K. T. A. (1928). Klin. Mbl. Augenheilk.*, **80**, 794.)

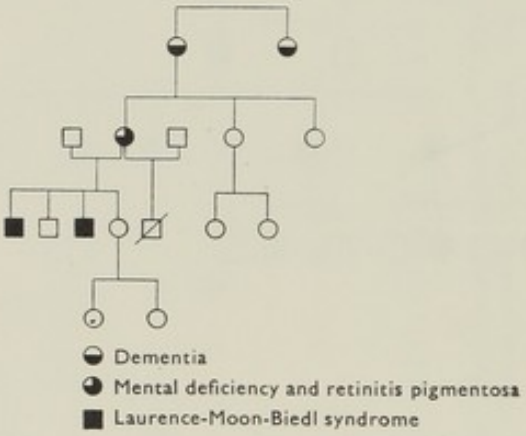


FIG. 200.—Variable expression. A pedigree showing partial manifestation of the Laurence-Moon-Biedl syndrome in ascendants. (*After van Bogaert, L., and Borremans, P. (1936). Ann. Med. (Paris)*, **39**, 54.)

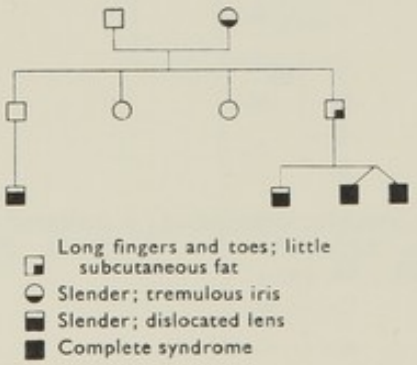


FIG. 201.—Variable expression. A pedigree of arachnodactyly. (*After Becker (1935). Klin. Mbl. Augenheilk.*, **95**, 547.)

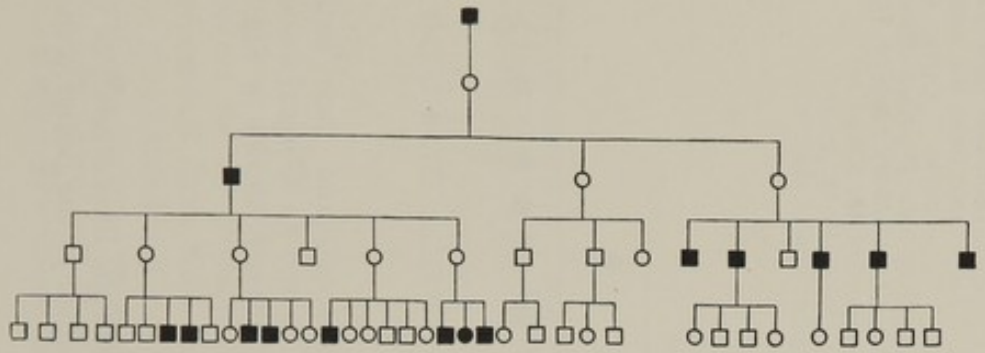


FIG. 202.—Possible allelomorphs; Nystagmus. Pedigree showing recessive sex-linked inheritance with manifestation in one woman. (*After Hemmes, G. D. (1924). Over hereditairens nystagmus. Utrecht; Thesis, Pedigree LL.*)

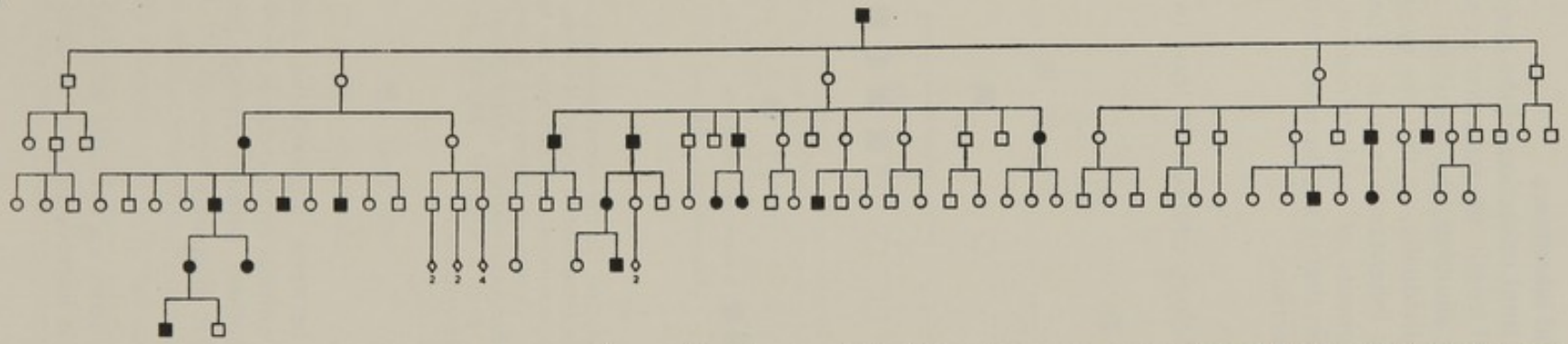


FIG. 203.—Possible allelomorphs; Nystagmus. A pedigree of dominant sex-linked inheritance with suppression of the manifestation in some one-third to one-half of the woman carrying the gene. It is suggested that the gene for dominant sex-linked nystagmus illustrated in this pedigree is an allele to that giving recessive sex-linked inheritance as shown in Fig. 202. (*After Niccol, W. (1915). Ophthalmoscope*, **13**, 224.)

Multifactorial inheritance

Since the total refraction of the eye is determined by a number of components such as axial length, the refractive power of the cornea and lens and the depth of the anterior chamber, the possibility arises that these different components are inherited individually, so that the eye would present a fruitful field for the study of polygenic inheritance in man. There is, however, the possibility that one of these components of total refraction may determine the others. Preliminary results suggest that this is the case and that axial length is the inherited determinant of total refraction.

Mutation

Ophthalmology contains at least two good examples of mutation (Figs. 204 and 205).

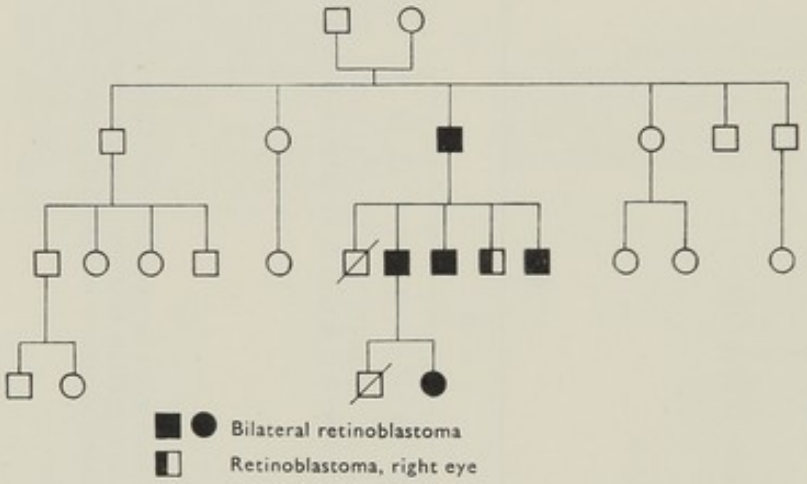
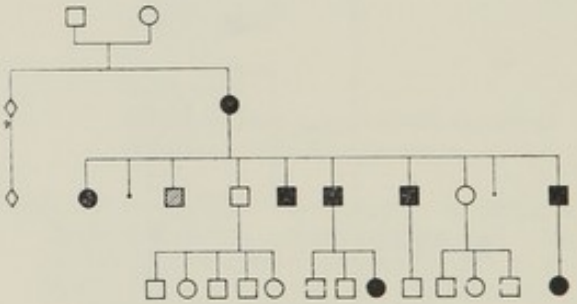


FIG. 204.—Mutation. In the second generation there is an isolated occurrence of retinal glioma, presumably due to fresh mutation. Dominant inheritance is seen from the subsequent course. (*After Griffith, A. D., and Sorsby, A. (1944). Brit. J. Ophthal.*, **28**, 279.)

FIG. 205.—Mutation. In the second generation there is an isolated case of apical dystrophy with macular coloboma, presumably due to a mutation. Dominant inheritance is seen from the subsequent course. (*After Sorsby, A. (1935). Brit. J. Ophthal.*, **19**, 65, *and subsequent observation.*)



Linkage

Linkage between haemophilia and colour-blindness, and their individual separation (without cross-over) is shown in Fig. 206*a* and *b*. Clinical association of three affections without linkage between three genes is shown in Fig. 12 on page 68 and is discussed there.

Cross-over

Fig. 207 shows an example of cross-over between the linked genes of colour-blindness and haemophilia; cross-over is also assumed in the pedigree shown in Fig. 192.

Phenocopies

Ophthalmology is particularly rich in examples illustrative of the concept of phenocopies, and is likely to help in clarifying this concept.

Phenocopies based on genetic identity.—This is exemplified by uniovular twins with albinism, an example is shown in Fig. 69.

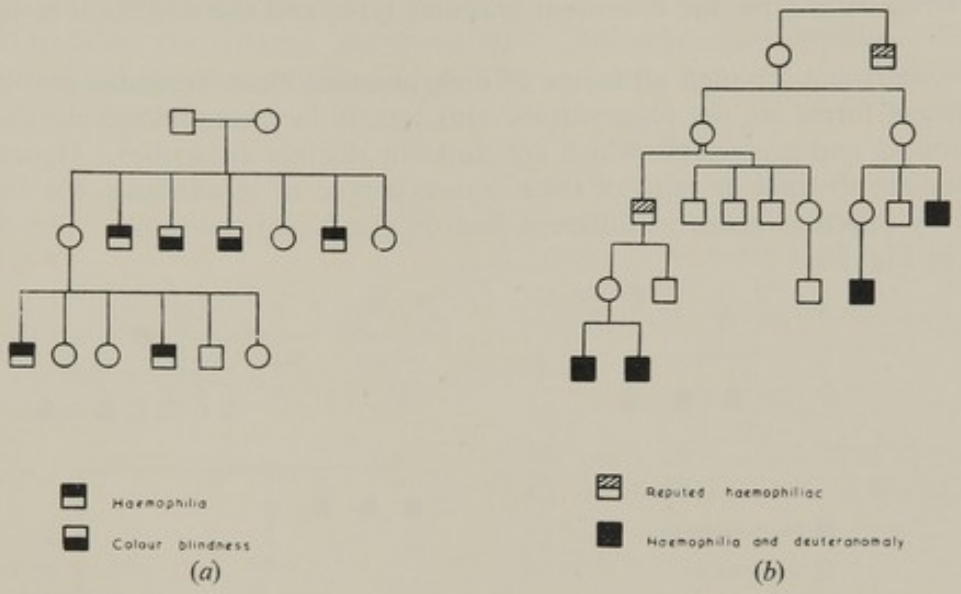


FIG. 206.—Linked genes. Inheritance of colour defect and haemophilia both carried on the X chromosome. (*a*) The genes were carried separately on the two X chromosomes. (*After Green, C. V., in Davenport, C. B. (1930). J. Genet.*, **15**, 401.) (*b*) The genes were carried on the same X chromosome. (*After Bell, J., and Haldane, J. B. S. (1937). Proc. R. Soc. (B).*, **123**, 119.)

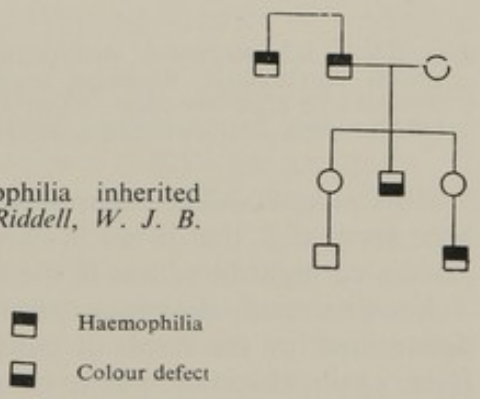


FIG. 207.—Cross-over. Colour defect and haemophilia inherited separately; cross-over in a female carrier. (*After Riddell, W. J. B. (1946). Ann. Eugen.*, **13**, 30.)

Genetically determined phenocopies without genetic identity.—Retinitis pigmentosa occurs as an autosomal dominant or recessive; it also occurs in an X-chromosomal form both with recessive and intermediate inheritance. It is possible that there are also dominant and recessive partially sex-linked forms. Whether these different types are all true phenocopies, or carry merely superficial resemblances, is not yet definitely established. The macular dystrophies are a further example of multiple modes of inheritance. Here, too, both modes of

inheritance and clinical similarities have still to be differentiated. Clear differentiation has been achieved in several affections.

The corneal dystrophies.—The confused mass of corneal dystrophies when once sorted out into recessive and dominant autosomal types brought out clearly three distinct forms with a different clinical course and different prognosis: the recessive macular type, the dominant granular type, and the dominant lattice-like type.

Dichromatism.—Though all forms of dichromatism show recessive sex-linkage, the different forms are not phenocopies; this was, in fact, established clinically for deuteranopia and protanopia which are clinically distinct anomalies. Genetically, too, they are distinct in spite of their common type of inheritance, for they are carried by different genes in different loci on the X chromosome. This is well shown in Fig. 208.

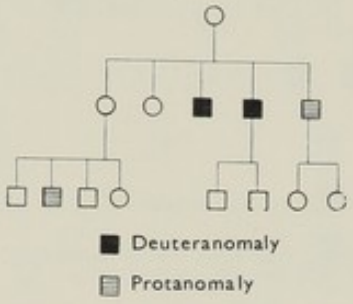


FIG. 208.—Lack of genetic identity in clinically similar conditions. Deuteranomaly and protanomaly transmitted independently by a woman carrier of both genes. (*After Brunner, W. (1930). Arch. Ophthal.*, **124**, 1.)

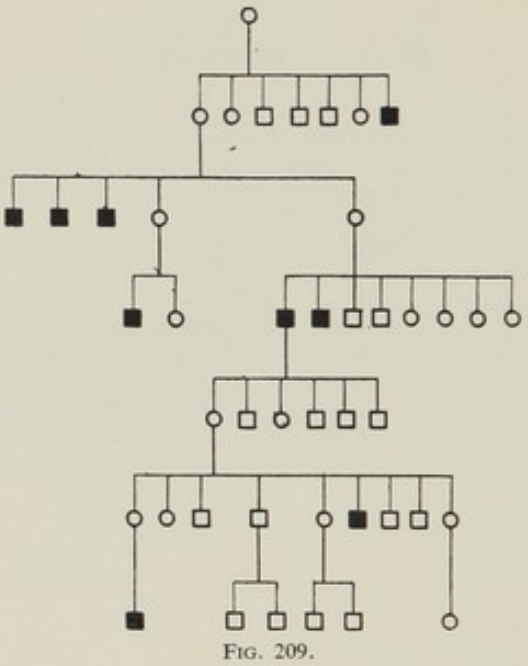


FIG. 209.

FIG. 209.—Lack of genetic identity in clinically similar conditions. Recessive sex-linkage in myopia with night-blindness. (*After Kleiner, W. (1923). Arch. Rass.-u. GesBiol.*, **15**, H.1.)

High myopia.—The separation of high myopia determined by an autosomal gene from that due to an X-chromosomal gene (Fig. 209) has emphasized the associated night-blindness in the latter type.

Non-genetically determined phenocopies.—Congenital cataract may be genetically determined, or the result of maternal rubella, or other environmental affection. Here, again, elucidation as to possible minor differences still requires much work. Buphthalmos, " holes " at the maculae, retinitis pigmentosa (Fig. 210), optic atrophy, the fundus lesions in generalized fundus dystrophy, are all examples of clinical appearances which are met both as genetically determined anomalies and as anomalies of environmental origin.

Transient pheno-differences with genetic identity

The concept of expression emphasizes that one and the same gene may give a different manifestation in different individuals possessing that gene, and it is assumed that the total genetic constitution acts as a modifying influence producing somewhat different clinical pictures. In contrast to this there are the different

clinical pictures seen during the course of an abiotrophic affection; these intermediate stages often bear no similarity to each other and are not readily recognized as different stages of one and the same process. The range of fundus appearances seen in generalized fundus dystrophy (Plate I, opposite page 3) is illustrative. Another example is seen in congenital cystic detachment. It is thus that two patients showing two different stages of one and the same affection, which had not yet run its full course, show markedly different manifestations—transient pheno-differences which will lead to an identical end-stage.

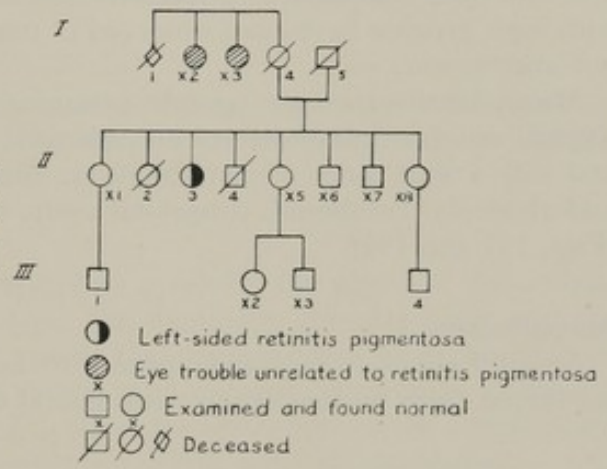


FIG. 210.—Pedigree chart in a case of unilateral retinitis pigmentosa. There is nothing to suggest a genetic character. (*After Joseph, R. (1951). Brit. J. Ophthal.*, **35**, 98.)

OCULAR AFFECTIONS OF UNCERTAIN STATUS

As long as genetic studies were confined to affections that were faithfully duplicated in different members of a family, the significance of heredity in eye disease appeared limited. Now that more complicated modes of inheritance than the simple autosomal recessives and dominants, and the significance of modifying factors, are clearly appreciated it is becoming clear that hereditary factors play a far greater part in pathology than was at one time suspected. Excluding affections of obvious environmental origin, such as the infectious diseases of the eye, there is hardly a condition in ophthalmology that does not require genetic study. It is not unlikely that heredity plays a considerable part in a mass of " degenerative " conditions seen in the eye—cataract, fundus lesions of the elderly, glaucoma, and in many ill-defined corneal affections. As the established knowledge on retinoblastoma shows, even tumour formation in the eye requires such investigations. The inflammatory affections which have yielded such poor return in the intensive studies on possible causative environmental factors are likewise not beyond genetic analysis. Iritis may as readily have genetic implications as rheumatoid arthritis, with which it is closely associated clinically and pathologically, has been proved to possess.

THE RECOGNIZED GENETIC ANOMALIES

Many generalized disorders have important ocular components, constant in some affections and inconstant in others. These affections are discussed elsewhere in the text. The eye is, however, also the seat of many hereditary disorders of an apparently purely local character of which the following are the more significant.

THE GLOBE AS A WHOLE

Microphthalmos

Pure microphthalmos.—Here there are no associated defects. Vision is generally defective, possibly owing to aplasia of the macula. The eyes are usually highly hypermetropic. Dental anomalies in the form of small or absent incisors have been observed. The mode of inheritance is uncertain, but is probably recessive.

Microphthalmos with other lesions.—Cataract is common in microphthalmic eyes and both dominant and recessive inheritance probably occur. Ectopic pupils with high myopia have been observed in one family. Other ocular anomalies are not uncommon.

Microphthalmos as an extreme variant of the typical colobomatous defects.—Typical colobomatous defects are inherited in an irregularly dominant manner, and with a wide range of manifestation: minimal coloboma of the iris, typical iris and choroidal coloboma, congenital cystic eye and anophthalmos may all occur (Figs. 197 and 198).

Anophthalmos

Anophthalmos is rare and appears to be recessive. It probably occurs in a sex-linked form in association with mental deficiency.

The glaucoma affections

Buphthalmos.—Most cases are sporadic but, excluding secondary buphthalmos, are probably genetically determined. The mode of inheritance is probably recessive. There is some suggestion that it may occasionally be dominant.

Glaucoma.—Inheritance is regularly dominant in most cases. Irregular dominance has been recorded, but it is likely that minimal glaucoma was overlooked in such families. There is also evidence for a recessive mode of inheritance. Anticipation and the existence of juvenile glaucoma as a distinct clinical type have been claimed in some pedigrees, but there is little to support these assumptions.

Refraction and its aberrations

Whether total refraction is determined polygenically is still uncertain. Extremes of corneal refraction are probably inherited in a dominant manner.

Anomalies of ocular movement

The extra-ocular muscles.—Dominant inheritance would appear to apply to ptosis with epicanthus, and to the different types of external ophthalmoplegia (isolated ptosis, ptosis with ophthalmoplegia, external ophthalmoplegia, and isolated palsies of individual muscles). External ophthalmoplegia with ptosis is seen both as congenital and adult types.

Concomitant squint.—Accepting the muscle imbalances as latent form of squint, dominant inheritance appears to apply to both convergent and divergent concomitant squint.

Nystagmus.—It has already been indicated that recessive sex-linked nystagmus and the apparently irregularly dominant nystagmus are determined by pathogenic

allelomorphs of the same gene (Figs. 202 and 203). It is likely that the recessive sex-linked form of nystagmus is the same affection as recessive sex-linked ocular albinism—a different aspect of the same entity being stressed by the two names.

THE CORNEA

Abnormalities in size and curvature

Microcornea, cornea plana and keratoconus—if in the latter, high degrees of corneal astigmatism are included—are all dominantly inherited.

Abnormalities in transparency

The concept of embryotoxon has proved useful in covering a wide range of congenital opacities of the cornea. The affection is probably recessive, whilst vortex-like veil is probably dominant.

The dystrophies of the cornea

The classification of the corneal dystrophies involving the whole of the corneal structure into the recessive macular type, the dominant granular type, and the dominant lattice-like type, has helped greatly the diagnosis and prognosis of these affections, but it is unlikely to prove valid for all corneal dystrophies. Some of these dystrophies appear to be confined to either the epithelium or the endothelium of the cornea, and the modes of inheritance are still not well established.

THE LENS

Anomalies in site and shape

Subluxation of the lens.—Both the congenital and the delayed forms of subluxation and luxation of the lens are dominant. Recessive inheritance has been recorded for congenital subluxation with ectopic pupils.

Cataract

Congenital cataract.—The many different forms of congenital cataract are generally inherited in a dominant manner. Recessive inheritance may, however, occur.

Postnatal cataract.—Coronary cataract, pre-senile cataract of the adult nucleus, and senile cataract are all generally inherited dominantly. Whether " senile " cataract is always genetically determined in unknown.

In some families different clinical types of cataract have been observed. To what extent they are evolutionary stages of one and the same fundamental affection is as yet unknown.

THE UVEAL TRACT

The iris

Aniridia

This is regularly dominant with variable expression, ranging from rudimentary atypical coloboma to gross malformation of the eye owing to secondary buphthalmos.

Anomalies in iris structure

The many varieties of anomalies in iris structure—including flocculi iridis—all appear to be inherited in a dominant manner (Fig. 199). One variety of hypoplasia of the iris, complicated by glaucoma, is known as a sex-linked affection.

The choroid

Congenital defects

Macular coloboma.—Macular coloboma occurring as an isolated anomaly, or in association with apical dystrophy of the hands and feet, is inherited in a regularly dominant manner (Fig. 205).

Abiotrophic defects

Choroideraemia.—This is an outstanding example of intermediate sex-linked inheritance (Fig. 189).

Choroidal sclerosis.—The modes of inheritance of both generalized and central choroidal sclerosis are still uncertain. Both probably show dominant and recessive forms, the usual mode of inheritance being dominant for the first type and recessive for the second.

Neoplasms.—Exceptionally, sarcoma of the choroid has been observed as a dominant affection.

THE RETINA

Congenital anomalies

Opaque nerve fibres and *Best's disease* are both inherited dominantly. In opaque nerve fibres the condition may be manifest in one eye only, and yet be transmitted to the eyes of offspring. *Cysts at the macula* are probably congenital in origin and become " holes at the macula " when they burst. Inheritance is probably dominant. *Congenital stationary night-blindness* (Fig. 179) is dominantly inherited, whilst *night-blindness with myopia* (Fig. 209) appears to have both a recessive sex-linked form and a recessive autosomal form. *Monochromatism* is generally recessive whilst the different varieties of *dichromatism* (Figs. 184–188) show recessive sex-linkage, deuteranomaly, protanomaly and tritanomaly, being conditioned by a different gene (Fig. 208); the different grades of severity within each group are determined by allelomorphs. *Congenital sex-linked detachment* is probably one of the varieties of pseudoglioma, whilst milder phases of the affection are represented by vitreous veils, and possibly also falciform detachment of the retina.

Abiotrophies

The retinitis pigmentosa group.—Taken as a group recessive inheritance is commonest, some forms being conditioned by autosomal genes, others by X-chromosomal genes. Clinically the recessive sex-linked form can be distinguished from the intermediate sex-linked form by the characteristic fundus shown by the female carriers in the intermediate type. That there are possibly also recessive and dominant partial sex-linked (Figs. 191 and 192) forms has already been indicated. It is likely that the autosomal recessive and dominant types represent a number of distinct clinical entities, for in some families, with either dominant or recessive retinitis pigmentosa, cataract is a constant association and is totally

lacking in other families; in some families glaucoma, ophthalmoplegia, or macular dystrophy occurs; the affection also occurs in mild or severe forms both in the recessive and dominant types. As yet the different autosomal forms have not been sorted out either clinically or genetically. Unilateral retinitis pigmentosa represents either a somatic mutation or an environmental effect (Fig. 210).

The macular dystrophies.—A recessive sex-linked form with colour-blindness has been isolated; whilst amongst the autosomal forms, dominant and recessive types are recognized genetically, and juvenile and adult forms clinically. The composite character of the group is also indicated by the fact that in some families the reaction is atrophic, in others exudative.

Generalized fundus dystrophy.—This dominant affection with onset at about the age of forty years illustrates well the evolutionary course of an abiotrophic affection, giving at different stages clinical pictures reminiscent of various environmental affections (*see* Plate I opposite page 3).

Tumours

Retinoblastoma is a dominantly inherited tumour (Figs. 196 and 204). Most cases are sporadic and probably represent fresh mutations.

THE OPTIC NERVE

Optic nerve

Leber's disease is the classical example of hereditary optic atrophy, and the mode of inheritance, though well established, is not readily explicable on current genetic theory (Fig. 193). Accessory factors have been postulated, but none of the postulates is very satisfying. The literature is perhaps unduly complicated, for cases of congenital optic atrophy—both of the dominant and recessive type—have been included. The status of hereditary optic atrophy seen in Japan is not clear.

Congenital anomalies of the optic disc

There is evidence of a genetic factor in pseudo-papilloedema, Drusen, epipapillary membrane, crater-like hole in the disc, and megalopapilla.

OTHER TISSUES

Lids

Epicanthus (Fig. 195) appears to be inherited in a regularly dominant manner. Genetic factors have been observed in blepharochalasis, elephantiasis, spasm of the lids, ankyloblepharon and other anomalies, including anomalies of the lashes.

Lacrimal apparatus

There is evidence for dominant inheritance of chronic dacryocystitis; whether congenital lacrimal obstruction is genetically related to chronic dacryocystitis is still uncertain.

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CHAPTER 19

II.—THE EAR

HARALD LINDENOV

OUTER EAR

Malformations

THE normal external ear may vary in form, size and structure, and as these variations are markedly hereditary, the external ear plays an important role in anthropological investigations. The borderline between variations and malformations, however, is vague.

Hypertrichosis of the auricle

Pronounced growth of hair on the auricles (*hypertrichosis auricularum*) is a conspicuous anomaly, the hereditary occurrence of which has been observed by

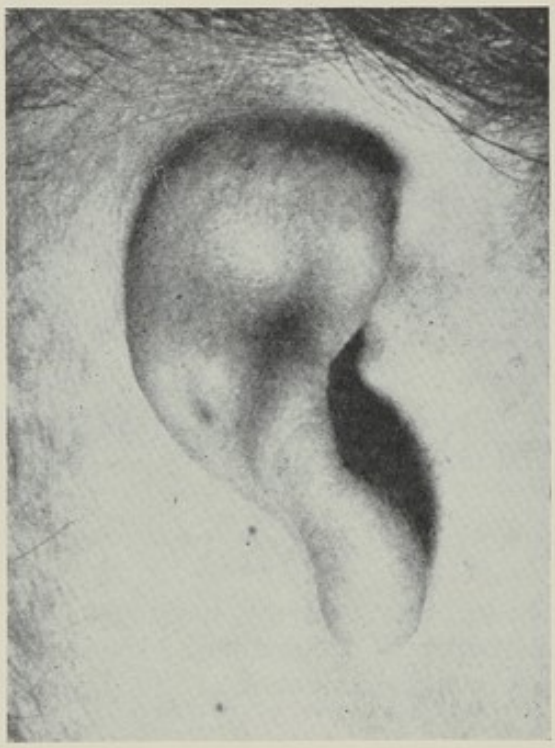


FIG. 211.—" Cat's ear " in Case V-14 of pedigree shown in Fig. 212. (*After Potter, E. L. (1937). J. Hered.*, **28**, 257.)

Tommasi (1907) in one family. In the affected members of this family, at the age of 18–19 years, a dense growth of long black hairs commenced to appear on the auricles, covering the anterior surface and the lower part of the posterior surface. In five generations all the men, a total of 11, were affected but none of the women. The anomaly is apparently transmitted by the Y chromosome, though there is the possibility that it is a dominant sex-limited characteristic.

Cat's ear

A deformity of the auricle, called "cat's ear" (Fig. 211), has been recorded as dominant by Potter (1937) (Fig. 212). The auricles were diminished in size and inverted so that their upper parts were cup-shaped, and the lobule projected rectangularly from the head.

This anomaly has been observed in combination with ptosis of the eyelids.

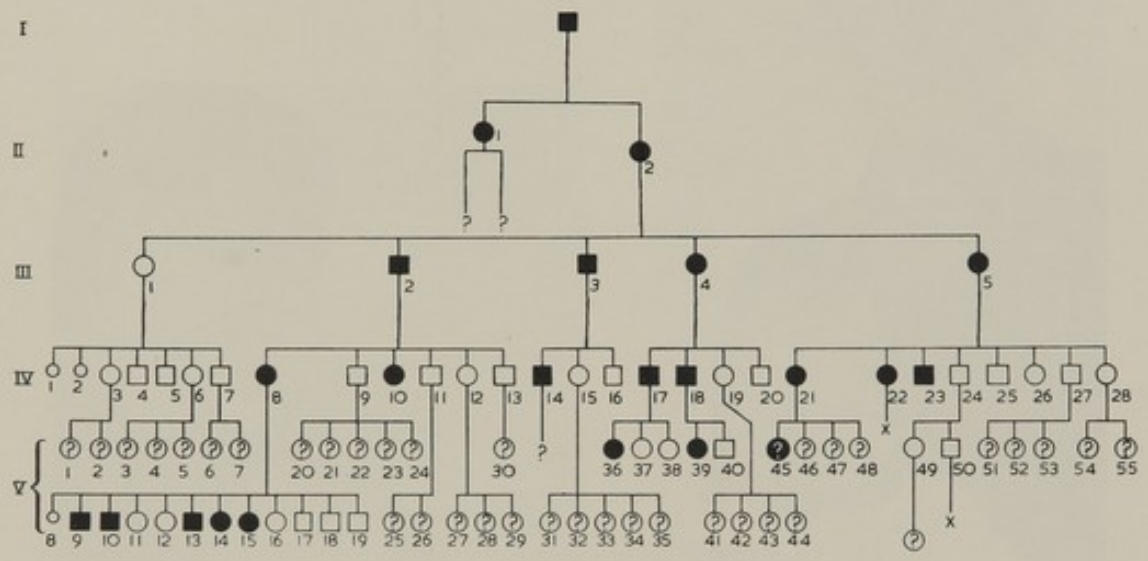


FIG. 212.—Pedigree of a family presenting "cat's ear". Simple dominant inheritance. (*After Potter, E. L. (1937). J. Hered.*, **28**, 257.)

Small ears

In "small ears" (*microtia*) (Fig. 213) the auricle is diminished in size, poorly defined in outline, and appearing as if folded on the concha. All degrees of this anomaly have been found—even absence of the auricle (*anotia*). Generally this deformity occurs together with occlusion of the meatus, with or without other malformations.

The few records available suggest that the anomaly is dominant (Fig. 214)—perhaps irregularly so—or possibly sex-linked.

Auricular appendages

Clinical aspects.—Auricular appendages (*naevi auriculares*) (Fig. 215) are roundish tumour formations with a broad or narrow base, varying in size from a pin-head to a thimble, as a rule located just anteriorly to the auricle, rarely on the auricle itself or behind it. In front of the ear these structures are often located at the level of the crus of the helix, sometimes in front of the tragus or lobule, sometimes along a line drawn from the opening of the external auditory meatus to the corner of the mouth. The overlying skin is normal. The consistency of the appendage is usually soft, but not infrequently palpation conveys the impression of a more firm structure in the depth. This is due to the fact that the appendages as a rule contain a demonstrable nucleus of cartilage.

These appendages are more often unilateral than bilateral, and they are equally frequent on the two sides. They are multiple more often than solitary, and in the

FIG. 213.—Microtia in base VI-12, and her son, VII-22 in pedigree shown in Fig. 214. (*After Hanhart, E. (1949). Arch. J. Klaus-Stift.*, **24**, 378.)

former condition they usually vary in size and are in rows or irregular, less frequently in clusters.

These structures are congenital, and after birth they may increase somewhat in size, but then they become stationary, without showing any tendency to malignant degeneration. They may also be combined with other malformations as, for instance, auricular deformity, atresia of the meatus, congenital fistulae and even more pronounced degrees of malformation. Auricular appendages are due to branchiogenic developmental disturbances (Aschoff, 1936), and sometimes they have a similarity to rudimentary auricles, so that their presence occasionally has caused a condition called polyotia. True polyotia, however, is very rare.

Heredity.—Familial occurrence of unilateral auricular appendages was first described by Thomson (1874) and of bilateral auricular appendages by Siemens (1921). Jenkins (1928) regards the inheritance to be recessive, and Brander (1939) to be dominant (Fig. 216). Twin studies have shown concordance as well as discordance.

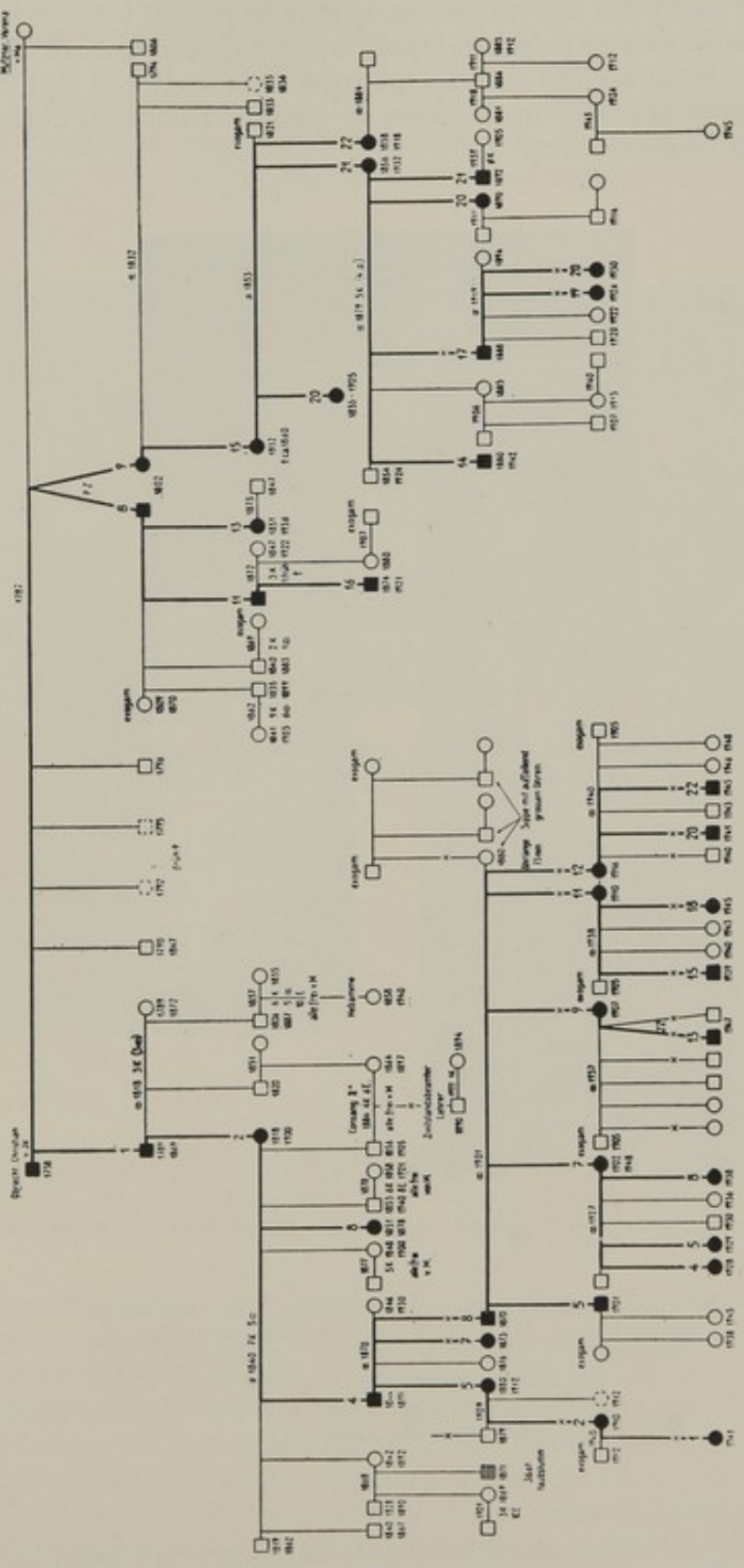


FIG. 214.—Uncomplicated microtia, regular dominance in seven generations. (*After Hanhart, E. (1949). Arch. J. Klaus-Stift.*, **24**, 376.)

It should be noted that this malformation may be present without being visible, being recognizable only by palpation; that auricular appendages are often removed surgically after birth, leaving a rather inconspicuous scar; and that the affection may often appear primarily in the form of a scar. Dominant inheritance may therefore easily be overlooked.

FIG. 215.—Auricular appendages in mother and daughter. (*After Brander, T. (1939). Acta dermat.-vernereol.*, **20**, 219.)

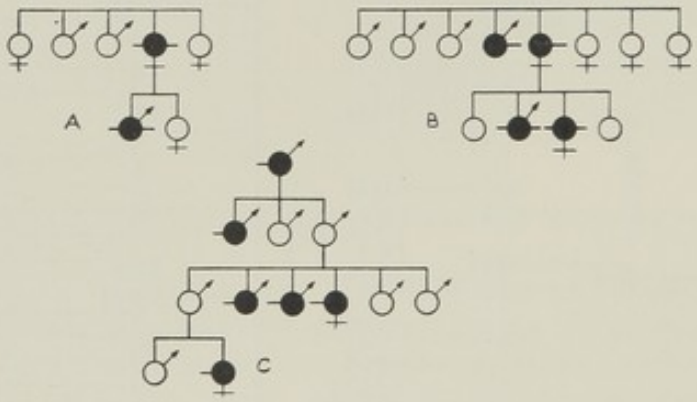
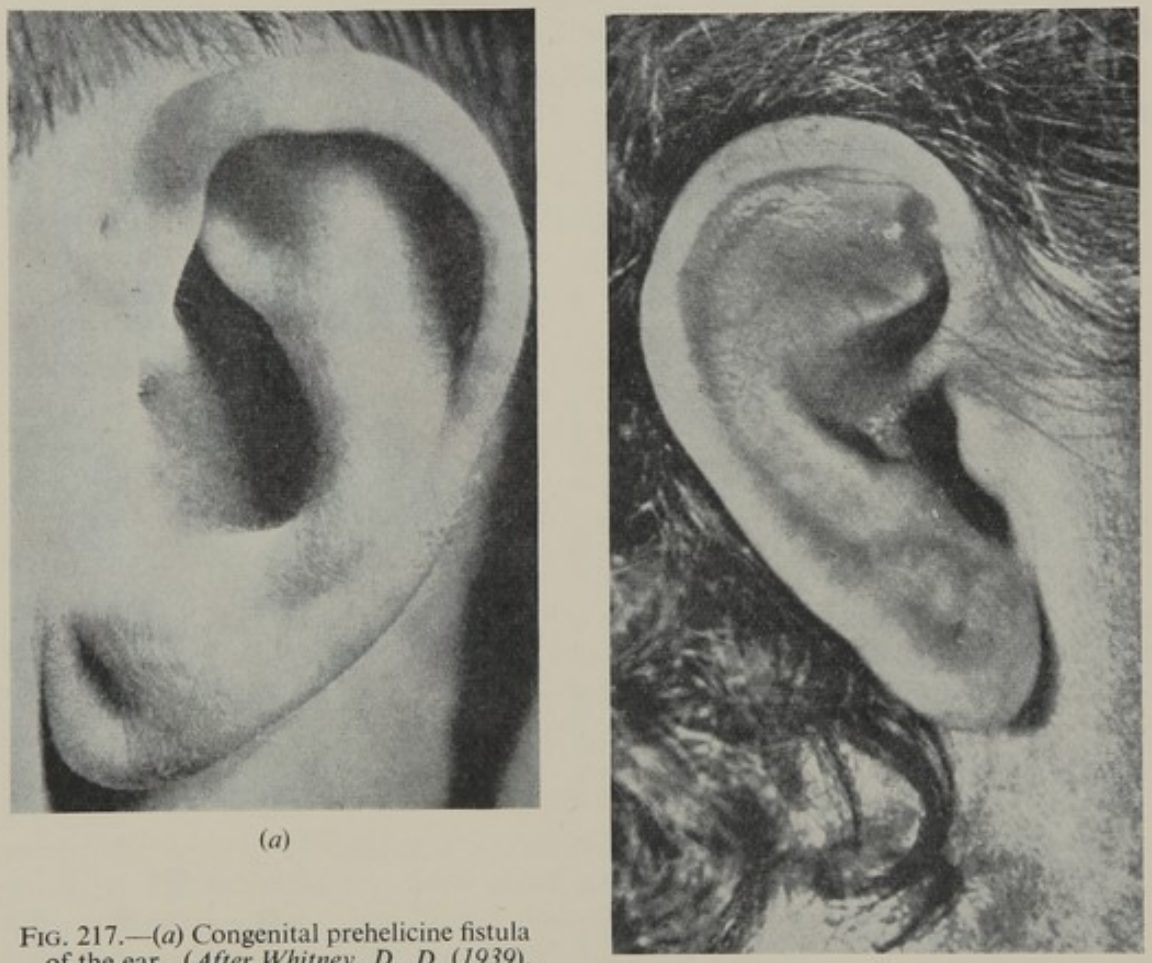


FIG. 216.—Pedigrees of families with auricular appendages; (*a*) after S. W. Siemens, (*b*) after T. Brander, and (*c*) after R. Jenkins. A horizontal line to the left designates left-sided, to the right, right-sided auricular appendages. (*After Brander, T. (1939). Acta dermat.-vernereol.*, **20**, 220.)

Congenital fistulae of the ear

Congenital ear fistula, of which solitary instances are rare, is an inconspicuous but markedly hereditary anomaly.

Clinical aspects.—The opening which is round, with a tendency to being oval, is usually about 1 millimetre in diameter, but it may be larger (up to 3 millimetres) or smaller, so as to be hardly visible. As a rule, it leads into a blind canal which usually is directed downwards, a little inwards and often a little forwards or backwards, varying in length from less than 1 to 10 millimetres, rarely more. Often, however, this canal is merely a superficial depression or a little pit of pin-head size.



(*a*) (*b*)

FIG. 217.—(*a*) Congenital prehelicine fistula of the ear. (*After Whitney, D. D. (1939). J. Hered.*, **30**, 323.) (*b*) Congenital fistula in the lobule. (*After Edmonds, H. W., and Keeler, C. E. (1940). J. Hered.*, **31**, 509.)

Usually the fistula is found about where the contour of the helix anteriorly merges with the skin of the face, sometimes just anteriorly to the tragus (Fig. 217*a*), it may occur on the helix when it is frequently in the middle of the lateral wall of the crus helicis, and only rarely in the cavum or cymba conchae (where it may be difficult to distinguish from a blackhead, though sometimes it can be recognized through the presence of a linear depression leading to the meatus). Finally, the fistula may be located in the middle of the lobule on the lateral as well as on the medial wall, or in both places, and here the opening of the fistula has a striking resemblance to the opening of the artefact holes for ear-rings (Fig. 217*b*).

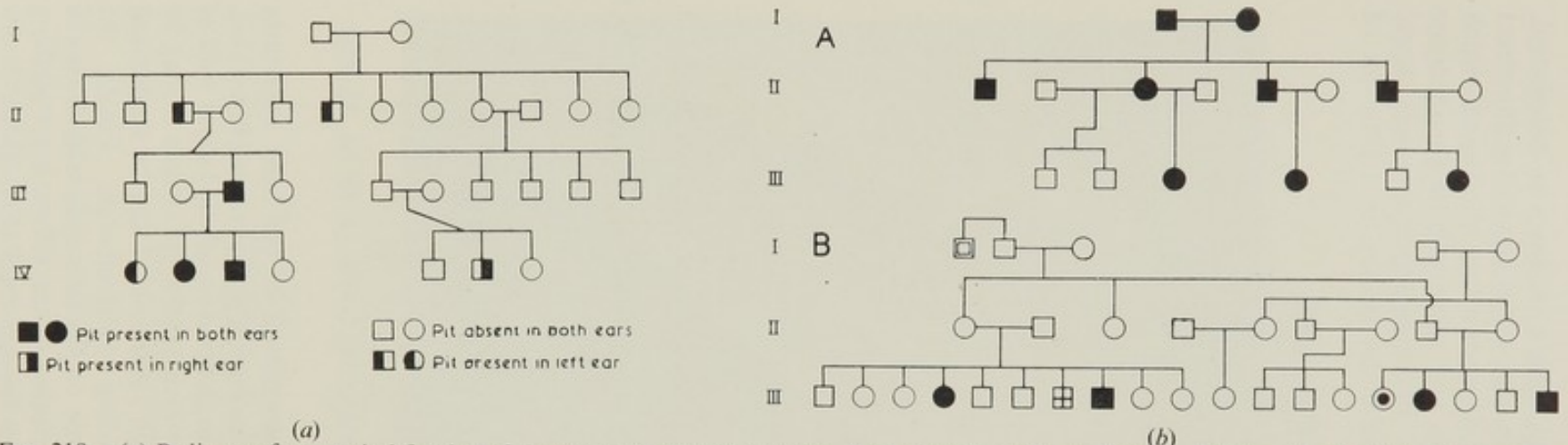


FIG. 218.—(*a*) Pedigree of congenital fistulae of the ear at the site of election. (*After Whitney, D. D. (1939). J. Hered.*, **30**, 324.) (*b*) Pedigree on occurrence of congenital fistulae in the lobule with variable localization. BI-1 and BIII-15 showed microtia of the right ear, the latter also atresia of the right meatus and a fistula in the area corresponding to the medial aspect of the right lobule. BIII-7 showed a small prehelicine sinus of the right ear. (*After Edmonds, H. W., and Keeler, C. E. (1940). J. Hered.*, **31**, 508.)

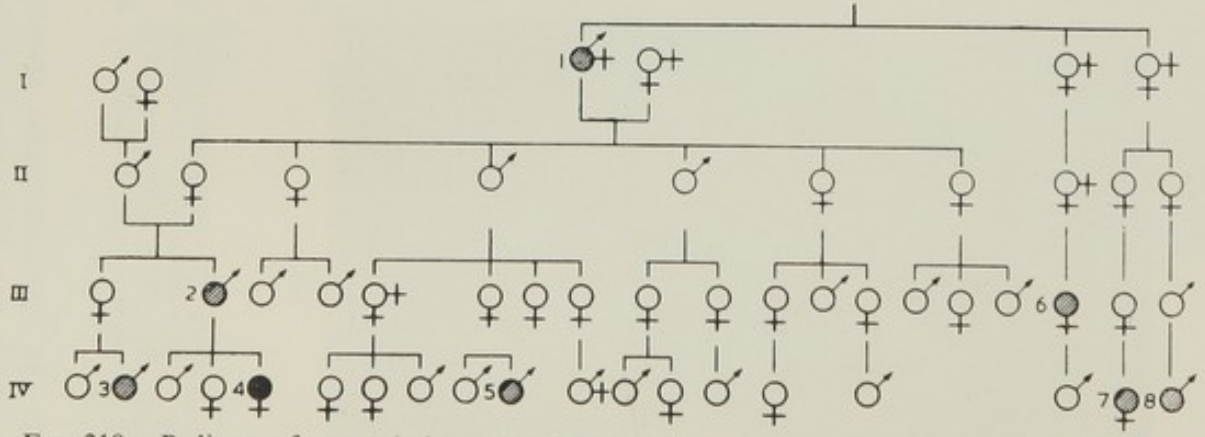


FIG. 219.—Pedigree of congenital atresia of the meatus. Cases 1, 2, 3 and 8; absence of one auricle. Case 4; a bilateral malformation. Case 5; a part of the left auricle is said to have been missing. Case 6; slight malformation of the right auricle, and Case 7; deformity of the left auricle. (*After Schwartz, M. (1938). Quoted by Albrecht, W. (1940). In G. Just's Handb. d. Erbbiol. d. Menschen*, **4**, 46.)

Occasionally the affection may be combined with cervical fistulae, auricular appendages or other auricular malformations.

Heredity.—Heusinger in 1864 noted the familial occurrence of the affection. In some families, as in that recorded by Kindred (1921), the anomaly is always on the same side and in the same place. In others, as in the pedigree reported by Whitney (1939), no such regularity is seen.

In Whitney's family the inheritance of the fistula was found to be simple, partly irregular (Fig. 218*a*). Most other records show irregular dominance. This is seen in the well-worked pedigrees of Edmonds and Keeler (1940) (Fig. 218*b*).

In a pair of uniovular twin sisters, McDonough (1941) found discordance in the inheritance of the anomaly, but the sister, who did not present the anomaly, had a son with this abnormality, whereas the affected sister had two sons without any fistula. McDonough stressed that discordance was found in all the 6 recorded cases of uniovular twins with this anomaly; only one of these cases showed some evidence of concordance, the fistula being represented by a tumour-like structure that might have been a cyst.

Selkirk (1935) has shown that the anomaly may readily be overlooked; the gene may be more penetrant than would appear in some pedigrees.

Exostoses

Exostoses in the meatus may arise from traumatic and inflammatory processes, possibly also in connexion with rheumatism and gout, but that there is a hereditary factor is evident from their frequency in some races—as, for instance, among the ancient Peruvians in whom they were found in 10 to 15 per cent as against 3 per cent among Europeans. Moreover, some geographical differences in incidence are known, and a few cases of familial occurrence have been reported.

Atresia of the meatus

Clinical aspects.—Congenital occlusion of the external auditory meatus, which may be membranous or, more often, entirely or partially osseous, is due to developmental arrest. The atretic plate separating the meatus from the middle ear may be more or less pronounced, and the meatus rather hypoplastic, but most often completely absent. In all the more severe cases the tympanic cavity shows thickened lateral walls, and diminished volume. The malleus is usually defective and the incus frequently rudimentary. The ossicles may be entirely absent and the tympanic cavity missing. In some cases—according to Altmann (1949) in one-third of those moderately severe—the internal ear is also deformed.

The auricle may be normal, but most often it is deformed or microtic; auricular appendages and anomalies of the adjacent skeletal part are not infrequent.

Heredity.—Only scanty reports on the familial occurrence of the affection have been published. Most cases are sporadic and are regarded as environmental in origin, but Krampitz (1912) observed the anomaly in a mother and her child; Torrigiani (1927) in two sisters; and Schwartz (1938) in several generations of a family (Fig. 219).

Eczema

A hereditary allergic diathesis appears to underlie many cases of eczema of the auricles as seen in infants, and eczema of the meatus and auricles as seen in adults.

MIDDLE EAR

Otitis media

The disposition to infection of the middle ear has been elucidated by the studies of Albrecht and Schwartz (1936). They showed that the mucous membrane of the middle ear is practically fully developed at birth, and in some infants it may be hyperplastic or hypoplastic. Such abnormal mucous membrane is specially prone to infection and shows diminished capacity for healing—the latter producing a tendency to recurrence and so to chronic inflammation. This agrees well with the clinical experience that ears in which the system of air-cells in the mastoid process is poorly developed, or in which the mastoid process is compact, are particularly prone to chronic otitis media, for according to these observers the character of the mucous membrane determines the type of pneumatization of the mastoid process.

There is thus an anatomical basis for a tendency to otitis media, and this tendency is more frequent in some families than others. It is true that catarrhal affections of the upper air passages by themselves dispose to the development of otitis media, but there are families in which such a catarrhal disposition is not particularly pronounced and yet show an increased frequency of middle ear infection (Stein, 1917) and others.

Gleissner (1939) has reported 7 families with particular disposition to scarlet fever; suppurative otitis media occurred in 11 out of 61 cases of scarlatina (18·1 per cent) as against 8 cases (2·7 per cent) in a control group of 295 cases of scarlet fever.

Acute otitis media

Concordance has been observed by Weitz (1924) in one pair of uniovular twin sisters, and by Paulsen (1925) in two pairs of uniovular twins.

Chronic otitis media

Impressive pedigrees have been recorded by Albrecht (1924) and Richter (1931) amongst others. Twin studies by Schwartz (1929) showed concordance in the pneumatization of the mastoid processes in 39 out of 61 pairs of uniovular twins as against 13 out of 35 pairs of biovular twins, but these studies also showed that external factors are also significant. The actual mode of inheritance remains obscure (Fig. 220) owing to the marked influence of environmental factors.

Otosclerosis

Clinical aspects.—Otosclerosis results from the focal formation of spongy and vascularized osseous tissue which later undergoes sclerosis. The site of election is the labyrinthine capsule, but other parts of the temporal bone may be involved. When a focus of reaction lies near the base of the stapes it tends to extend to it, giving rise to stapedial ankylosis and so to the clinical picture of otosclerosis, with its characteristic deafness.

The lesion generally does not become manifest until after puberty, and is frequently associated with degenerative changes in the auditory nerve.

Heredity.—Early pedigrees (Fig. 221) suggested simple or irregular dominant inheritance, but they probably represented selected cases, though some later studies, Chumba (1942) and Kabat (1943) and Amidon (1948) have the same trend. On the other hand in 7 recent pedigrees, Haike (1948) found simple recessive inheritance in 5 cases, irregular dominance in one and uncertain inheritance in one more.

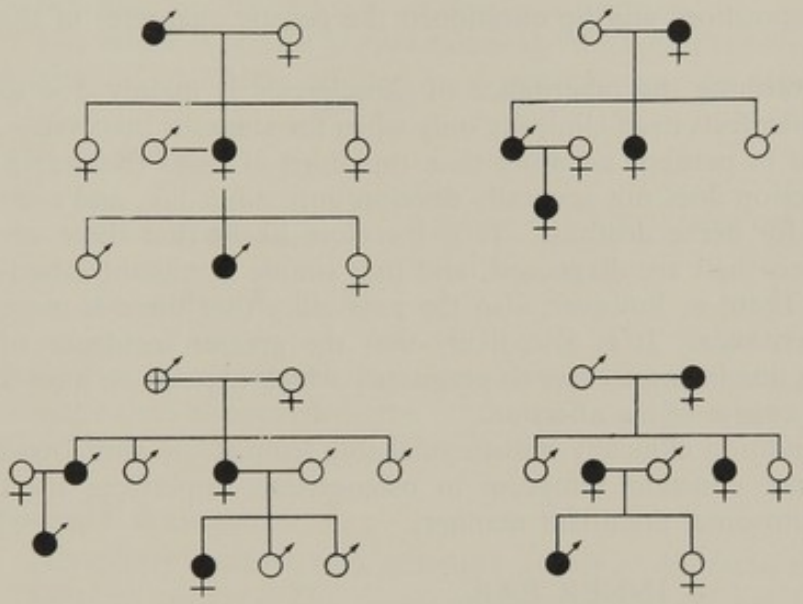


FIG. 220.—Pedigrees on subacute and chronic suppurative otitis media. + designates a marked degree of deafness, probably on account of chronic otitis media. (*After Albrecht, W. (1924). Z. Hals-Nasen- und Ohrenheilk.*, **10**, 52.)

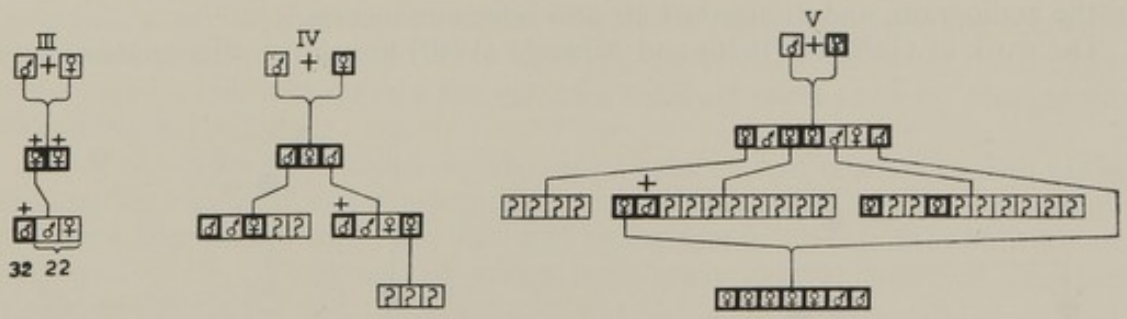


FIG. 221.—Early pedigrees on otosclerosis. III after O. Körner (1905). IV and V after V. Hammerschlag (1904). + designates the cases examined personally by the author. (*After Körner, O. (1905). Z. Ohrenheilk.*, **50**, 106.)

On a full survey of published pedigrees together with 60 new families, Davenport, Milles and Frink (1933) hold that otosclerosis is due to two dominant factors, one of which (A) is autosomal, the other (X) sex-linked to the X chromosome. This would explain the ratio of 1 : 2 as between otosclerotic men and women.

On this view, the genetic formula for otosclerotic men would be XYAa, and for women XxAa.

Albrecht (1932) has reported on a pair of uniovular twins—two brothers who in their youth lived apart and under highly different conditions. Both developed otosclerosis almost at the same time; and on examination, at the age of 39 years, the audiograms were alike in all details. Several other twin studies have shown concordance in this respect.

In a series of 106 patients, Schmidt (1936) found 57 with familial disposition and 49 without such disposition, and he questioned the genetic character of the affection.

The difficulty in establishing the inheritance of otosclerosis is mainly due to the fact that the lesion manifests itself clinically only when the stapes is involved—an event that may occur in perhaps no more than one-third of cases (Schwartz, 1940). Moreover, the lesion does not generally develop until adult life, and even then may be mistaken for nerve deafness. It is therefore likely that there are more cases of otosclerosis than are diagnosed, and that simple dominant inheritance may well apply. There is, however, also the possibility that there is more than one mode of inheritance. It is also likely that the greater incidence of otosclerosis in women is due in some cases to pregnancy which appears to have a deleterious effect on the course of the affection.

Otosclerosis—or a condition clinically indistinguishable from it—is also found as a frequent though not constant symptom in osteogenesis imperfecta itself inherited in a regular autosomal dominant manner.

INNER EAR

Labyrinthine deafness

Labyrinthine deafness may be hereditary or acquired.

Clinical aspects.—Clinically there is a decrease in the upper-tone limit in the tuning-fork test and impairment of hearing, in particular for the higher frequencies in the audiogram, and diminished air and bone conduction.

The work of Guffarth (1936) and Albrecht (1940) has shown that anatomically

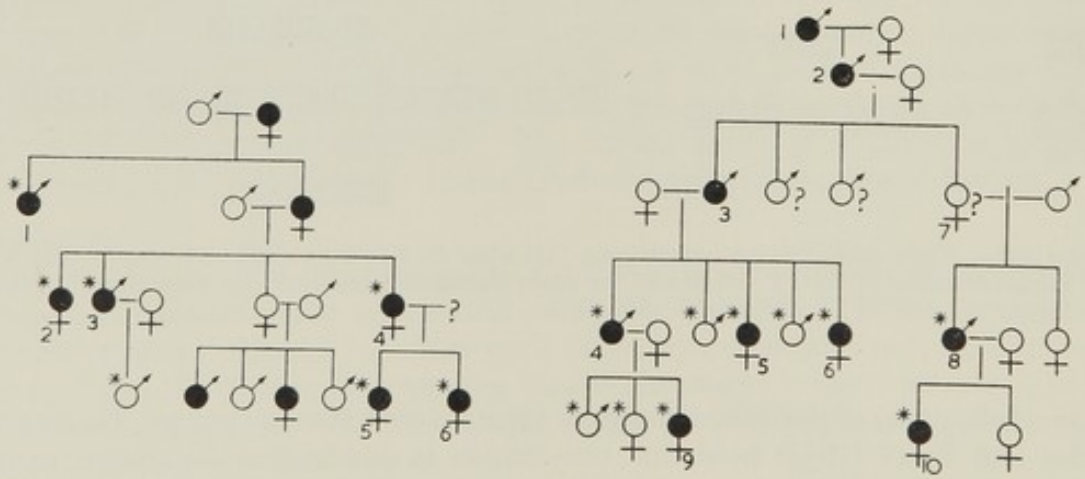


FIG. 222.—Pedigree on hereditary inner ear deafness. An asterisk designates the cases examined. (*After Albrecht, W. (1923). Arch. Ohrenheilk.*, **110**, 35.)

the hereditary form of labyrinthine deafness conforms with the Mondini type of Siebenmann's group 2b.

The deafness, which is often progressive, may be present in all possible degrees, from senile deafness to congenital deafness so pronounced as to result in deaf-mutism.

Heredity.—Simple dominance was found by Albrecht (1923) in 10 personal pedigrees, and in many recorded in the literature (Fig. 222). Uniovular twins show concordance, and Macfarlan (1927) found in two uniovular middle-aged twin sisters an almost identical degree of deafness.

The lesion is almost always bilateral, but Smith (1939) described a family with 9 cases of unilateral deafness in 4 generations. All these patients were charac-

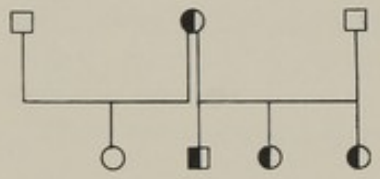


FIG. 223.—Unilateral hereditary inner ear deafness localized to the left side. (*Personal observation, 1951.*)

terized as stone-deaf on the side affected (sometimes right and sometimes left); a somewhat similar pedigree is shown in a personal observation recorded in Fig. 223.

Sporadic deaf-mutism

Hereditary deaf-mutism generally occurs in sporadic form.

Clinical aspects.—The diagnosis is generally evident from the history of the patient. Speech, if present at all, is either very defective or of that type which is characteristic of the deaf-mute who has been taught to speak: monotonous, hollow, cumbersome, jerky and exaggerated.

Fähndrik (1935) and Albrecht (1940) have shown that anatomically these cases fall in the Siebenmann's group 2a or group 2b, Scheibe's type. The vestibular apparatus is not involved. In some cases the defective development of the nerve paths may be followed up into the gyri of Heschl; in other cases no abnormality was found in the brain.

Heredity.—The early studies on the inheritance of deaf-mutism by Bell (1884) stressed the significance of consanguineous marriages. In 1898, Fay—a philologist—reported his studies on no less than 4,471 marriages in which one or both parents were deaf-mutes. This material suffers from grave defects, indicated elsewhere (Lindenov, 1945).

On his own material, Berg (1919) held that the inheritance of deaf-mutism probably is monohybrid recessive—a view confirmed by Lundborg's (1920) critical assessment of it. Similar findings were recorded by later observers (Albrecht, 1921; Lindenov, 1945) (Fig. 224).

Dimeric recessive inheritance has been suggested to explain the birth of normal children to two apparently recessively deaf-mute parents. These cases are, however, not entirely convincing—the diagnosis of recessive deaf-mutism was not beyond doubt in every instance.

The possibility of rather wide variations in the manifestations of the affection

has been pointed out by Luchsinger and Hanhart (1944) on the basis of their studies on three pairs of uniovular twins. They found a relatively great discordance in the hearing of such twins. The possibility of unilateral manifestation also arises from a personal observation.

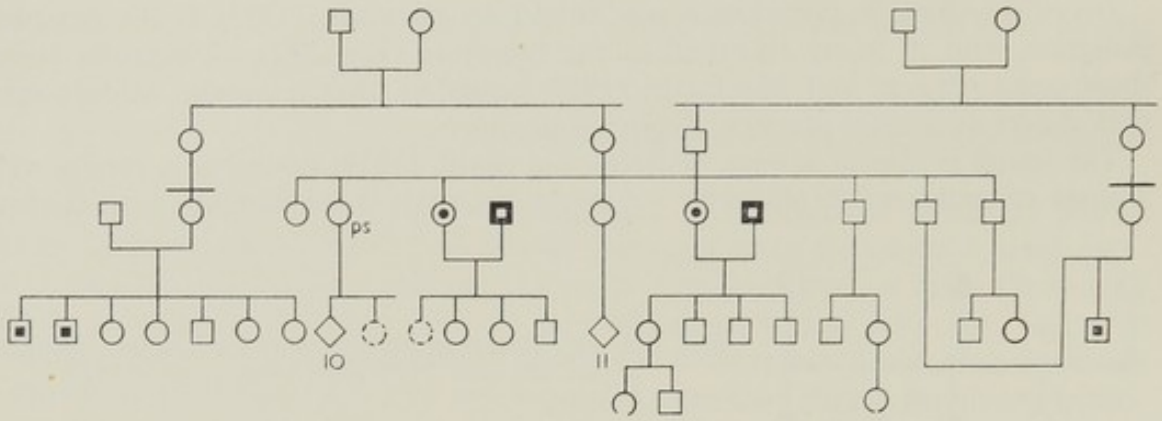


FIG. 224.—Pedigree on sporadic deaf-mutism, illustrating recessive inheritance. The large black dot in the middle designates sporadic deaf-mutism, whilst a thick margin designates deaf-mutism from some exogenous cause. The two symbols shown in broken outline signify that there is no information on the hearing. ps. = psychosis. (*After Lindenov, H. (1945). The Aetiology of Deaf-Mutism with Special Reference to Heredity, pedigree No.* 52. *Op. Dom. Biol. hered. hum. Kbh.*, **8**. Copenhagen; Munksgaard.)

Association with other affections

Sporadic deaf-mutism may be associated with other affections.

(*a*) *Deaf-mutism with retinitis pigmentosa.*—This association was observed as early as 1858 by v. Graefe and stressed in 1914 by Usher. In my own material it was found in 20 out of the total 109 sporadic deaf-mutes (Lindenov, 1945).

In reviewing the data on 480 deaf-mutes, retinitis pigmentosa was not found scattered throughout the entire material but distributed in certain families, seven of which showed cases of sporadic deaf-mutism. In the sibs in these families there were altogether 20 deaf-mutes with retinitis pigmentosa, as against 2 with deaf-mutism alone, and one with retinitis pigmentosa alone; 33 had normal sight and hearing. These figures agree but poorly with those that would be expected if the two lesions were transmitted separately or were determined by two linked genes. The assumption of a pleiotropic gene distinct from the gene for uncomplicated deaf-mutism is possibly supported by one of our pedigrees which shows a normal child born to two sporadic deaf-mutes, one of whom also had retinitis pigmentosa.

(*b*) *Deaf-mutism and mental deficiency.*—Hanhart (1924) and others have stressed this association. In my own material oligophrenia was not common except in the cases of sporadic deafness associated with retinitis pigmentosa.

(*c*) *Deaf-mutism and hereditary ataxia.*—This is a somewhat more infrequent finding. In my own material all the sporadic deaf-mutes with retinitis pigmentosa showed a swinging gait—possibly an abortive form of hereditary ataxia.

(*d*) *Deaf-mutism, retinitis pigmentosa, oligophrenia and ataxia.*—Hammerschlag (1932) holds this to be a definite entity, analogous to findings in Japanese dancing mice. Similar findings are observed in the dog, cat and guinea-pig.

The combination of all the four affections mentioned was found by Hammerschlag in two of his own cases and in three cases reported by Frey. Steinberg (1937) also found this combination in 6 out of 26 patients presenting retinitis pigmentosa.

Bearing on the analogy to Japanese dancing mice, it should be noted that partial albinism is occasionally seen with hereditary deaf-mutism (*see also* Fig. 52 on page 137, and Fig. 67 on page 182). (Hammerschlag (1908), Mende (1926) and Kling (1932)).

OTHER AFFECTIONS

Ménière's disease

This may be an aspect of the allergic diathesis in some cases. It may, however, occur as an independent affection in some families (Albrecht, 1926).

Acoustic tumours

These are discussed elsewhere (page 318).

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CHAPTER 20

TEETH

MARTIN A. RUSHTON

ABNORMALITIES OF NUMBER

Deficiency in number of teeth

A DISTINCTION has to be drawn between teeth which fail to develop and those which merely fail to erupt. The interpretation of many of the older records is made difficult by lack of radiological evidence on this important point. Deficiency in number is frequently associated with some abnormalities of size and shape.

Deficiency in number associated with generalized defects

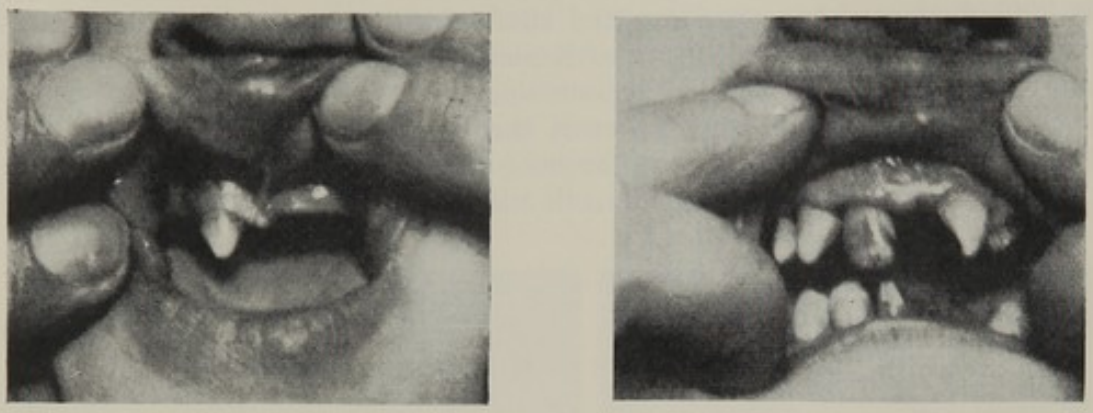
(*i*) *Anidrotic ectodermal dysplasia.*—Severe deficiency is common in the sex-linked recessive type of anidrotic ectodermal dysplasia: both dentitions may be absent or there may be a few teeth of either dentition. Such teeth as are present tend to be conical or in the second dentition horn-shaped, curving backwards, and the molars have "hooked" cusps. In the incomplete dominant type the dental deficiency may be less severe, especially in women, and only a few teeth may be conical or missing (Fig. 225*a* and *b*), the others being normal. In some families (Fig. 226*a*) a moderate similar dental defect (Fig. 226*b*) is associated with rather fine fair hair but the members are strongly built and sweat normally. The defect appears to be inherited as a dominant and the extent of the deficiency varies between different affected members.

(*ii*) *Other affections.*—Etheridge's case of a girl with many teeth congenitally absent on one side with homolateral absence of scalp hair and eyebrow has been discussed by Cockayne (1933) as a somatic mosaic. Böök (1950) has recorded absence of premolars associated with premature whitening of the hair and excessive sweating of palms and soles caused by a simple autosomal dominant gene. The penetration of the gene as regards hypodontia and greying was complete with no sex difference, but there was variation in the number of premolars missing and the age when greying began. Absence of some teeth in association with microphthalmos has been recorded in a number of families; and in hypertrichosis lanuginosa severe dental deficiency, usually of both dentitions, has been the rule. Fackenheim recorded polydactyly associated with absence of all except 6 teeth. Four marriages of normal with affected persons produced 12 normals and 7 affected and the inheritance is thought to be dominant. Absence of teeth in association with webbed digits has been noted in some isolated cases.

Deficiency in number of teeth without associated defects

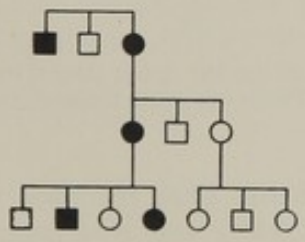
Familial deficiency in the number of teeth without other recognized anomalies is not uncommon. In some families a particular tooth or group of teeth is missing

but in others the distribution of the defect is different in the various affected members of the family.

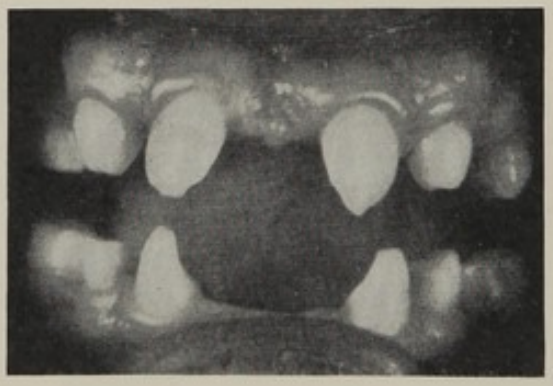


(*a*) (*b*)

FIG. 225.—Anidrotic ectodermal dysplasia, incomplete dominant type. (*a*) Boy aged 4 years who had only one conical deciduous tooth and two unerupted pointed teeth of the second dentition. (*b*) His mother had some teeth missing or pointed but did not have the other ectodermal defects. A brother and several cousins were also affected. (*After Rushton, M. A. (1934). Proc. R. Soc. Med.*, **27**, 725.)



(*a*)

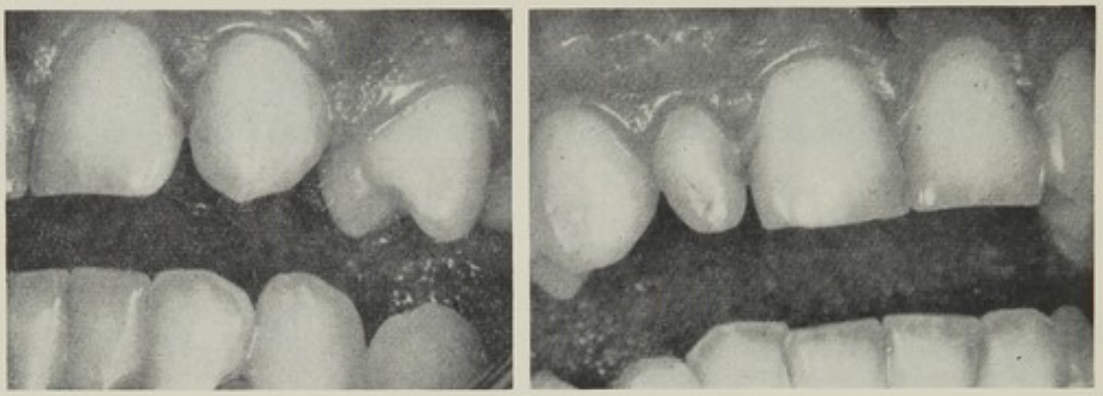


(*b*)

FIG. 226.—(*a*) Ectodermal dysplasia. A pedigree of a family showing absence of several teeth; some other teeth were pointed and the hair fair. Those not having the dental defect are dark. It is not always the same teeth which are affected in different members of the family. (*b*) Appearances in III 2 in (*a*). Six incisors and many other teeth are absent; upper central incisors and lower canines are deformed; many deciduous teeth are still in place at 20 years. There is fine fair hair and normal sweating.

(*i*) *Incisors.*—Absence of the same 6 incisors has been noted by Dahlberg in 18 out of 59 members of one family in 5 generations: 7 marriages between affected and normal persons produced 15 affected and 23 normal offspring. The most common defect is absence or rudimentary development of one or both upper lateral incisors (Fig. 227*a* and *b*): it is a simple dominant character without sex limitation. Keeler (1935) using 11 of the more complete pedigrees found 23 marriages between normal and affected persons producing 38 normal and 45 affected offspring. While in most affected families the defect varies in extent between the affected individuals—from one tooth dwarfed to both teeth missing—occasionally the defect is precisely the same in all (for example, upper right lateral

incisor missing and upper left conical). There are several pedigrees where both parents were affected. Two of these (McLeod, 1934; Bradlaw, 1934) indicate transmission of the defect through one normal female, but in McLeod's pedigree this individual may have had dwarfed lateral incisors since only missing teeth were there recorded. The pedigree of Keeler and Short shows in the children of a marriage between two affected persons one child with additional teeth missing (lower premolars) which may represent the homozygous state (Keeler, 1935). The same thing occurred in some of the children of unrelated parents both affected in McLeod's families, the additional teeth missing being premolars.



(*a*) (*b*)

FIG. 227.—(*a*) Anomalies of incisors. Congenital absence of the left upper lateral incisor; the central incisor and canine tooth are in contact. (*b*) From the same patient; there is dwarfing of the corresponding upper right tooth.

Absence of all central incisors in both dentitions has been recorded in three generations of a family by Huskins (Cockayne, Keeler) and was regarded by him as an example of sex-linked recessive inheritance. It has been pointed out that as one female was fully affected this is not acceptable. The defect was transmitted through an affected male and several unaffected females, and an incomplete dominant factor has been suggested.

(*ii*) *Premolars.*—Hamano recorded a pedigree showing absence of some premolars in 5 affected persons in 3 generations and though this is incomplete it suggests a dominant character. Absence of some premolars is quite a common malformation but accidental removal of a premolar germ during extraction of a deciduous molar is sometimes a cause of absence of a single tooth.

(*iii*) *Various incisors and molars.* Beadle has recorded a pedigree in which a varying number of incisors and molars were absent in 7 out of 15 children resulting from 3 marriages between normal and affected persons. It is consistent with a dominant factor. There are a few similar pedigrees.

Excess in number of teeth

Additional teeth are thought to be somewhat more common than missing teeth in Europeans, and in some African races fourth molars and extra premolars are much more common than in Europe. In spite of this there are very few pedigrees indicating a familial distribution. Keeler records an additional tooth

in the palate in a woman, her daughter, and two brothers, but not her son; and another family of four generations in which four members had a supernumerary tooth and four a " twisted " tooth. If, as he suggests, these are alternative manifestations of a single factor, the inheritance is consistent with a dominant. Webster described a family with an additional palatine tooth in a mother, one of two twin daughters, and a son. There are other fragmentary records of an additional lateral incisor in sisters, also in cousins.

Supplementary teeth are frequently associated with the defects of cleido-cranial dysostosis.

ABNORMALITIES OF SIZE AND SHAPE

Variations in size and shape of some or all teeth are often strongly associated with racial groups and an enormous mass of information on these aspects is to be found in works on anthropology. In addition, some frank malformations of the teeth are believed to be more common in certain races.

Abnormally large upper central incisors have been recorded in two families of three generations (Keeler), both pedigrees being consistent with a dominant factor. Unusually small teeth are often found in hereditary opalescent dentine and osteogenesis imperfecta, and sometimes in persons who have other teeth congenitally absent or in their relatives. A distinction can be drawn between teeth which are small and malformed (conical or peg-shaped) and teeth which, though small, are of normal shape.

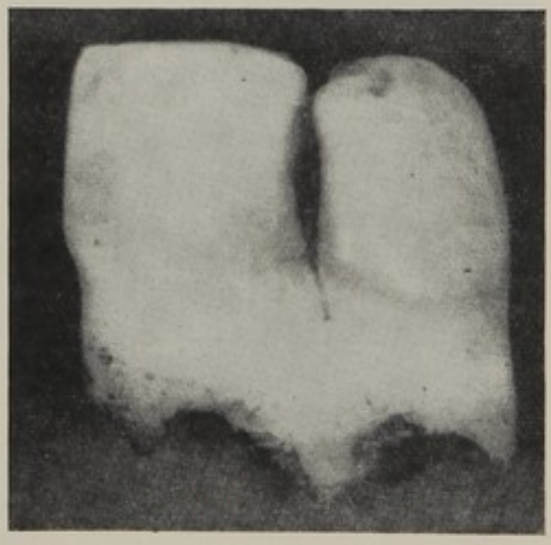


FIG. 228.—Fusion of deciduous lower incisor teeth. The roots, which are united, have undergone physiological absorption.

Unilateral enlargement of several teeth on one side of both jaws up to 50 per cent increase in diameter in association with homolateral facial hyperplasia has been recorded in 15 cases (11 males) and in a few cases in association with hemihyperplasia of the whole body. The second deciduous molars, permanent canines and first molars show the greatest enlargement and the expression of the abnormality must start before the middle of intra-uterine life. The eruption of both enlarged and normal teeth on the affected side is often precocious by several

years. The dental condition is not known to be inheritable, though in one family the tendency to facial asymmetry may have been.

A common malformation is developmental fusion of two tooth germs or incomplete dichotomy of one (Fig. 228). Moody and Montgomery recorded three pedigrees of persons with developmental fusion of two deciduous lower incisors, the permanent teeth being normal. The teeth concerned were described as united to form one big double tooth, and there were 11 marriages between affected females and normal males producing 16 affected females, 4 normal females, and 8 normal males. There were no affected males and inheritance was through affected females only, except that the progenitors of one family are shown as normal.

The degree of fusion can vary from a condition in which two teeth are represented by a single large tooth with slight indications of its composite nature to one in which the developmental fusion affects only the roots and is so inconspicuous that it is not discovered unless an attempt is made to extract one of the teeth. It is possible, therefore, that some individuals shown as normal in the pedigrees may have been inconspicuously affected.

ABNORMALITIES OF STRUCTURE

Pedigrees of brown teeth by earlier authors are believed to refer to several different structural disorders and not to a single condition (Fig. 229).

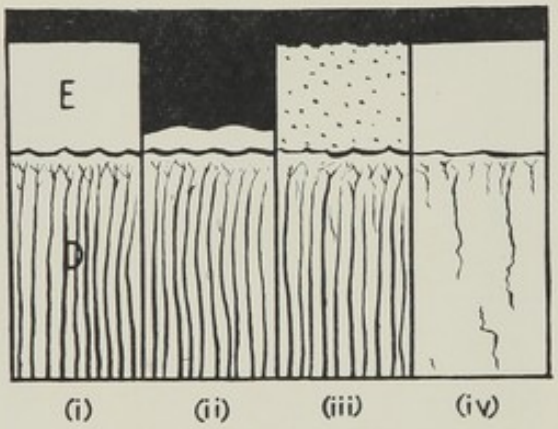


FIG. 229.—Diagram to represent structure of normal and three kinds of brown teeth: (i) normal; (ii) hereditary enamel hypoplasia with normal dentine and thin layer of well-calcified enamel; (iii) hereditary enamel hypocalcification with normal dentine and normal thickness of poorly calcified enamel; and (iv) hereditary opalescent dentine with dentine containing few tubules and with normal enamel. E, enamel; D, dentine.

Enamel

Hereditary disorders of enamel structure affecting all teeth of both dentitions are of two principal kinds: that in which the enamel is quantitatively deficient and that in which the quantity is normal but the calcification remains incomplete.

Hereditary enamel hypoplasia (agenesis of the enamel)

Clinical aspects.—The teeth are yellowish or brownish and covered by a very thin layer of enamel which is hard and often smooth to a probe. Owing to the thinness of the enamel the shape of the teeth is abnormal, resembling teeth from which the enamel has been removed, and for the same reason there are intervals between neighbouring teeth. In adults the teeth are likely to be found worn down to mere stumps. The condition may be recognized in radiographs (Fig. 230).

In less severe cases more of the enamel may be present and the deficiency may be shown by vertical grooves on the surface (Fig. 231); this has to be distinguished from the horizontal grooves produced by many kinds of illness during the period of tooth formation. Although hard, the structure of the enamel may be disordered showing a glassy laminated appearance under the microscope in many parts: the dentine is normal. Some of the teeth, especially the posterior molars, fail to erupt and may undergo partial resorption.

From the limited number of pedigrees available it is thought that inheritance is as a dominant.

(*a*)

(*b*)

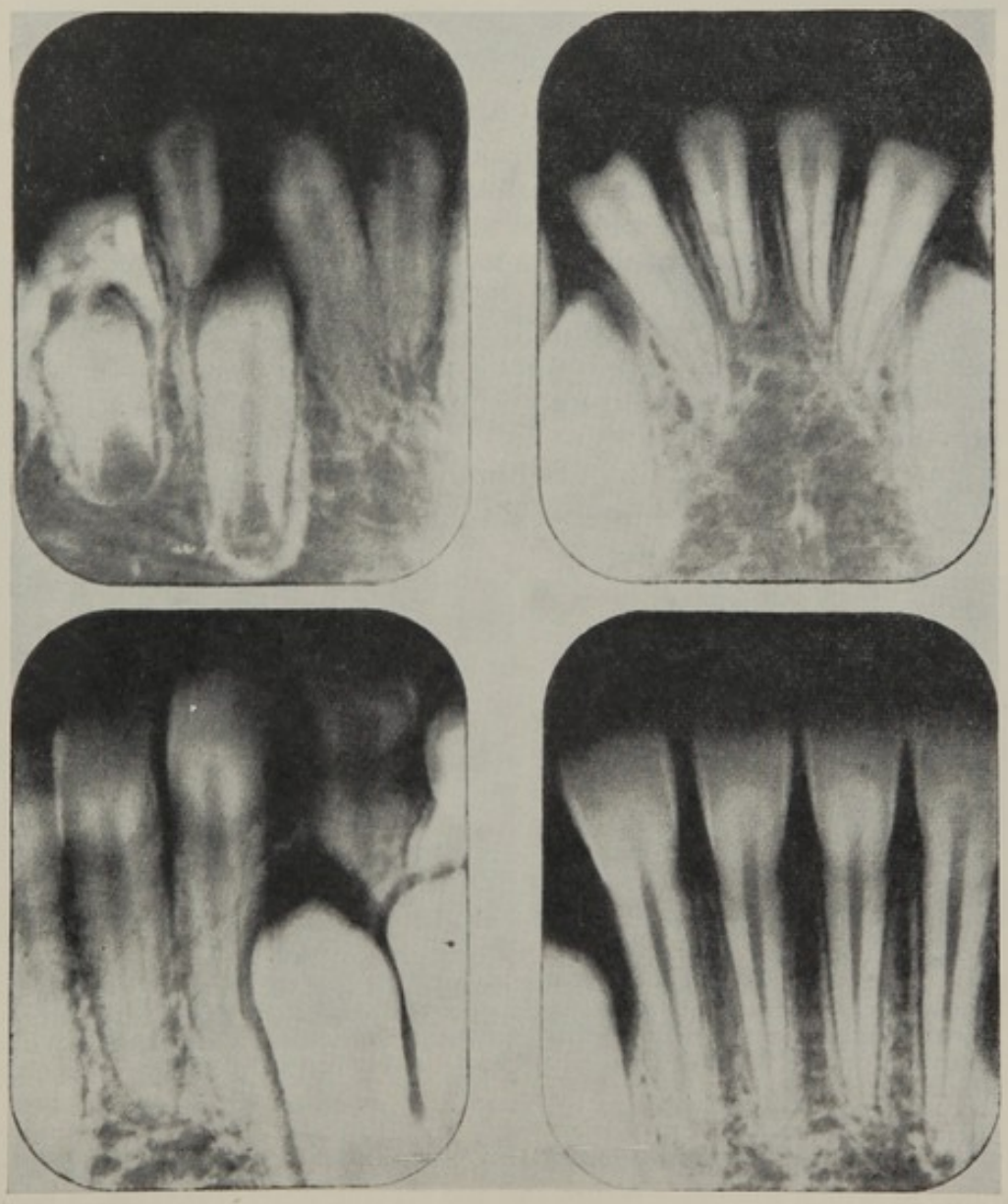


FIG. 230.—Hereditary hypoplasia of enamel. (*a*) Radiographs of lower anterior teeth in an affected child aged 7½ years. (*b*) Radiographs from a normal child for comparison. The almost complete absence of enamel can be detected on erupted and unerupted teeth, and the former already show marked attrition.

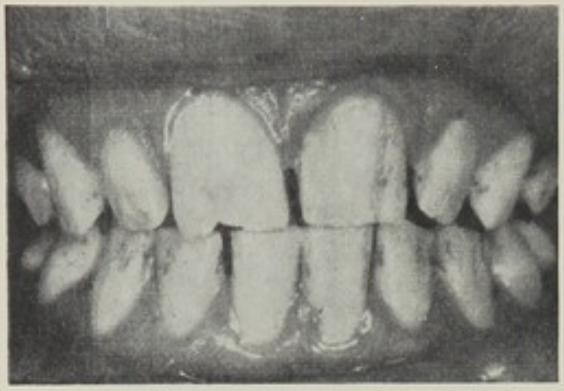
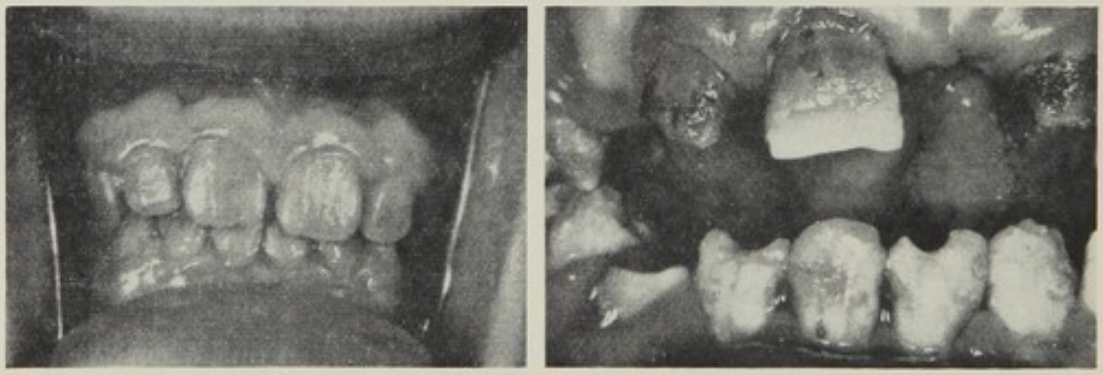


FIG. 231.—Hereditary hypoplasia of the enamel: a mild form showing vertical grooves in enamel of dull appearance, and lack of contact between teeth. Condition traced for 4 generations, 5 marriages between affected and normal persons producing 13 affected and 7 normal offspring (Dr. E. W. Fish's case).

Hereditary enamel hypocalcification

The teeth vary in colour from chalky white to buff, orange or brown and the enamel is originally present in normal quantity (Fig. 232*a*) although much of it may be lost early. The surface of the enamel has a matt appearance and is rough to a probe: it may be sufficiently soft to be scraped away with an instrument. The deficient calcification can be observed in radiographs of unerupted as well as erupted teeth. Sometimes patches of better calcified enamel cover considerable parts of a few teeth or are quite irregularly disposed (Fig. 232*b*). The histological structure of the enamel and other dental tissues is normal, and the defect is that the enamel has not undergone the normal maturation during which the greater proportion of mineral salts is added and the organic matrix undergoes changes which render it soluble in acids. The brownish colour increases with age and is usually absent from newly erupted teeth.



(*a*) (*b*)

FIG. 232.—Hereditary enamel hypocalcification. (*a*) Teeth of a boy aged 15 years. The enamel is a golden buff colour, lacking in gloss and rough to a probe. (*b*) Teeth of a boy aged 12 years. The enamel is buff in colour with calcified white patches. Rapid irregular wear of the lower incisors is shown. A brother and cousin were similarly affected.

Few pedigrees are available and sporadic cases are more often encountered, sometimes in several siblings. Weinmann and his colleagues (1945) give a pedigree of six generations in which 18 descendants of an affected immigrant from Britain to America were affected, compared with 23 normals. In no instance was the anomaly inherited from an unaffected parent and there was no sex difference. It

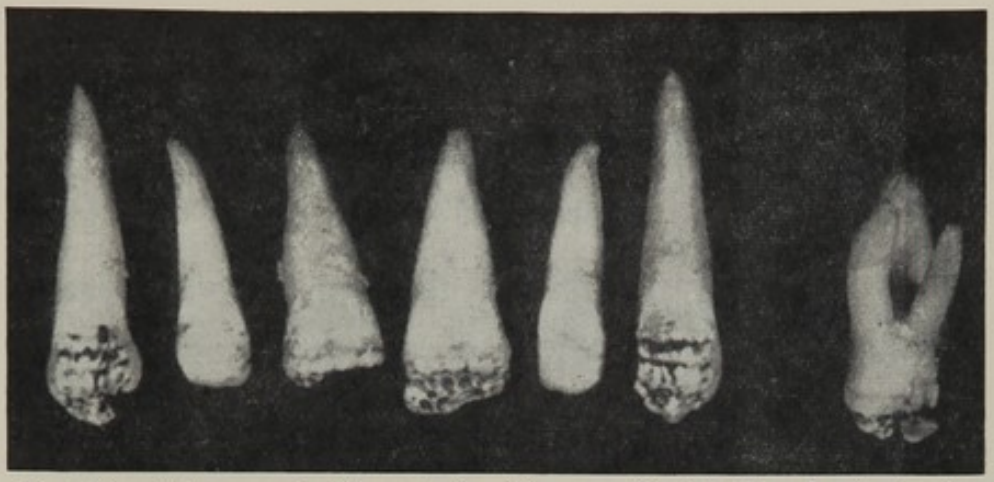


FIG. 233.—" Honeycomb " hypoplasia. Six upper front teeth and a first molar illustrating " honeycomb " hypoplasia of the enamel, the distribution of which indicates disturbed enamel formation between a few months of age and three years. The lateral incisors and premolars were nearly normal.

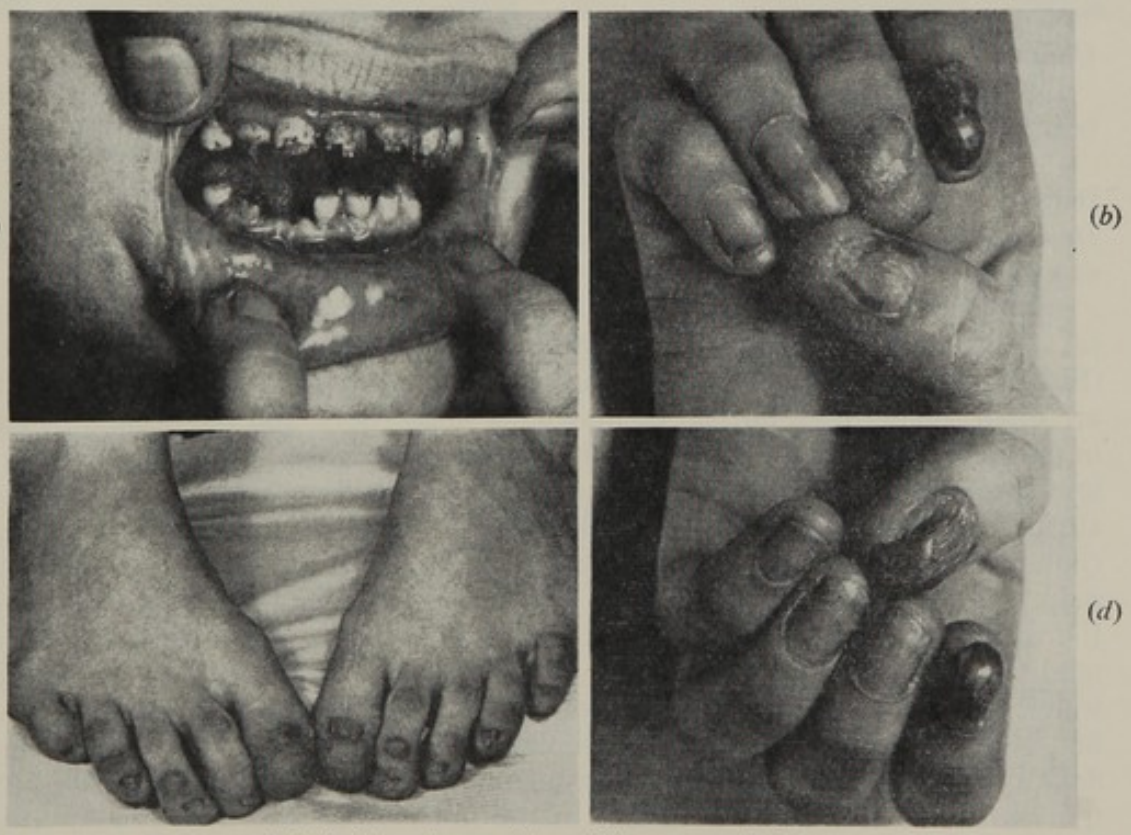


FIG. 234.—Epidermolysis bullosa dystrophica. Woman aged 26 years. (*a*) All teeth present affected by hypoplasia of the enamel. Exposed dentine had a " barley-sugar " colour. (*b*)–(*d*). Sub-epidermal bullae from one month of age. Dystrophy of nails. (*After Richard, Cernéa, Nespoulos and Paul (1949). Rev. Stomat.*, **50**, 352.)

is thought that inheritance is as a dominant. A less typical family was recorded by Bampton. Inheritance was again as a dominant, or possibly dominantly sex-linked, but in this family the deciduous teeth of the affected members were usually

white and only turned brown gradually in a few cases: the permanent teeth of the same individuals erupted brown.

Hypoplasia of dental enamel associated with general disorders

(*i*) *Lamellar cataract and fits.*—Various families showing a triad of symptoms of hypoplasia of enamel, cataract and fits are recorded. The deciduous teeth are normal but the permanent teeth with some exceptions show a pitted " honeycomb " hypoplasia (Fig. 233). It has been said that only those with large cataracts show the dental anomaly. The fact that the fits occur in infancy during the period of formation of the permanent teeth, and the distribution of the dental anomaly, suggest that the dental lesions are the result of a metabolic disturbance, such as hypocalcaemia, occurring at that period only. The inheritance is as a dominant. Two other varieties of cataract associated with enamel hypoplasia are mentioned by Cockayne, both dominant characters.

(*ii*) *Hereditary skin disorders.* Hypoplasia of enamel, sometimes with deficiency in number or size of the teeth, may accompany the recessive form of epidermolysis bullosa dystrophica (Fig. 234).

Unilateral hypoplasia

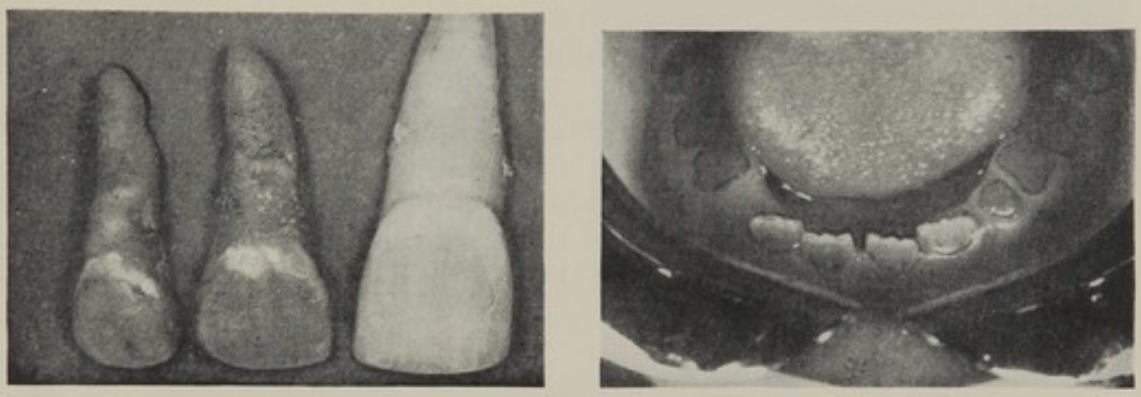
Extensive hypoplasia of dental enamel confined to one side of the mouth has been recorded and may result from genetic factors.

Dentine

Hereditary opalescent dentine (*odontogenesis or dentinogenesis imperfecta, maladie de Capdepont*)

All the teeth of both dentitions are affected and vary in appearance from a dirty to a pinkish or brownish colour often with blue reflections from the enamel (Fig. 235*a*). They may also be of nearly normal colour or very translucent. They are often smaller than normal or may have small roots, and the deciduous teeth in particular wear down quickly so that they are often seen as amber-like stumps level with the gum (Fig. 235*b*) and in these the pulps may become exposed by attrition with resulting abscesses. The dentine is abnormal in that it is soft and contains few tubules: most of these are at the periphery and do not extend to the pulp, indicating that the odontoblasts soon cease to exercise their normal functions. It may also be deficient in collagen. The pulp cavities of the permanent teeth tend to become obliterated early by abnormal dentine formation, a condition which can be recognized in radiographs. The enamel is of normal structure but its calcification tends to be incomplete and in some cases it is very liable to flake away from the dentine. The inheritance is as a dominant (Fig. 235*c*). So-called transparent teeth may be a variant of the same defect but Moody and Montgomery (1934) reported 3 generations of a family in which 2 marriages between affected females and normal males produced 3 normal males, 3 normal females, and 2 affected females. No males were affected and one normal female had an affected daughter. All those with the defect were the last children of parents then middle-aged and both dentitions were affected. Another defect, the so-called " rootless teeth " of Ballschmiede (Herbst and Apffelstaedt, 1930), may result from an allied abnormality of dentine formation. There was some deficiency in

number and the teeth possessed very little root. The dentine was thick, there were no pulp cavities, and sometimes there were multiple associated epithelial cysts. Three generations were affected and the inheritance appears to be that of a dominant. In an apparently similar sporadic case the writer showed that the dentine of the crowns of the teeth was normal but that of the roots had changes somewhat resembling those in hereditary opalescent dentine.



(*a*) (*b*) (*c*)

FIG. 235.—Hereditary opalescent dentine. (*a*) Upper right incisors from an affected woman compared with a normal left central incisor (personal observation). (*b*) Lower teeth of an affected girl aged 8 years. The deciduous teeth are worn flat and level with the gum. The erupting permanent incisors are a greyish-brown colour (Dr. E. W. Fish's case). (*c*) Pedigree of girl whose teeth are shown in (*b*).

Dentine anomalies in general disease

Osteogenesis imperfecta.—A condition of the teeth which is the same as hereditary opalescent dentine is seen in patients suffering from osteogenesis imperfecta. In a few cases the teeth have a highly translucent and even glass-like appearance. The deciduous teeth are more likely to appear abnormal than the second dentition.

Porphyria congenita.—The colour of the teeth may vary from pink to a brownish-red and even purple, both dentitions being affected. The abnormal pigment is chiefly deposited in the dentine and cementum during their formation and very slightly in the enamel also.

ABNORMALITIES OF ERUPTION

Early tooth eruption

There are a number of records of teeth erupted at birth or soon afterwards in a few members of a family but pedigrees are very short. Asana reported premature eruption of lower incisors in two children born to the same father by different

wives. Usually inheritance is from an affected parent but Cockayne records a family in which the aunt and niece only were affected. Association with onychogryphosis and in another family with the dominant type of polydactyly has been noted. Murray recorded a pedigree in which the affected persons had two incisors erupted at birth with hyperplasia of the nail-bed. Two marriages between normal and affected persons produced 9 normal and 6 affected offspring.

Retarded tooth eruption

Failure of eruption of a specific tooth in two succeeding generations and also in identical twins has been recorded.

Cleido-cranial dysostosis.—Retarded tooth eruption is a characteristic feature of this affection.

Retardation is progressive, so that while eruption of the deciduous teeth is only slightly delayed that of some of the permanent teeth may be delayed for years and many may not erupt at all (Fig. 236). Those permanent teeth which

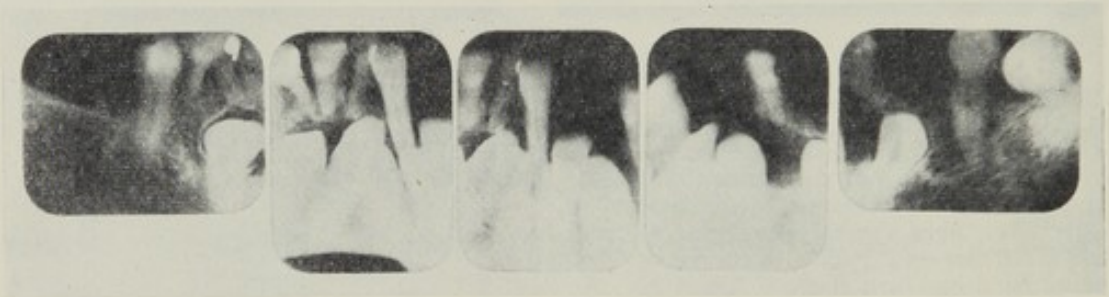


FIG. 236.—Cleido-cranial dysostosis. In addition to the classical bone defects, many teeth in both jaws failed to erupt. X-ray films of the mandible show seven anterior teeth unerupted and a cyst in connexion with these. Four deciduous teeth are still in place at the age of 35 years.

normally erupt first are the least likely to fail to erupt. The roots of the teeth which do not erupt are frequently deformed, presumably for mechanical reasons, and cysts may eventually form about the crowns. Supernumerary teeth are often present also in the anterior and premolar regions. Many deciduous teeth are long retained. The upper jaw is poorly developed, but the lower is of normal size giving an appearance of prognathism.

Failure of tooth eruption of a type resembling that found in cleido-cranial dysostosis, with or without supernumerary teeth, is found in some families without any evidence of cranial or clavicular defect. Sometimes this is associated with other abnormalities, such as short terminal phalanges, and in one such family a single member had a clavicular defect. It seems likely that these conditions represent a partial expression of the same syndrome.

Gingival hyperplasia.—Delayed and incomplete tooth eruption is found in connexion with congenital general hyperplasia of the gums (Fig. 237) and familial distribution of the gingival hyperplasia is occasionally observed. Weski (1911) recorded a family of 5 generations consisting of 19 females and 20 males, of which 9 females and 7 males were affected. Mirolli (1931) observed 4 generations with

10 marriages between normal and affected persons and 28 offspring, of whom 17 were normal and 11 affected to various degrees: there was no sex difference.

Delayed eruption with gingival hyperplasia and bilateral corneal opacities has been recorded and considered to depend probably on a single dominant gene.

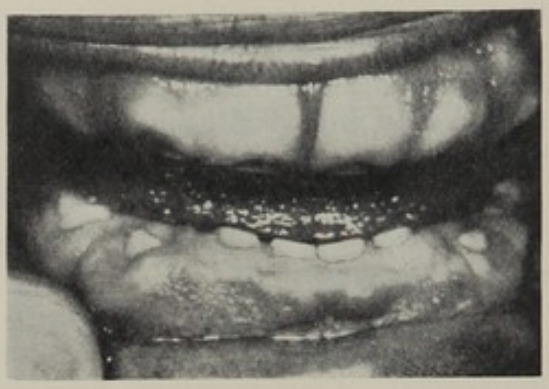


FIG. 237.—Hyperplasia of the gums with delayed and incomplete tooth eruption. In a boy aged 5 years; the tips of the deciduous teeth only have erupted and the gums are greatly thickened but not inflamed. The father had a similar condition.

ABNORMALITIES OF ARRANGEMENT

In defects of the jaw without general associations

Abnormality in the arrangement of the teeth or malocclusion depends in many cases upon defects of jaw growth, which in turn may result from genetic influences. Highly detailed resemblance is commonly found in the teeth of monozygotic twins in respect of spatial arrangement, size, chronology of development of individual teeth and other qualities. Fig. 238 shows models of the teeth of two such twins who have the five listed characteristics in common. Lundström (1948) summarized the literature on genetic and non-genetic factors as regards tooth-size and occlusion based on studies of identical and fraternal twins, and added a detailed analysis of his own material. His conclusions do not admit of any brief summary but his figures demonstrate the greater dissimilarity of fraternal twins in the characters studied.

The deformity known as Angle's Class III, in which the lower jaw is excessively long and the upper is poorly developed, often has a familial distribution: it was notoriously characteristic of members of the Habsburg family for many hundred years (Fig. 239*a* and *b*) and Rubbrecht (1939) gives some other pedigrees in which, however, the sexes are not distinguished. In the Habsburgs the retention of the character in the family was reinforced by several cousin marriages and by marriages between families having a similar defect. The mode of inheritance is apparently dominant.

The more common deformity, Angle's Class II, in which there is a receding chin (Fig. 240) is also probably influenced by genetic factors since Humphreys and Leighton (1950) found both the siblings and mothers of affected children to be affected significantly more often than those of normal children.

In defects of the jaw with general associations

Abnormal arrangement and occlusion of the teeth is also consequent upon such hereditary manifestations as cleft palate, oxycephaly, achondroplasia, facio-mandibular dysostosis and other disorders affecting jaw growth. In cleft palate

the derangement of the teeth seen is frequently more attributable to the older types of operation than to the original malformation. An additional tooth may be present or a tooth may be absent in the neighbourhood of the alveolar cleft especially as regards the deciduous dentition, but missing permanent teeth may be the result of early operations. In oxycephaly the greatly reduced growth of the upper jaw leads to the upper teeth occupying a position too far posterior with respect to the lowers and having insufficient room to form a regular arch or, in the case of some of them, to erupt at all. The palate is small and narrow and may show a deep groove in the midline (Fig. 241). The lower jaw, which is of normal size, appears by comparison to protrude.

SOME OTHER AFFECTIONS

Cysts of the jaws

There are a few short pedigrees on the occurrence of epithelial cysts of the jaws. An observation over three generations of a family is given by Thoma and Blumenthal. Four marriages between affected and normal persons produced

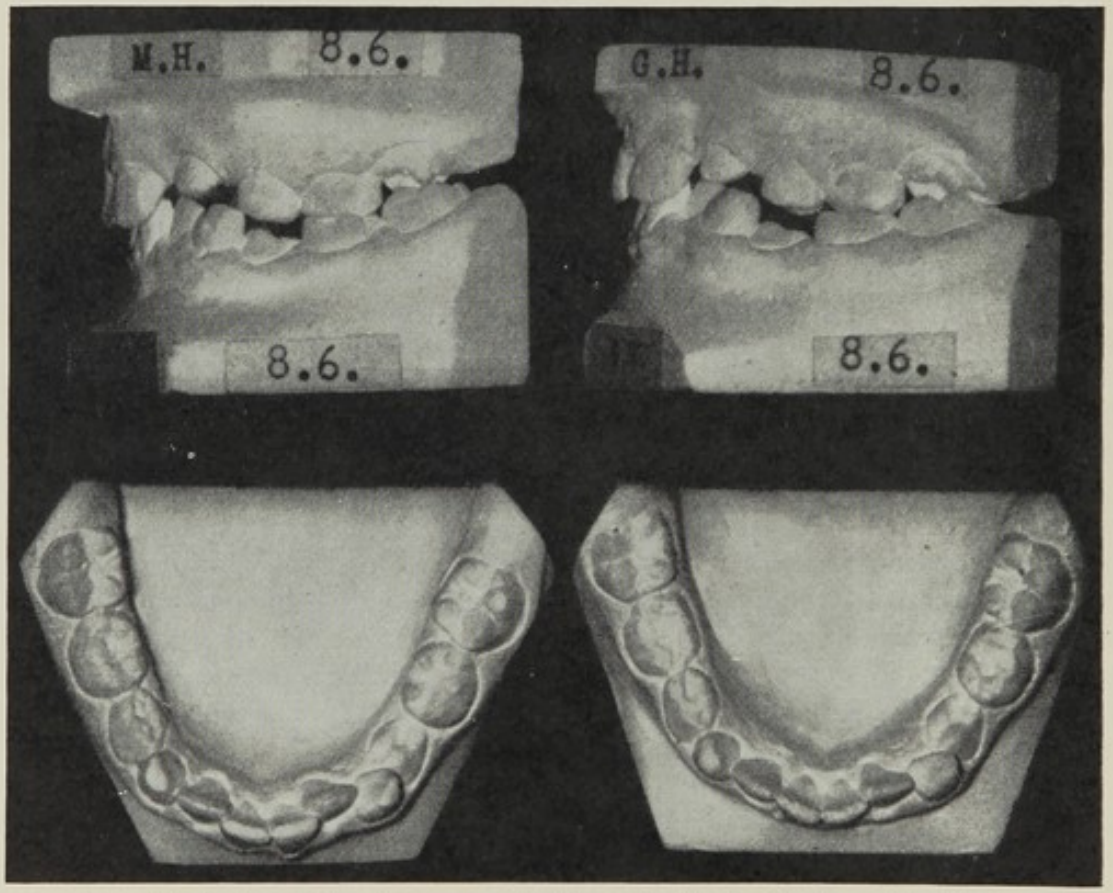
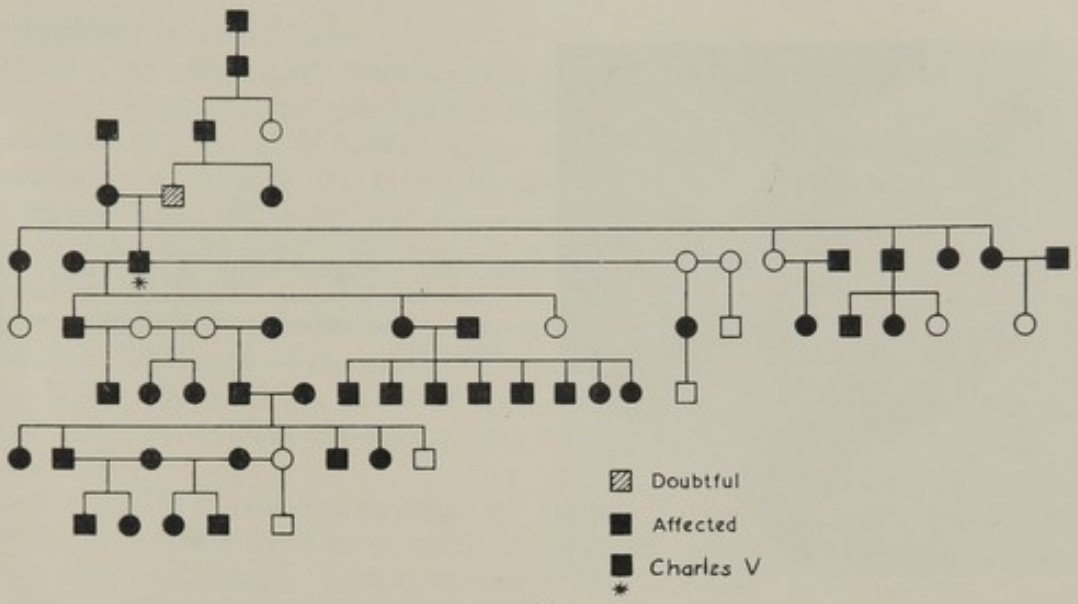


FIG. 238.—Similarity of development and defects in identical twins. Models from the mouths of two monozygotic twins aged 8½ years. The following special points of resemblance were noted: in both, left upper lateral incisor and first molar are just erupting, the left lower lateral incisor is instanding, and the left lower first deciduous molar is below the plane of occlusion. Radiographs show that both the second upper premolars will be absent in each case. (*Photographs by courtesy of the Orthodontic Dept., Dental School, Guy's Hospital, London.*)



(*a*)

(*b*)

FIG. 239.—Angle's Class III deformity. The lower jaw is excessively long and the upper is poorly developed. (*a*) Pedigree of House of Habsburg from A.D. 1377 to 1700. The Emperor Charles V* married an affected cousin and there are later cousin marriages between affected individuals. There is dispute as to whether Charles' father, Philippe le Beau, was affected or not. His mother was, also her father, Ferdinand of Aragon and Castile. (*After Rubbrecht, O. (1930). Rev. belge Stomat.* **27**, 175.) (*b*) The Emperor Charles V. There is a typical anomaly.

22 offspring of whom at least 10 were affected, but there were also 4 affected out of 8 in the offspring of two apparently normal members of the family.

Jones recorded as " cherubism " a condition observed in 4 out of 5 children of unaffected parents in which there was a symmetrical polycystic appearance of the

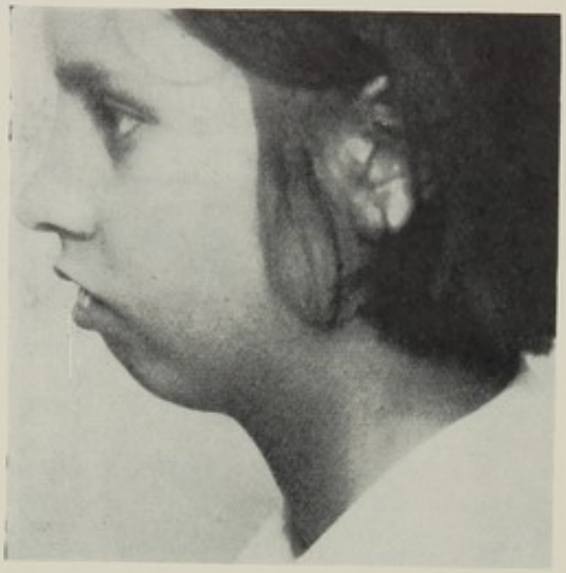
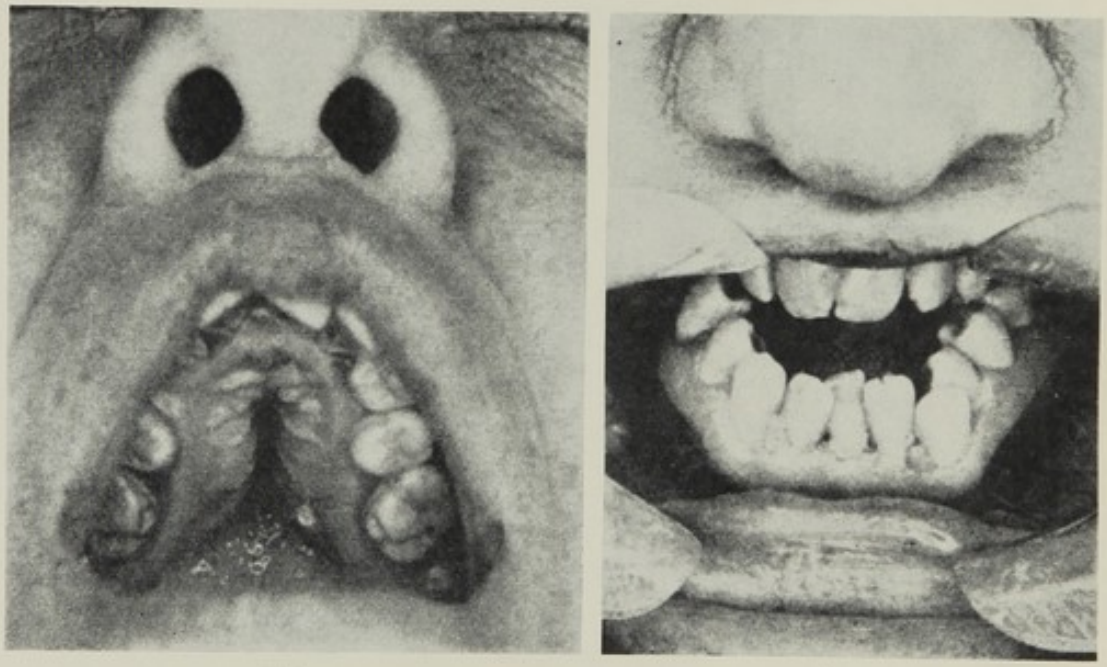


FIG. 240.—Angle's Class II deformity. The lower jaw is poorly developed, with receding chin. The upper incisors project over the lower lip.



(*a*) (*b*)

FIG. 241.—The jaws in oxycephaly. (*a*) Small and narrow palate. (*b*) "Open bite" with apparent protrusion of the lower jaw due to deficient growth of the upper.

jaws in radiographs and a characteristic facies. Histological examination later showed the appearances of fibrous dysplasia of bone. A possibly similar family was observed by Thomas. The condition occurred for five generations and is shown as being handed down through an affected parent, except in one case where the deformity was unilateral. There were six marriages between affected and normal persons producing 15 offspring of whom 6 were affected.

Susceptibility to dental caries

There is no satisfactory evidence that susceptibility to dental caries in man is affected by genetic factors, though it is likely that that is the case. Klein (1946) in an analysis of a group of 5,400 persons found that the highest DMF experience (teeth decayed, missing and filled) in offspring occurred when both father and mother had high DMF rates, mid-range experience occurred in offspring of parents both having middle rates, and lowest experience when parents both had low rates. When the DMF level of the mother was low, differences in that of the father were closely related to the level of the sons but only slightly to that of the daughters. When the DMF level of the father was low, differences in the level of the mother were closely related to the levels of both son and daughter. He concluded that dental caries in children involved strong familial vectors which probably have a genetic basis.

Keeler (1935) quotes the pedigree of Sedgwick in which 11 individuals in 3 generations suffered from early decay of the teeth, the incidence being consistent with a dominant factor. Cockayne considered Sedgwick's pedigree might be an example of hologynic inheritance since all those affected were females, and every female in 3 generations was affected except one who was too young; and the only 3 males had sound teeth. Keeler himself recorded a family of 3 generations in which early decay of a specific tooth, the upper right lateral incisor, appeared to depend upon a hereditary factor. In such a case the tendency to early decay could be dependent primarily upon an anatomical variation such as a deep cervical pit, the distribution of which was determined by genetic factors.

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CHAPTER 21

THE ALIMENTARY SYSTEM

CEDRIC CARTER

THE ANALYSIS of genetic influences in the development of disorders of the alimentary system is much less developed than that of most other systems. Apart from the neoplastic diseases considered elsewhere, systematic studies have so far been made for only six conditions: clefts of the lip and palate, peptic ulcer, pyloric stenosis, Hirschsprung's disease, multiple intestinal polyposis and fibrocystic disease of the pancreas. The latter is conveniently included under diseases of the alimentary system, though it is probably a generalized disease of the mucous glands.

There is good evidence that fibrocystic disease of the pancreas is largely determined genetically and that only one or two factors are mainly concerned. Very extensive studies of the familial incidence of hare-lip and cleft-palate have been made in Denmark and, though the findings make it clear that genetic factors play some part in the causation of the deformities, they cannot be determined by unifactorial inheritance of full penetrance; the families are probably not homogeneous. The fact that many sibs of children with pyloric stenosis are also affected, suggests that genetic factors are important in its causation; more will be known about the mode of inheritance when the incidence in the children of affected individuals is established. Only one small study has so far been made of the familial incidence of Hirschsprung's disease; this is sufficient to show that there is a familial concentration of the disorder, but no firm conclusions may yet be drawn on the mode of inheritance. Peptic ulcer poses a difficult problem in genetic analysis since it is such a common condition; probably as many as 10 per cent of the population suffer from it at some time in their lives, but family studies again show an undoubted concentration within families. Both familial intestinal polyposis of the large bowel and the rarer Peutz's syndrome are probably due to dominant genes of full penetrance.

CLEFTS OF THE LIP AND PALATE

Hare-lip is due to a failure of the maxillary process on that side to fuse with and overgrow the lower part of the fronto-nasal process; there is often an associated cleft palate on the same side, but lateral cleft palate does not occur independently of hare-lip.

Midline cleft palate arises later in embryonic life from a failure of fusion of the shelfs of mesoderm which grow inwards from the lateral borders of the maxillary process to fuse with each other. Midline clefts of the palate are not associated with hare-lip and do not extend beyond the incisor foramen which marks the junction of the lateral maxillary shelfs with the primitive palate formed by the fronto-nasal process.

There is evidence that genetic factors play a part in the causation of both these two groups of deformities and genetically too the two groups appear to be distinct since the increased incidence of such deformities in near relations of propositi is confined to deformities of the same group (Fogh-Andersen, 1942).

There is no definite evidence yet that any particular environmental factors play any part in the causation of these deformities. In rats cleft palate may be produced in the foetus by depriving the mother animal of riboflavine before and during pregnancy; but there is no evidence that malnutrition plays any part in man and there is no variation in incidence by social class. There is also no variation in the incidence of these deformities in man according to birth-rank or maternal age and there is no striking association of any particular type of maternal illness with the development of these deformities in the foetus (Fogh-Andersen, 1942).

Hare-lip with or without cleft palate

Varieties

Phenotypic.—Simple hare-lip may vary from a small notch in the edge of the lip to a complete division of the lip extending into the nostril. Usually there is an associated cleft in the alveolar margin, but this may be small even in cases of complete hare-lip. The malformation may be unilateral, when it is most often on the left side (Fig. 242), or bilateral; when bilateral the defect is usually greater on

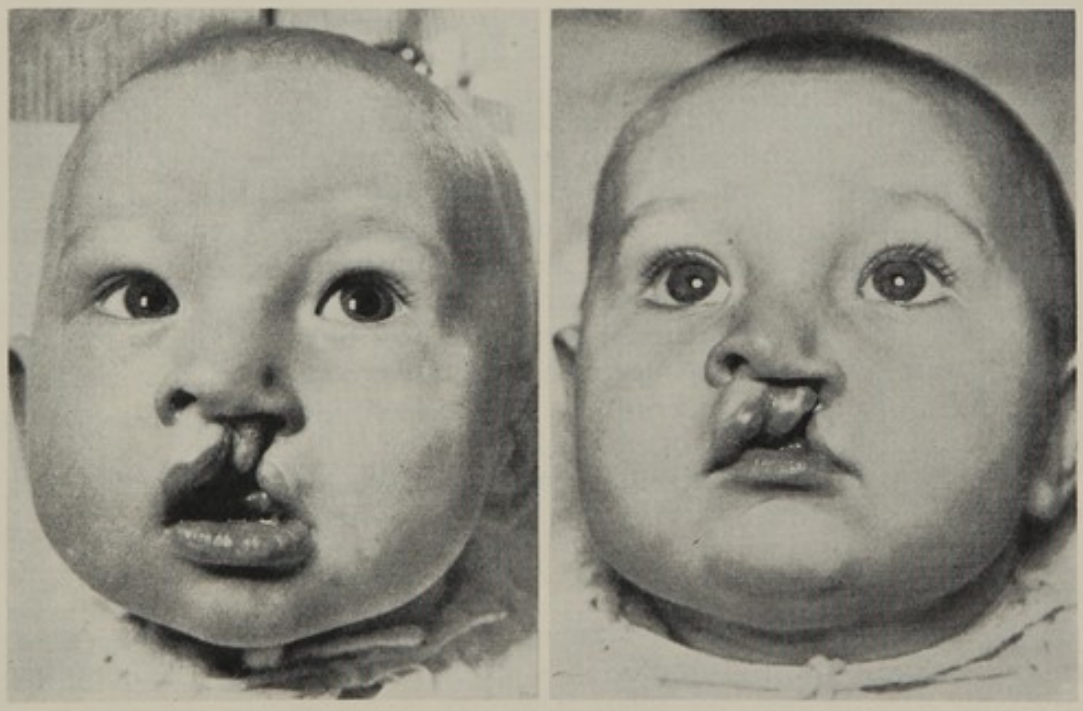

FIG. 242.—Brothers affected with a similar degree of hare-lip and cleft palate.

the left side. The commonly associated cleft in the palate on the same side may be complete but is often interrupted by one or more bridges. In cases of bilateral hare-lip the cleft may be unilateral or bilateral; when bilateral it is usually asymmetrical and more marked on the left side.

Genotypic.—All degrees of the malformation may occur within the same family and where one of a pair of identical twins has full bilateral hare-lip and cleft palate the other may show lesser degrees of the malformation or none at all. There is no reason at present to postulate more than one genotype for those cases unassociated with other malformations and the phenotypic variation may be regarded as variation in the degree of manifestation of the genotype.

Microforms.—It has been claimed that abnormalities of the lateral incisor teeth and also in the shape of the palate are unduly frequent in unaffected relatives and are minor manifestations of the same gene. There is as yet no good evidence of this.

Associated malformations

There is no striking incidence of other malformations in association with clefts of the lip and palate in children who come to surgical clinics or among the affected relatives of such children: but hare-lip and cleft palate occur not uncommonly in children born with other deformities and who do not survive. In the rather small series of well-described birth material hare-lip with or without cleft palate appears to be associated most often with major malformations of the central nervous system, while isolated and midline cleft palate is associated most often with skeletal malformations. Hare-lip and cleft palate in association with other malformations may well have a different causation from the uncomplicated cases seen at surgical clinics.

The incidence in the general population

The most reliable figures are for Denmark (Fogh-Andersen, 1942). The incidence of clefts of the lip and palate of all types in a number of large maternity hospitals in the second quarter of this century was 1·5 per 1,000 births (live and still). This is in good agreement with the number of children (about 50) requiring operation in Denmark annually. The records in maternity hospitals are not sufficiently detailed for the instances of hare-lip with or without cleft palate to be separated from those with cleft palate alone; but the records of cases coming to surgical clinics suggest that there are three cases of hare-lip with or without cleft palate to one of cleft palate alone. From this the incidence of hare-lip with or without cleft palate is 1·12 per 1,000 total births.

This figure is in good general agreement with smaller English and American hospital series.

Sex incidence

In the series from Denmark the proportion of males was 347 in 498 or 71·4 per cent (s.e. 2·4 per cent). The proportion of males rose with the severity of the defect, for double hare-lip and cleft palate it was 88 in 105 or 83·8 per cent (s.e. 3·6 per cent).

Consanguinity in the parents

The proportion of consanguineous marrages among the parents of children with the deformity is no higher than the rate in the general population, even in large series.

Familial incidence

Monozygous twins.—Counting only those pairs in which the type of twinning is well established and which form part of an unselected series there are three pairs on record in which both twins were affected and nine pairs in which only one was affected. A pair of monozygous concordant twins may differ considerably in the degree of defect which each of them has.

Dizygous twins.—Again referring only to unselected series there are 3 pairs which were both affected and 53 pairs in which only one was affected.

Full siblings.—In the Danish study, based on 489 index cases, the proportion of affected siblings (counting each sibship once for each child that was an index case) was 56 in 1,140 or 4·9 per cent (s.e. 0·7 per cent). Excluding twins of the index cases it was 54 in 1,122, or 4·8 per cent (s.e. 0·7 per cent). Among the children born after the index case the proportion was 15 in 255 or 6·7 per cent (s.e. 1·7 per cent). These proportions are in good general agreement with unselected series from Germany and Holland, though differences in the classification used make exact comparison impossible. Where both parent were normal in the Danish series the proportion of affected siblings was 48 in 1,081 or 4·4 per cent (s.e. 0·6 per cent) and it is of interest that the proportion was not significantly altered in those families where some member of the family other than a parent was also affected; in the few instances where one parent was also affected the proportion of affected sibs was higher, 8 in 58 or about 14 per cent, though in these sibships only 1 child in 13 born subsequent to the propositus was affected.

Half siblings.—In the Danish study there were 55 of these on the father's side, of whom one was affected, and 47 on the mother's side all of whom were unaffected.

Other relations.—In the Danish study the proportions were: parents, 17 in 992 or 1·7 per cent (s.e. 0·4 per cent); parents' siblings, 43 in 5,343 or 0·8 per cent (s.e. 0·1 per cent); cousins, 19 in 7,703 or 0·3 per cent (s.e. 0·1 per cent); and children, 3 in 554 or about 2 per cent.

The figures for children may well be too high since only two of the index cases had children and these were supplemented by the children of affected relations who were not in the direct line of ascent.

Individual pedigrees

Fig. 243*a–e* illustrates some individual pedigrees taken from the Danish series. They show a striking familial incidence and also the variations in manifestation that may occur within the same family.

Analysis

The twin incidence and the steady rise in the incidence of the malformation with increasingly close relationship to the index case strongly suggest that, at any rate in surgical clinic cases, genetic factors play an important part in the causation of the deformity. The finding that the proportion of affected siblings is independent of the existence of other affected members, other than parents in the family, suggests that the families are in large part homogeneous and that there is an hereditary predisposition in the great majority of instances. Assuming this is so the evidence from identical twins suggests that the manifestation rate of the gene or genes concerned must be incomplete, perhaps less than 30 per cent.

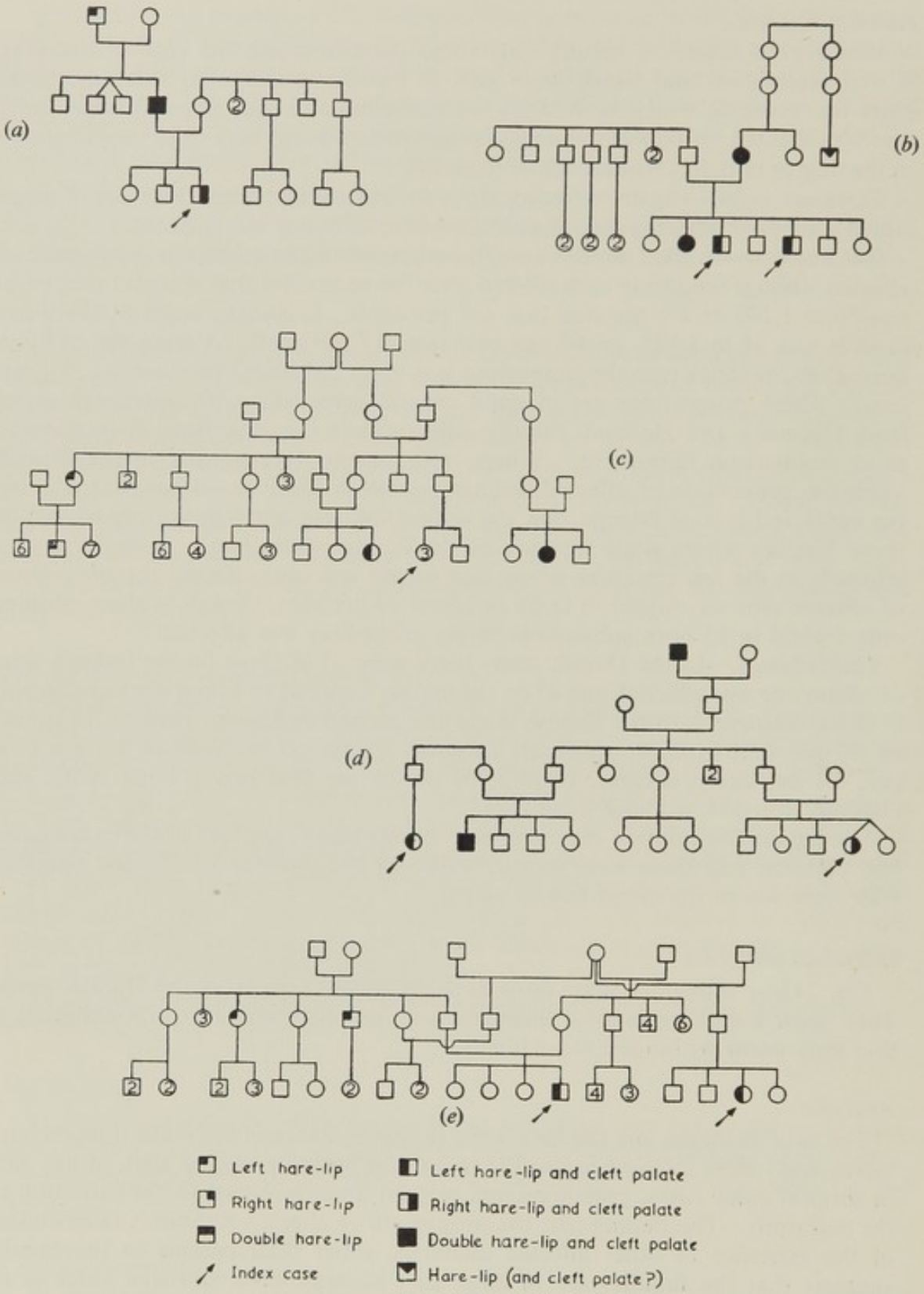

FIG. 243.—(*a*)–(*e*) Pedigrees of hare-lip—with or without cleft palate. (*After Fogh-Anderson, P. (1942). Inheritance of Hare-lip and Cleft Palate. Op. Dom. Biol. hered. hum. Kbh.*, **4**. *Copenhagen; Munksgaard.*)

The sex incidence has been interpreted as due to sex-linkage, but there is no good evidence of this and the increasing preponderance of males with increasing severity of the lesion suggests that there is some sex-limitation with a higher manifestation rate in males, rather than any form of sex-linkage.

The frequency of the deformity in the general population, if most instances are to have the same genetic basis, is too great for the consanguinity rate among the parents of affected children to provide much information on the dominant or recessive nature of the genes mainly concerned.

The significantly higher incidence of the defect in the siblings than in the parents (and possibly children) of index cases suggests recessive inheritance, though the allowance made for the tendency of the more severely affected individuals to die in infancy or at any rate not to reproduce can only be a rough approximation to the truth. Striking individual pedigrees such as those illustrated above, when allowance is made for their selection, provide little information about the mode of inheritance, being compatible with incomplete dominant or recessive inheritance. Such families do not occur sufficiently often to suggest that the condition is more strongly genetically determined in some families than in others.

The observed familial incidence is explained most economically by postulating monogenic recessive inheritance with about 20 per cent manifestation, but this is far from being proved. This hypothesis implies a gene frequency of about 1 in 14.

Eugenic prognosis

Rough estimates of the chances of different degrees of relations being affected taken from the Danish investigation are: siblings when both parents are normal, 1 in 20; siblings when one parent is affected, 1 in 10; and children of an affected married to a normal individual, 1 in 50.

Cleft palate alone

Varieties

Phenotypic.—Affected individuals differ only in the extent of the median cleft. This may involve the soft palate alone, or the soft palate and some part of the hard palate up to the incisor foramen. Occasionally the cleft may be in part or entirely submucous.

Genotypic.—There is insufficient information to show whether the families are genetically homogeneous, but there are indications that they are not and also that some instances may be largely determined by non-genetic mechanisms.

Associated malformations

There is a tendency for children born with isolated cleft palate to have other malformations; many of these are abnormalities of the hands and arms, legs and feet. There is no such tendency among children coming to surgical clinics or in the affected relations of index cases.

Incidence in general population

In Denmark this is about 0·04 per cent and hospital statistics from other countries, based on smaller series, are in good agreement with this.

Sex incidence

In contrast to the male preponderance among individuals with hare-lip with or without cleft palate there is a marked excess of females with cleft palate alone. In the Danish series the proportion of females was 133 in 205 or 64·9 per cent. This preponderance is less marked with small than large clefts.

Consanguinity

The proportion of consanguineous marriages among the parents is not raised above that in the general population.

Familial incidence

Twins.—Only a very few pairs are recorded in which the type of twinning is well established and which belong to unselected series. There are four such monozygous pairs and in all of these only one twin was affected; there are eleven dizygous pairs and in only one of these were both twins affected.

Full siblings.—In the big Danish investigation the proportion of affected siblings (counting each sibship once for each child that was an index case) was 13 in 517 or 2·5 per cent (s.e. 0·7 per cent); only one of the sibs was a twin of an index case and this twin was unaffected. Where both parents were normal the proportion of siblings affected was 9 in 493 or about 1·8 per cent; but the proportion is probably considerably higher in those families in which some member other than a parent was also affected; in few families of this type in the series it was 3 in 25. Where one parent was affected the proportion of siblings affected was 4 in 24.

Half-siblings.—In the Danish series there were 28 of these on the mother's side and 19 on the father's side; none of them was affected.

Other relations.—In the Danish study the proportions were: parents, 7 in 405 or about 1·7 per cent; parents' siblings, 10 in 2,085 or 0·48 per cent (s.e. 0·16 per cent); cousins, 11 in 3,156 or 0·35 per cent (s.e. 0·11 per cent); and children, 5 in 70 or about 7 per cent.

The figure for children may be too high since only nine of the index cases had children and to these were added the children of affected relations not in the direct line of ascent: but taking only children of propositi the proportion affected was much the same—2 in 27.

Individual pedigrees

Fig. 244*a–d*, taken from the Danish series, illustrates a striking familial incidence.

Analysis

The familial incidence in comparison with that in the general population leaves no doubt that genetic factors play a part in the causation of the disease in at least a proportion of cases. Individual families with a strikingly high familial incidence appear more often than one would expect by chance and suggest that genetic determination plays a greater part in some families than others. This is also suggested by the indication that a higher proportion of the sibs of index cases are affected in those families where some member other than a parent is also affected. The twin series are too small to provide much information; but some

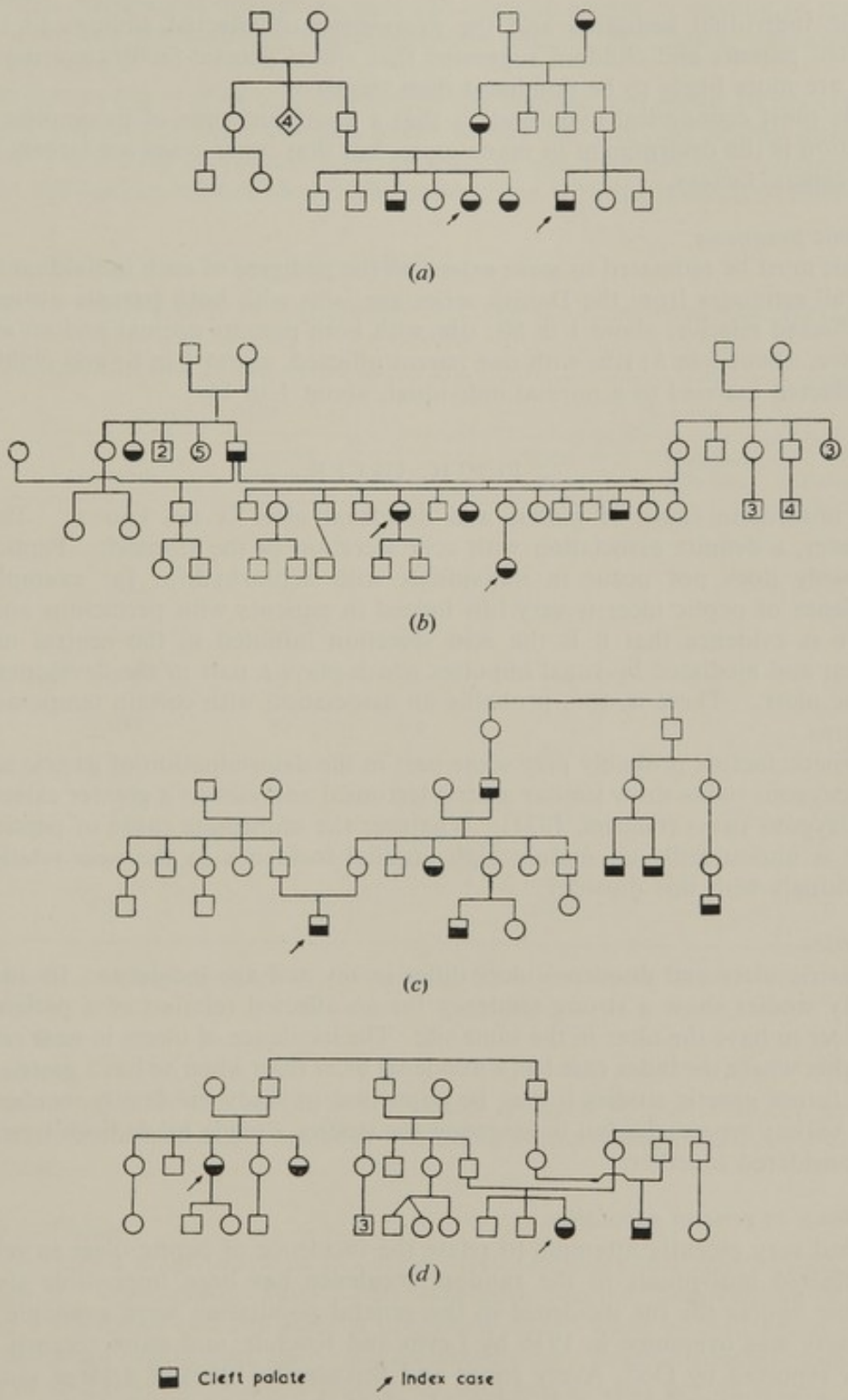

FIG. 244.—Pedigrees of isolated cleft palate. (*After Fogh-Anderson, P. (1942). Inheritance of Hare-lip and Cleft Palate. Op. Dom. Biol. hered. hum. Kbh.*, **4**. *Copenhagen; Munksgaard.*)

of the individual pedigrees and the proportion of affected siblings to that of affected parents and children suggested that where genetic factors are important they are more likely to be dominant than recessive.

The most economical hypothesis is that a dominant gene of incomplete manifestation is the determinant in many cases, but that other cases are largely due to non-genetic factors.

Eugenic prognosis

This must be estimated to some extent on the pedigree of each individual family. Overall estimates from the Danish series are: sibs with both parents normal and no affected relative, about 1 in 80; sibs with both parents normal and an affected relative, about 1 in 8; sibs with one parent affected, about 1 in 6; and children of an affected married to a normal individual, about 1 in 15.

PEPTIC ULCER

The immediate cause of gastric and duodenal ulcer is not known. There is, however, a definite association with acid secretion in the stomach. Peptic ulcer probably does not occur in individuals with achlorhydria; for example, the incidence of peptic ulcer is very low indeed in patients with pernicious anaemia. There is evidence that it is the acid secretion initiated in the central nervous system and mediated by vagal impulses which plays a part in the development of peptic ulcer. There is, too, probably an association with certain temperamental patterns.

Genetic factors probably play some part in the determination of gastric acidity; monozygous twins show similar gastric test-meal analyses to a greater extent than do dizygous twins (Glatzel, 1931). Whatever the immediate cause of peptic ulcer there is undoubtedly an unduly high familial incidence in the near relations of individuals with this disorder.

Varieties

Gastric ulcer and duodenal ulcer differ in sex and age incidence. In addition, family studies show a strong tendency for an affected relation of a patient with an ulcer to have the ulcer in the same site. The incidence of ulcers in near relatives is higher where the index case has a duodenal ulcer than when he has a gastric ulcer.

In future genetic studies it may be important to study the family incidence for each variety separately, but in assessing the studies already made both types must be considered together.

Incidence in general population

Until very recently attempts to relate the incidence of peptic ulcer in relations of affected individuals to the random incidence has been impossible since no reliable figures for the incidence in the general population were available. This difficulty was overcome in 1936 by Levin and Kuchur, and more recently in the study reported by Doll, Avery Jones and Bukatzsch (1950) of a large sample of the industrial population in London. Each of the individuals studied were interviewed and further investigated where their medical history suggested that an ulcer might be present; several ulcers were found which had not been diagnosed

previously. Social-class differences were not marked, except in relation to the site of the ulcer and occupational differences were slight. The figures obtained are shown in Table I.

These figures are in good agreement with the findings that about 10 per cent of the adult population show chronic ulcers or the scars of old healed ulcers at necropsy. Those for individuals over 65 years of age were not quite comparable with the rest and so are not used in the comparison with the familial incidence.

TABLE I

INCIDENCE OF PEPTIC ULCER BY AGE GROUPS IN A SAMPLE OF THE INDUSTRIAL POPULATION IN LONDON

Age	Men			Women		
	Total number	Number affected	Per cent	Total number	Number affected	Per cent
14–	199	0	0·0	133	0	0·0
20–	300	4	1·3	445	2	0·4
25–	1,128	28	2·5			
35–	1,375	63	4·6	236	2	0·8
45–	1,089	80	7·3	249	4	1·6
55–	625	39	6·2			
65+	155	9	5·8	17	2	0
	4,871	223	0	1,080	10	0

After Doll, R., and Buch, J. (1950). "Hereditary Factors in Peptic Ulcer." *Ann. Eugen.* **15**, 135.

Sex incidence

For duodenal ulcer the proportion of males is about 80 per cent: for gastric ulcer the proportion of males has been increasing in this century and is now about 50 per cent.

Familial incidence

Twins.—Only a single series is available, from Germany (Camerer, 1935). In this series of 7 monozygous pairs 1 pair were both affected; one member of this pair had a duodenal and the other a prepyloric ulcer: while of 7 dizygous twin pairs 1 pair were concordant, both with duodenal ulcer. Several isolated examples of pairs of monozygous twins both affected with peptic ulcer are on record, and in all these the ulcers have usually occurred in similar sites in each member of the pair.

Other relations.—Doll and Buch (1950) conducted a family investigation at about the same time and in the same district (North London) as the survey by Doll and his colleagues of the general industrial population and so were able to compare the incidence in siblings and parents of their index cases with that which might be expected by chance. This family investigation was less searching than that of the sample of the general population and so probably underestimated the extent of the increased incidence in the near relations of index cases. The table summarizing their findings is reproduced in Table II.

There is a significant increase among the number of affected individuals found both among brothers (56 instead of 25) and sisters (14 instead of 5·7). The incidence among fathers (6 instead of 1·1) also reaches the 0·01 level of significance if those over 65 years of age are included, which brings the number affected to 10 and the expected number affected to 3·68.

The evidence to date

The significantly higher incidence of ulcer in brothers of index cases might be attributed to environmental factors: but the higher incidence too in fathers, in a condition which is independent of social class and occupation, leaves little doubt that genetic factors are concerned in the development of peptic ulcers. The small series of 7 monozygous twins with only 1 pair concordant shows that the manifestation of the genetic factors concerned is far from complete.

It is improbable that single genetic factors of large effect are directly concerned, and if single genetic factors are ultimately implicated it is likely that they will be found to set indirectly through their control of characters which predispose to ulcer formation—such as the central nervous control of acid secretion, the blood supply of the stomach, or the resistance of the gastric mucosa to digestion by its own secretions.

CONGENITAL PYLORIC STENOSIS

The essential nature of this disorder is not known. The hypertrophy of the circular muscle fibres and, to a lesser degree, of the longitudinal muscle fibres of the pylorus is presumably secondary to some dysfunction as yet undiscovered. The condition has been found as soon as seven days after birth and it has been found in premature babies before the expected date of birth. It has been shown that the condition may develop later in children who showed no radiological evidence of pyloric stenosis in the latter part of the first week of life. Half a dozen instances have been reported in which the tumour was present without giving rise to symptoms; probably some other factor in addition to the tumour must be present before symptoms arise.

There is some evidence that genetic factors play a part in the causation of the deformity, and no sure evidence that any environmental factors are concerned except perhaps some factor associated with birth order. In a thorough investigation based on a large number of children with pyloric stenosis treated in Birmingham hospitals McKeown, MacMahon and Record found no striking variation in the incidence by social class, by season of the year, by maternal age or with any particular type of pathological pregnancy; but there is probably some variation in manifest incidence by birth order. In the Birmingham series pyloric stenosis was

TABLE II

OBSERVED INCIDENCE OF PEPTIC ULCER IN SIBLINGS AND PARENTS OF AFFECTED INDIVIDUALS COMPARED WITH THE EXPECTED INCIDENCE

Age	Brothers			Sisters			Fathers			Mothers		
	Total number	Number affected	Expected	Total number	Number affected	Expected	Total number	Number affected	Expected	Total number	Number affected	Expected
14–	6	0	0·0	7	0	0	—	—	—	—	—	—
20–	10	0	0·13	80	2	0·36	—	—	—	—	—	—
25–	63	2	1·56									
35–	143	12	6·55	138	6	1·17	1	1	0·05	1	0	0·0
45–	153	31	11·24	258	6	4·14	5	2	0·40	19	0	0·3
55–	84	11	5·24				10	3	0·62			
All under 65	459	56	24·72	483	14	5·67	16	6	1·07	20	0	0·3

After Doll, R., and Buch, J. (1950). "Hereditary Factors in Peptic Ulcer." *Ann. Eugen.*, **15**, 135.

most common in the first-born and became progressively less frequent with increasing birth order; 51 per cent of 478 cases of pyloric tumour were first-born and only 36 per cent of 853 controls (in an additional 20 instances of pyloric stenosis the birth rank was not ascertained). At a London children's hospital the proportion of first-born among children where the diagnosis was made in the medical wards and confirmed at operation was closer to, but still on the whole above that for all children in the area born in the same years; of 401 children, born between 1946 and 1950, 199 or 50 per cent were first-born (in an additional 7 cases in this period, birth order was not ascertained) while the percentage of all children first-born in recent years in Greater London is about 43.

Varieties

No varieties are differentiated; the tumours differ only in size and vascularity.

Associated malformations

There is no definite association with other malformations.

Incidence in the general population

Four estimates are available from England. Davison reported that in Newcastle between 1939 and 1949 there were 49 instances of pyloric stenosis in 17,457 live births, an incidence of 2·8 per 1,000 (s.e. 0·4 per 1,000). Lawson for Dundee between 1940 and 1946 found 32 instances in 21,288 live births an incidence of 1·5 per 1,000 (s.e. 0·3 per 1,000). McKeown, MacMahon and Record for Birmingham between 1940 and 1949 found 578 cases in 194,216 births, an incidence of 3·0 per 1,000 (s.e. 0·1 per 1,000). Wallgren for Göteborg in Sweden, between 1934 and 1940, found 102 cases in 25,642 live births, an incidence of 4·0 per 1,000 (s.e. 0·4 per 1,000). These incidences, some of which are significantly different from others, may depend on different criteria for diagnosis rather than real regional variations.

Sex incidence

There is general agreement in a number of large series that close to 80 per cent of all affected children are males.

Consanguinity

There is probably no real increase in the proportion of consanguineous marriages among the parents of children with pyloric stenosis, though in one series (Cockayne and Penrose) 4 of 212 parents were first cousins. In the Birmingham series the incidence was 2 in 477 marriages or 0·4 per cent, the proportion in the general population.

Familial incidence

Twins.—There are only two small series on record (Ford, Brown and McCreary; and Powell and Carter) which were unselected and in which the type of twinning was well established; here, of 5 monozygous pairs 2 were concordant, while of 6 like-sex dizygous pairs 1 pair were concordant in that both had tumours, though only one of this pair had symptoms, the other 5 were discordant (Fig. 245). There were 5 unlike-sex pairs and these were all discordant.

Siblings.—Two large series of sibships have been recorded. In that of Cockayne and Penrose (1934) the proportion of brothers of 212 index cases, excepting the twins of index cases affected, was 5 in 168 or 2·6 per cent (all 212 of the index cases came from different sibships). The proportion proved affected among those born after the propositi was higher but not significantly so; 5 in 78 or 6·8 per cent. Of the sisters 2 in 140 were affected, both of these were among the 54 sisters born after the index case. There were 3 further brothers and 1 sister who were possibly affected. Of the twins of index cases 3 of unlike sex were not affected, while of 3 of like-sex (all males) 2 were affected and 1 unaffected, but these were not classified according to type of twinning.

FIG. 245.—Identical twin boys of whom only the one on the left had pyloric stenosis.

In the series from Birmingham (McKeown, MacMahon and Record, 1951) bases on 466 fraternities, the proportion of brothers affected, other than twins of the index case, was 20 in 328 or 6·1 per cent (s.e. 1·4 per cent). The proportion among those born after the first affected individual in the sibship, where this was an index case, was 12 in 122 or 9·8 per cent (s.e. 2·9 per cent). Of 319 sisters other than twins 5 were affected, 1·6 per cent, and of those born after the index case 2 in 119 were affected, 1·7 per cent. Of the twins of the male index cases 1 in 7 was affected as was 1 in 10 of the twins of the female index cases, but the type of twinning was not established.

Little information is yet available for half-siblings. In the Birmingham series of 32 half-sibs with the same mother 1 was certainly and 3 possibly affected.

Parents.—Since it is only a generation ago that an effective method of treatment of pyloric stenosis became widely known it is not surprising that only isolated instances of parents of affected children being themselves affected have been reported. Carter and Savage (1951) reported 2 instances among 480 children treated at a London hospital between 1943 and 1947 where the father was reported

to have been affected; in only 1 instance was the father's condition confirmed at operation. At the same hospital among 218 children treated between 1948 and 1950, where the diagnosis was made by a physician and confirmed at operation by a surgeon, there were 4 instances in which the mother was treated as a baby there for pyloric stenosis (in 3 the diagnosis was confirmed at operation, and in the other treated before Rammstedt's operation was introduced the diagnosis was not in doubt) and also 1 instance in which the father had been shown, at operation by a member of the staff of the hospital, to have pyloric stenosis at a nearby nursing home. These are small numbers but suggest that mothers, but perhaps not fathers, are more often affected than one would expect by chance.

Children.—No information is yet available.

First cousins.—McKeown, MacMahon and Record found that of 2,081 maternal cousins 8 were probably affected, an incidence of about 3·8 per cent, while of 1,903 paternal cousins 3 were probably affected, an incidence of about 1·5 per cent: so there is no suggestion of any raised incidence among first cousins.

Individual pedigrees

Sibships with three members affected are not uncommon. Apart from this there are few families on record in which several members are affected where the diagnosis has been confirmed at operation. One family in which four first cousins all in different sibships and in all of which the diagnosis was confirmed at operation in the same hospital has been recorded and is illustrated in Fig. 246*a*. Another unpublished family is illustrated in which the mother was treated medically before the introduction of the operation in this same hospital, and had two sons in which the condition was diagnosed and confirmed at operation in this hospital and a daughter, by another husband, who was also found affected at operation at another London children's hospital (Fig. 246*b*).

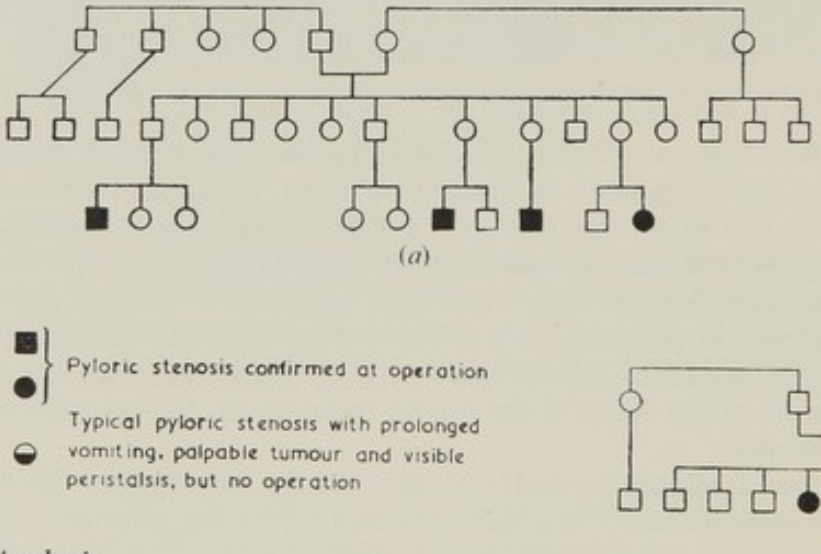

FIG. 246.—Pedigrees of pyloric stenosis. ((*a*) *After Carter, C. O., and Savage, T. R. (1951). Arch. Dis. Childh.*, **26**, 50.)

Analysis

The high incidence in the sibs of affected children and the suggestion of an even higher incidence in the monozygous twins of affected individuals imply that genetic factors play some part in the development of the malformation. There is

no reason at the moment to attribute the sex-incidence to sex-linkage rather than sex-limitation: nor is there much reason to prefer a recessive to a dominant role for the genetic factors concerned. However, if a recessive gene was predominantly concerned it must have a gene frequency of about 1 in 9 and this would fit better with the failure to detect any increase in the incidence of the condition in first cousins than would incomplete dominant inheritance.

Further twin studies and an accurate estimate of the incidence of the disease in parents, children and half-siblings of children with pyloric stenosis would clarify the genetic background of the condition.

Eugenic prognosis

From the series reported by Cockayne and Penrose and that reported by McKeown, MacMahon and Record it appears that the chance of a subsequent brother being affected is about 1 in 12 and for a subsequent sister about 1 in 50. No information is yet available for the prognosis for children of individuals who have had pyloric stenosis.

FIBROCYSTIC DISEASE OF THE PANCREAS

The cause of this condition is not precisely known. It is considered by several paediatric pathologists (Farber, Bodian) to be due to a generalized abnormality of the mucous glands; but the symptoms of the disease are in the main due to the affection of three organs, the small intestine, the pancreas and the bronchioles. A proportion of the cases present with neonatal intestinal obstruction, the remainder with intestinal and respiratory signs and symptoms—failure to thrive, fatty foul-smelling stools, recurrent respiratory infection.

There is good evidence that genetic factors play a major part in the causation of the disease and no environmental factors have yet been shown to have more than a secondary role.

Varieties

There is no evidence of any genotypic varieties of the condition.

Associated malformations

There is no increased incidence of other malformations.

Incidence in the general population

No accurate estimates are available. The condition is found in between 1 and 4 per cent of post-mortem examinations in children's hospitals in England and the United States of America, suggesting a high incidence, but none of these hospitals know at all accurately the population from which they draw. Further, many cases are still undiagnosed. The incidence probably lies somewhere between 1 in 1,000 and 1 in 10,000 births.

Parental consanguinity

No increase in the proportion of first cousin marriages among the parents of children with this condition above that in the general population has yet been

demonstrated. In a series of 118 index cases from Boston, one pair of parents were first cousins. In a series of 77 sibships from London there were no instances of parental consanguinity.

Incidence among relatives

Twins.—Of the twins recorded two pairs only formed part of an unselected series, one of these like-sexed dizygous and the other of unlike sex—both pairs were discordant. Of the remaining eight pairs, in each of which the type of twinning was not known, two pairs were certainly and two probably concordant. There is no known instance of monozygous twins discordant for the condition.

Siblings.—Three fairly large series of sibships have been recorded (two from North America and one from England) and several small series. In a disease of this kind, where many affected children die undiagnosed and, on occasions, the diagnosis is only made when the second member of the family is affected, it is difficult to decide which of the affected members have been ascertained independently. It is best, therefore, to follow Haldane's suggestion and calculate the proportion affected on two hypotheses, that the sibships are likely to be ascertained once for each child affected (p_1) and that the sibships are a random sample of all sibships at risk (p_2). The true proportion is likely to be somewhere between p_1 and p_2.

The values of p_1 and p_2 have been calculated for the three large series, and are shown in Table III (only sibships of more than one child are included).

TABLE III

	Number of sibships	Number of children in sibships	Number of affected children	p_1	p_2
Andersen and Hodges	31	91	44	0·22 s.e. 0·05	0·34 s.e. 0·07
Lowe, May and Reed –	95	345	145	0·20 s.e. 0·03	0·30 s.e. 0·03
Bodian and Carter –	62	169	81	0·18 s.e. 0·04	0·29 s.e. 0·05

It will be seen that the true proportion of affected siblings is likely to be close to 1 in 4 or 25 per cent in all three series. In the London series it is also possible to discover the proportion of siblings affected born after the index case—6 in 27, again close to 25 per cent. This is not possible in the series from Boston or in the New York series, but in the latter 7 of 28 children born after the eldest child proved affected in the sibship were affected.

There is no suggestion from the distribution of affected children that the sibships are not homogeneous. The number of sibships with one, two or three members affected in each size of sibship in the three large series is in good agreement with that expected in the assumption that the probability of a child in those sibships being affected is 1 in 4 (Table IV).

TABLE IV

Family Size / Number affected		Two		Three			Four				Five			
		1	2	1	2	3	1	2	3	4	1	2	3	4
Andersen and Hodges	–	11	1	8	4	1	0	0	0	1	0	0	0	1
Lowe, May and Reed	–	23	4	27	8	2	8	6	0	2	4	4	0	1
Bodian and Carter	–	29	7	10	6	0	1	3	1	0	2	0	0	0
Total	Observed – –	63	12	45	18	3	11	10	2	2	6	4	0	2
	Expected – –	64	11	48	16	2	16	8	2	1	6	4	1	0·2

Other relations.—(a) *Parents and children.* No information is yet available for children. No histologically proved examples of fibrocystic disease of the pancreas have been recorded hitherto in adults and no children with a well-formed clinical diagnosis of the disease have survived into adult life. None of the parents of the London series had any symptoms suggestive of fibrocystic disease of the pancreas.

(b) *Aunts and uncles.* The diagnosis of the condition in aunts and uncles, dying in childhood, of affected children can only be conjectural with a disease so recently recognized; but the proportion who have a history suggestive of fibrocystic disease of the pancreas is certainly small. In the London series of 524 aunts and uncles none had a history suggestive of the disease. In the Boston series one aunt or uncle was proved to be affected.

(c) *First cousins.* Several instances of first cousins of index cases also affected are known. In the Boston series there were 2 first cousins proved affected and 3 considered probably affected, but the total number of first cousins, about whom information was collected, is not stated. In the London series there was one first cousin proved affected, but none probably affected, among 482. These figures suggest that the incidence in first cousins is higher than that in the general population and also that the incidence among first cousins is only a small fraction of that among full siblings.

(d) *Stepsibs.* Not many records of stepsibs have been published. In the London series there were 11 stepsibs of whom 8 were certainly unaffected, 1 was alive and well but less than two years old and 2 were premature and died in the first few hours of life. No analysis of stepsibs was made in the two American series but the pedigrees illustrated show 11 stepsibs in each series all probably unaffected.

Individual pedigrees

Two pedigrees from the London series (Fig. 247*a* and *b*) and two from the Boston series (Fig. 247*c* and *d*) are illustrated.

Analysis

No definite conclusion has been reached on the mode of inheritance, but the most economical hypothesis at the moment is that the condition is due to a recessive gene.

The relatively low incidence among aunts and uncles, first cousins and, probably,

stepsibs compared with an incidence of about 1 in 4 among full brothers and sisters makes it improbable that a single dominant gene with incomplete manifestation is responsible; but with a recessive of gene frequency about 1 in 70 one would expect about 1 first cousin in 280 and 1 stepsib in 140 to be affected; the few figures available are quite compatible with these expectations.

The recessive gene hypothesis would be confirmed if an increase in the rate of parental consanguinity could be shown, but the general frequency of first cousin marriages since World War II is small in Great Britain (about 4 per 1,000 in children attending a London hospital) and fibrocystic disease of the pancreas is

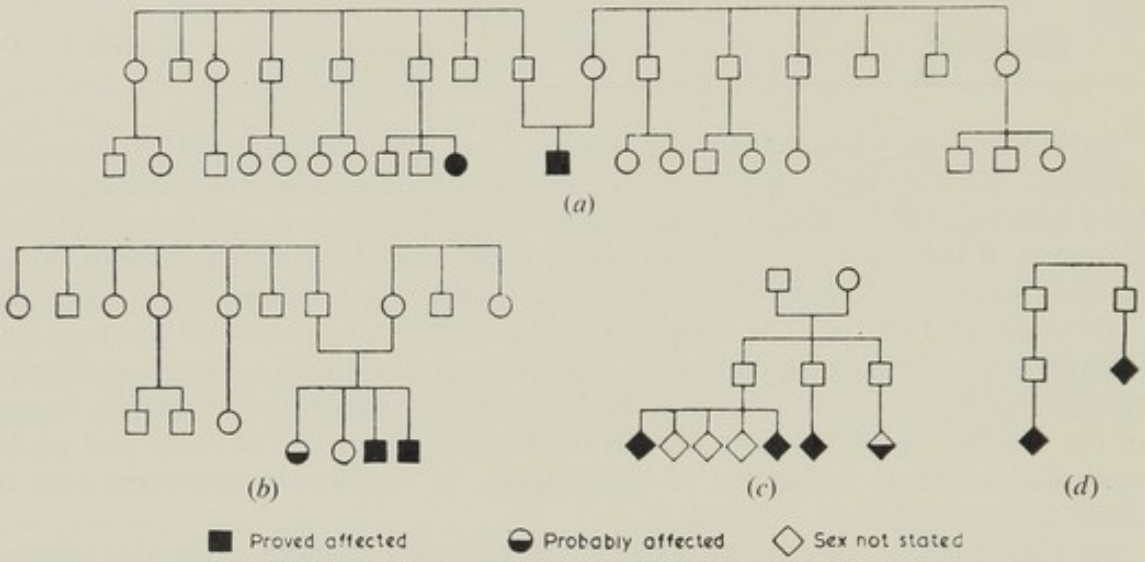

FIG. 247.—Pedigrees of fibrocystic disease of the pancreas. ((*a*) and (*b*) *From the Hospital for Sick Children, Great Ormond Street, London.* (*c*) *and* (*d*) *After Lowe, C. U., May, C. D., and Reed, S. C. (1949). Amer. J. Dis. Child.*, **78**, 349.)

not an uncommon disorder, so that large series will be needed to test whether there is an increase in the consanguinity rate.

The higher estimates of the frequency of this lethal condition imply an unusually high mutation rate to the recessive gene postulated, unless the heterozygotes are unusually fertile.

Eugenic prognosis

Parents who have had one or more affected children should, on the information at present available, be told that the chance of each subsequent child being affected is 1 in 4, or 25 per cent. The chance of stepsibs and all other relations being affected is probably small.

HIRSCHSPRUNG'S DISEASE

Pathology

The morbid anatomy of this condition has recently been described by Bodian (1949) and recently, too, the radiological methods of making the differential diagnosis from other causes of chronic constipation have been established. Radiologically and at necropsy a dilated segment of colon and sometimes small

intestine is seen which terminates in a varying length of bowel of normal width. Histologically the appearance of the dilated portion of the bowel is normal apart from some hypertrophy of the muscle, while the appearance of the macroscopically normal part of the bowel is characterized by the absence of ganglion cells in the myenteric plexuses together with a marked enlargement of the nerve-fibre bundles running between the muscle coats. In the short transitional segment the ganglion cells are small and ill-formed. The abnormality is fully present, though there is less muscle hypertrophy, in the cases who die in the first few days of life from intestinal obstruction.

Varieties

Instances of Hirschsprung's disease may be differentiated into those with short segments and long segments of bowel affected; but the division is artificial and one family has already been reported in which one child had a short segment and another a long segment of bowel affected.

It is not yet certain whether the rare instances of localized aganglionic segments with normal gut above and below are varieties of Hirschsprung's disease.

Associated malformations

In the small series reported there is no suggestion of an increased incidence of other malformations. Retinitis pigmentosa has been observed, possibly incidentally.

Parental consanguinity

No instance of consanguinity was found among the parents of the 37 index cases among the London series.

Sex incidence

There is a great preponderance of boys; in the London series there were 3 girls out of 40.

Incidence in general population

Many instances of the disease remain undiagnosed. In a London children's hospital about 4 cases are seen yearly and these are drawn from all over the country. The general incidence is perhaps of the order of 1 in 50,000 to 1 in 100,000.

Individual pedigrees

Two individual pedigrees are recorded selected from the London series (Fig. 248*a* and *b*): also one large sibship reported from America (Fig. 248*c*).

Familial incidence

Twins.—In the two pairs where the diagnosis was well established and which formed part of an unselected series, the monozygous pair (both boys) were both affected and the dizygous pair (also both boys) were discordant. Another pair of twins (both female) both affected are also on record, but there is no information on the type of twinning.

Siblings.—Only one small unselected series of sibships has been reported hitherto (Bodian, Carter and Ward). Here of 32 brothers of 37 propositi 4 were proved

affected (2 of these being a pair of monozygous twin siblings of an index case (Fig. 249), while none of 28 sisters were affected. If ascertainment is by individuals the proportion affected is 22 per cent. Of the brothers born subsequent to the

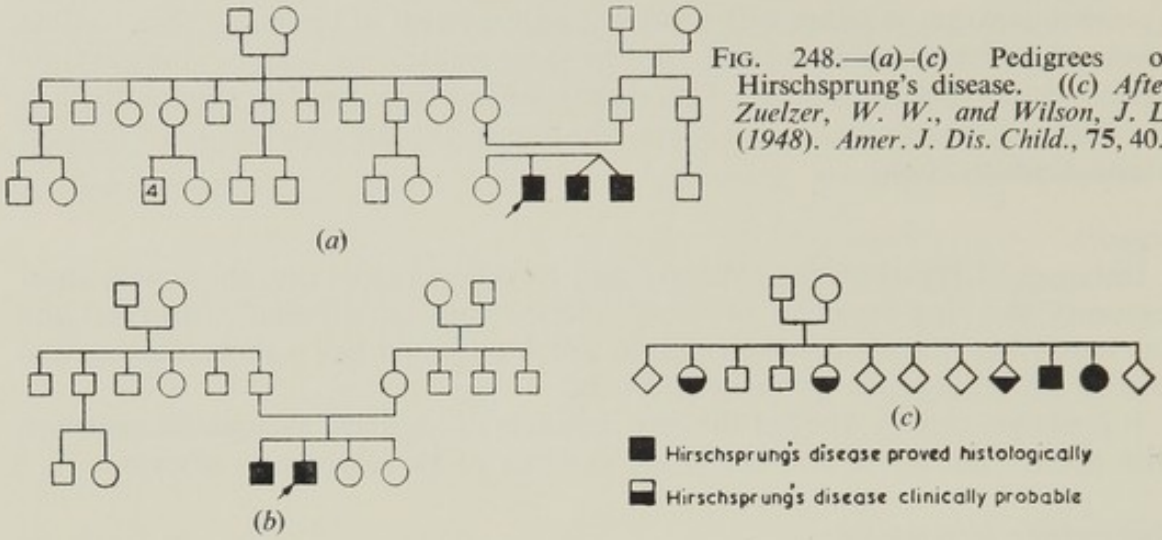

FIG. 248.—(*a*)–(*c*) Pedigrees of Hirschsprung's disease. ((*c*) *After Zuelzer, W. W., and Wilson, J. L. (1948). Amer. J. Dis. Child.*, 75, 40.)

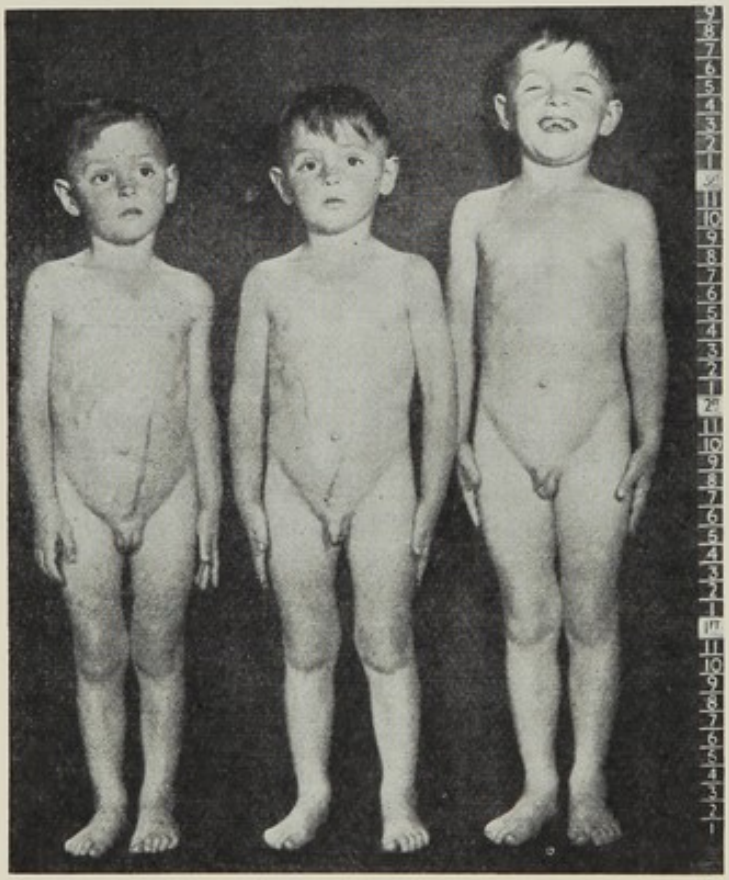

FIG. 249.—Identical twin boys and elder brother, all three of whom have been cured by recto-sigmoidectomy for Hirschsprung's disease.

propositus 3 in 13 were affected, again giving a proportion affected about 1 in 4. These figures are, however, based on small numbers and the random error might be large.

Parents.—Until the introduction of the operation of recto-sigmoidectomy by Swenson and Bill in 1948 the condition was probably nearly always fatal so that one cannot expect to find instances of the disease among parents. There is, however, one histologically proved example (Rosen, Bargen and Waugh, 1950) of Hirschsprung's disease in an adult and this man had three fit children (their sex is not reported).

Relations.—The incidence among aunts and uncles, and first cousins, male as well as female, is low. In the London series there were no individuals with a medical history suggestive of the disease among 136 uncles and 137 male first cousins, and none among 113 aunts and 121 female first cousins.

Analysis

The increased incidence among the brothers of affected children in the London series leaves little doubt that genetic factors play some part in the development of the disease: no simple genetic mechanism would account for the familial distribution hitherto observed.

Eugenic prognosis

The chance of a subsequent brother being affected is probably fairly high, perhaps about 1 in 5, but this estimate is based only on one small series.

The risk to children of affected individuals will only be apparent when the children, now for the first time cured by operation, come to have children of their own.

MULTIPLE POLYPOSIS OF THE INTESTINE

Multiple intestinal polyposis occurs in two forms. In the more common variety, " familial intestinal polyposis " the lesion usually, perhaps always, is confined to the colon and rectum. There are no associated abnormalities. In the rarer form, known as Peutz's syndrome, the polyps are found mostly in the small intestine, but also in the stomach, colon and rectum. In this syndrome there is also spotty pigmentation of the buccal mucosa and of the skin of the face and the fingers and toes. In both types of polyposis the polyps are originally adenomas; in both types some of these polyps may become malignant.

Familial polyposis of the large bowel

Varieties

There is little variation in the clinical and pathological features of the disease and no reason to suppose that the disease is not homogeneous.

Incidence in the general population

The condition is certainly rare, but no good estimates are available of its frequency in the general population.

Sex incidence

Males and females are equally often affected.

Consanguinity in the parents

There is no reported increase in parental consanguinity.

Familial incidence and genetic analysis

The first and most thoroughly investigated single series of families (33 in all) is that reported from a London hospital by C. E. Dukes. The index cases in these families are not distinguished and so it is impossible to deduce the proportion of each type of relation affected. The overall pattern, however, strongly suggests that a dominant gene of full penetrance is responsible, and that probably all sporadic cases are due to new mutations. In 22 of the 33 families more than one member was affected, and in all but one of these members of more than one generation were affected. In one family there was good evidence that 4 generations were affected and in 12 families that 3 generations were affected. There was no confirmed instance where skipping of generations occurred. In the 4 apparent exceptions the cause of death of the apparently unaffected member who transmitted the condition was in doubt. The 12 families in which members of only one generation, in 11 of them only a single individual, were affected, may all plausibly be attributed to new mutations. In only one of them were the clinical features different from those typical of cases obviously inherited. The 13 affected members of these families had had 15 children between them, but none of these children had yet been clinically examined, and 9 of them were still under the age of 20 years, about which serious symptoms are usually first induced.

Individual pedigrees

Fig. 250 illustrates a typical pedigree from the London series.

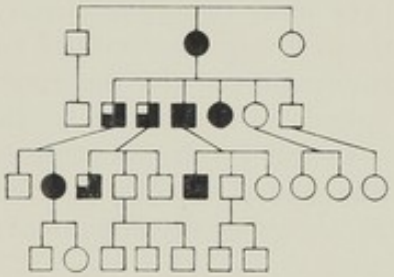

FIG. 250.—Pedigree of familial intestinal polyposis. (*After Dukes, C. E. (1952). Ann. Eugen., Lond.*, **17**, 1.)

Eugenic prognosis

The chance that a child of an affected individual will also have the condition is one in two. The chance of a member of one of these families who is found unaffected on thorough clinical examination in adult life transmitting the condition is small.

Peutz's syndrome

There are about a dozen families reported in the world literature in which the syndrome of polyposis of the small intestine, stomach and large intestine has occurred together with spotty skin pigmentation; many of these have not been fully investigated. It is uncertain yet whether the pigmentation of the buccal

mucosa, the skin of the face round the mouth and nose, and on the backs of the fingers and toes, can be present without intestinal polyposis. It is also uncertain whether intestinal polyposis can occur in these families without pigmentation of mucosa and skin; the pigmentation, except that in the mouth, tends to fade in adult life.

The condition is certainly rare, but no accurate estimates of its incidence are available. Males and females appear equally often affected. No incidences of parental consanguinity have been reported.

Familial incidence and genetic analysis

The original family described by Peutz illustrated in Fig. 251 strongly suggested

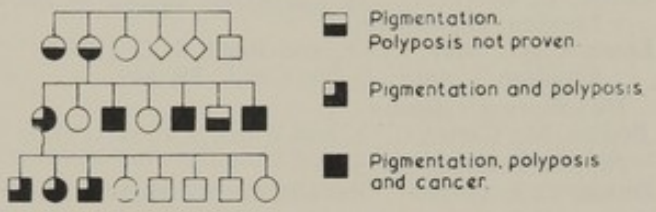

FIG. 251.—Pedigree of Peutz's syndrome. (*After Jeghers, H., McKusick, V. A., and Katz, K. H. (1949). New. Eng. J. Med.*, **241**, 993 and 1031.)

that a dominant gene was responsible. The families reported since can all be interpreted in the same way. Several sporadic instances must be assumed on this hypothesis to be due to new mutations, but this is to be expected with a condition that frequently causes death in childhood from intussusception.

Eugenic prognosis

A prognosis can only be given with reservations until a larger series of families has been reported. At the moment it would appear that the children of individuals with Peutz's syndrome would have a one in two chance of being affected.

OTHER AFFECTIONS

Genetic factors may well play an important part in the causation of several other diseases and deformities which have not yet been fully investigated. For example, instances are known of probably monozygous twins and also of non-twin siblings both with imperforate anus; the same is true of tracheo-oesophageal fistula. These are rare conditions and it is improbable that these are random associations. Some remarkable isolated pedigrees of appendicitis, cholecystitis and chololithiasis have been published; but these are very common conditions and require investigation by the methods used by Doll and Buch (1950) for peptic ulcer. Several authors have described anatomical abnormalities of the appendix in several members of a family undergoing operation for appendicitis, and they suggest that it is those anatomical abnormalities that are inherited. Ulcerative colitis has been reported in probably monozygous twins and also in several members of a family. There are also a number of instances reported of two siblings both developing hepatic cirrhosis and splenic enlargement, suggesting that in some instances the condition producing hepatic cirrhosis may be largely determined by genetic factors; but further clinical and pathological differentiation of this group of disorders is needed before genetic analysis is likely to be useful.

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CHAPTER 22

THE RESPIRATORY ORGANS

H. LINDENOV

THE NOSE

THE FORM and size of the nose are hereditary characters. For this reason the nose plays an important role in anthropological investigations.

Malformations

Embryological considerations

The nose arises entirely from the stomatodaeum, which is located between the anterior part of the head and the pericardial region, posteriorly separated from the fore-gut by the buccopharyngeal membrane.

With its progressive development the stomatodaeum is bordered above and anteriorly by the fronto-nasal process, laterally by the mandibular arches, which on their meeting and fusion also constitute the lower border. On each side, the lateral border is completed by the maxillary process which arises from the upper end of the mandibular arch. The buccopharyngeal membrane disappears in the fourth week, and thus communication with the pharynx is established. On either side of the fronto-nasal process, an olfactory pit now appears, which grows upwards and posteriorly, thus dividing the fronto-nasal

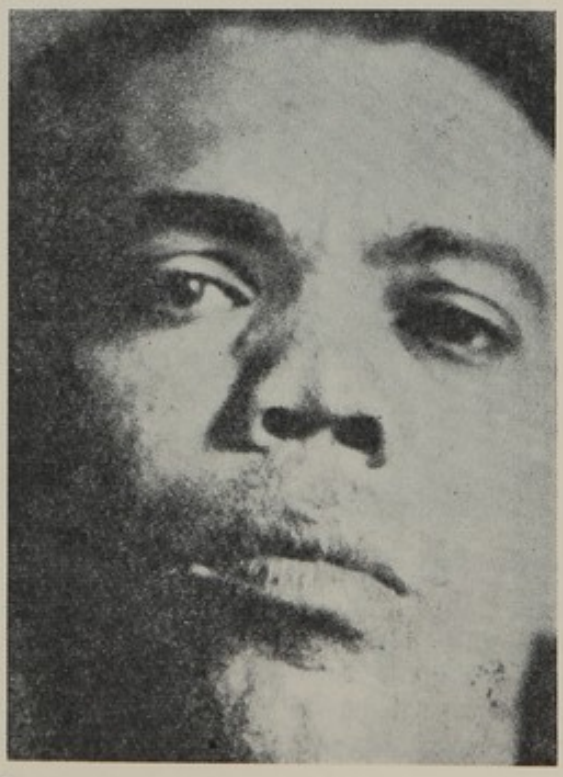
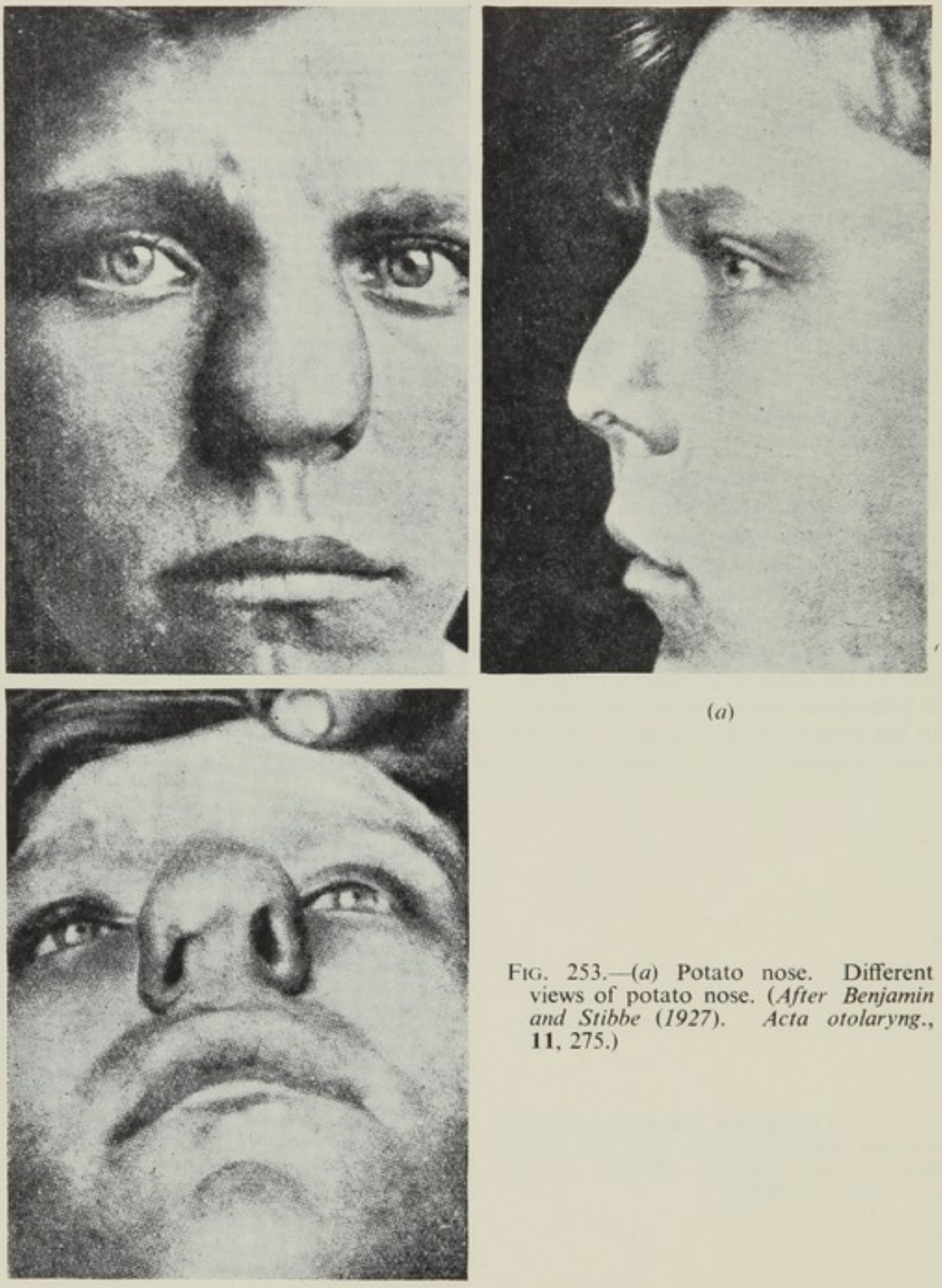


FIG. 252.—" Orang-utan " nose, in proband of pedigree shown in Fig. 253 (*b*). (*After Benedek and Rakonitz (1940). J. nerv. ment. Dis.*, **91**, 609.)



(*a*)

FIG. 253.—(*a*) Potato nose. Different views of potato nose. (*After Benjamin and Stibbe (1927). Acta otolaryng.*, **11**, 275.)

process into three portions, a middle one and two lateral. On either lateral corner of the middle portion a globular process now develops, and between these two globular processes there is an upwards triangular area which develops into the ridge of the nose. Downwards there is a quadrangular area, which develops into the columella, while the transverse ridge separating the two parts subsequently forms the tip of the nose. The

globular processes also take part in forming the philtrum. The lateral processes develop into the alae nasi.

Prior to the fusion of the maxillary processes with the lateral nasal processes, these elements are separated by the oculo-nasal sulci which are solid cords of cells before they develop into the naso-lacrimal sacs and ducts.

Malformation resembling the nose in orang-utan

This deformity (Fig. 252), due to a developmental arrest, has been recorded over three generations in association with myoclonic torsion dystonia (Benedek and Rakonitz, 1940). The nose was short, narrow at the root, with a broad ridge and flat tip, extraordinarily large nostrils, and the base turned upwards.

" *Potato nose* "

In this malformation the upper part of the ridge of the nose is distended like a balloon, especially transversely so that the profile is fairly normal (Fig. 253*a*). The balloon-like portion is elastic and its skeletal part consisted in one plate of cartilage and no nasal bones. The two halves of the nose had fused but incompletely so that the tip is widened, with a suggestion of bifid nose.

A pedigree on potato nose has been recorded by Benjamin and Stibbe (1927) and supplemented by Nieuwenhuijse (1943), who considered it to show irregular dominance (Fig. 253*b*). In Nieuwenhuijse's proband, the right frontal sinus was small, and the left missing; there was also a marked omega-shaped notching of the hard palate.

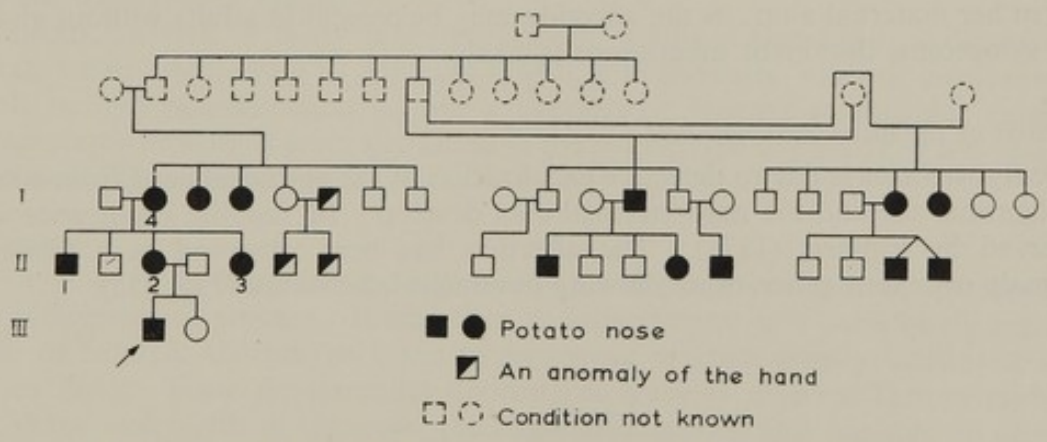


FIG. 253.—(*b*) Pedigree of potato nose. *After Nieuwenhuisje* (*1943*). *Genetica*, **23**, 291.)

Median malformations

Defective fusion of the two median processes which normally unite in the second week of foetal life to form the fronto-nasal process, may give rise to various malformations such as medial nasal cysts, open or closed fistulae, median notching of the premaxilla or hare-lip, and bifid nose.

Median cysts were recorded in a pair of uniovular twins by Furniss (1938) and identical, very pronounced, S-formed deviations of the nasal septum have also been observed in uniovular twins (Pastore and Olsen, 1941; Howie, 1946).

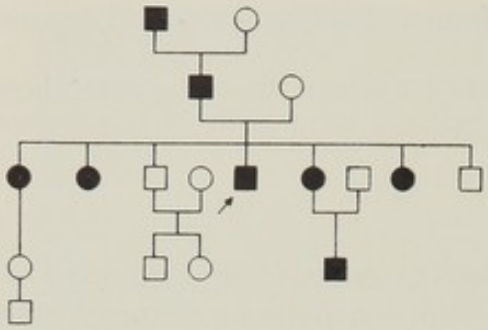


FIG. 254.—Pedigree of severe degree of deviation of the nasal septum. The father was treated surgically; the eldest son presented a marked deviation of the septum to the left; the second son had a marked deviation to the right; the youngest son has been operated upon for marked deviation of the septum to the right (personal observation).

Fig. 254 shows a pedigree suggestive of dominant inheritance of deviated nasal septum.

Choanal atresia

This rare and ill-understood developmental anomaly consists of occlusion of the posterior choana—membranous or osseous, or both—and may be present on one side, and occasionally on both sides.

Clinically, there is difficulty in sucking or taking the bottle. If the malformation is bilateral, only spoon feeding is possible and the child often dies of pneumonia. The unilateral affection may be symptomless or give the symptoms of nasal stenosis with mucoid secretion from the side occluded. When the affection is bilateral there is mouth breathing and rhinolalia.

The occurrence of bilateral choanal atresia in two sibs has been recorded by Wright (1922). Lang (1912) observed it in a woman, in three of her five children, and in her maternal aunt; as the affection may be present in adults without giving any symptoms, dominant inheritance is likely.

Stenosis of the naso-lacrimal duct

Dacryostenosis is due to defective canalization of the epithelial cord from which the lacrimal sac and the naso-lacrimal duct develop. Its familial occurrence was observed by Emmert (1876). The affection has been observed as a bilateral anomaly over four generations showing dominant inheritance (Fig. 255).

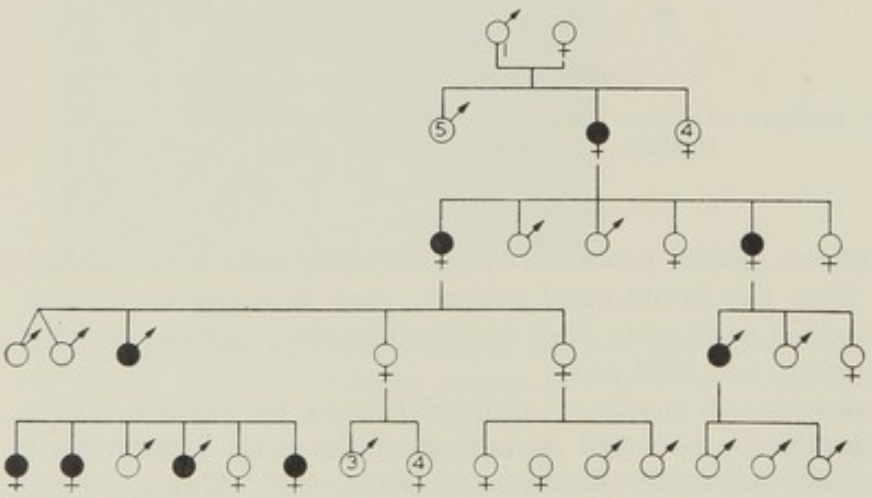


FIG. 255.—Inheritance of congenital stenosis of the naso-lacrimal duct over four generations. (*After Wogwitka (1948) Canad. med. Ass. J.*, **59**, 358.)

Rhinitis

In his concept of "exudative diathesis" Czerny (1905) stressed that the respiratory passages may show a susceptibility to mucosal affections, sometimes localized—so that as a rule the same mucosal area is attacked repeatedly—and sometimes generalized, with variation of the localization.

Acute catarrhal rhinitis

Disposition to acute catarrhal phenomena in childhood may often be followed through generations—as has been shown by v. Pfaundler and others (Fig. 256).

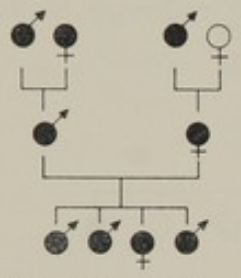


FIG. 256.—Pedigree of a family with tendency to mucosal catarrh in childhood. (*After v. Pfaundler, cited by Albrecht (1940). In G. Just: Handb. Erbbiol. Menschen*, **4**, 63.)

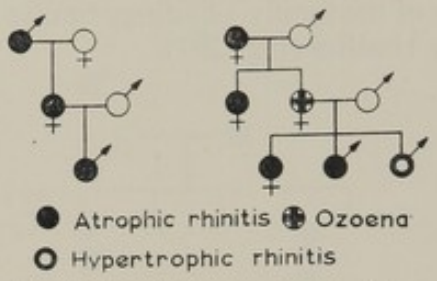


FIG. 257.—Pedigrees on atrophic rhinitis and ozoena. (*After Undritz (1928). Arch. Ohreheilk.*, **119**, 275, *pedigrees* 3 *and* 4.)

Chronic hypertrophic rhinitis

Chronic catarrh is fairly prevalent among adults. Here, too, a disposition asserts itself. According to Albrecht (1940), a hyperplastic mucous membrane is liable to hypertrophic catarrh, and a hypoplastic mucosa to atrophic catarrh. Hyperplastic mucosa is generally found in the pyknic type of build, and hypoplastic mucosa in the asthenic type.

Polyposis

Polyposis in the nose or its sinuses may develop also without the presence of any inflammatory process. It may then be looked upon as a particularly marked form of catarrh, the polyps being hypertrophic mucosa grossly infiltrated with serous fluid. Their development depends on various external factors such as the shape and width of the nose, the climate, infections and possibly an allergic state.

That polyposis has an hereditary basis is suggested by the fact that the hypertrophic mucous membrane itself is hereditarily determined. Moreover, some patients under apparently identical conditions develop polyposis, and other do not; furthermore, the affection often is bilateral. Albrecht (1940) has reported the finding of concordant polyposis in the left maxillary sinus in two uniovular twins, while 3 of their sibs also showed polyposis.

Chronic atrophic rhinitis

This affection manifests itself in a dry and glossy nasal mucosa and often in a lesser degree throughout the entire pharynx, larynx and trachea. In severe cases

crusts are formed in the nose, and tend to become foetid (*ozoena or foetid atrophic rhinitis*). Occasionally the crust formation extends down to the trachea, but usually the mucous membranes, other than those of the nose, merely become coated with a layer of tenacious mucus. Zinser (1936) found among 61 cases of ozoena a corresponding mucosal affection of the pharynx in 96·5 per cent, and of the larynx in 68·9 per cent. The patients were mostly asthenics.

The aetiology of the affection is largely unknown; a genetic factor was suggested as early as 1903 by Gradenigo. An investigation comprising 19 families has been reported by Albrecht (1926). He found that the disease was transmitted only to consanguineous relatives, never to conjugal partners, nor to neighbours or close friends of the family—findings similar to those observed by Gradenigo, by Busacca and by Undritz (Fig. 257).

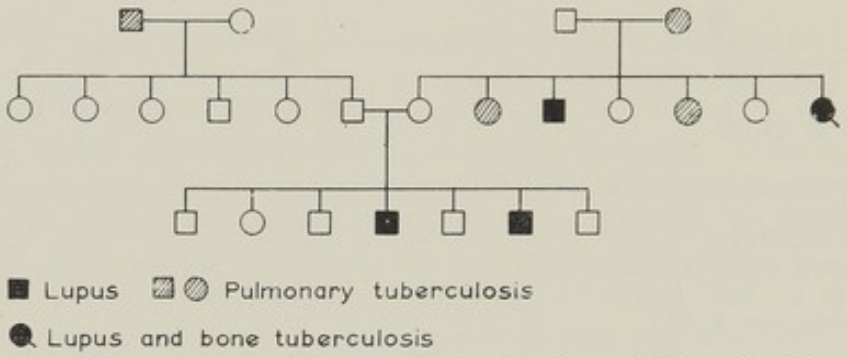


FIG. 258.—Pedigree of lupus. (*After Berghaus (1936). Z. Hyg. Infektionskr.*, **117**, 760.)

In many cases the inheritance is clearly dominant. In others this is not so obvious, possibly because external factors, including non-specific infections, the shape and width of the nose, the climate and the nutritional state, may all play a part, so that all sorts of transitions are observed—from manifest dominant inheritance to solitary cases in which the hereditary factor does not manifest itself even though present.

Other affections

Rhinophyma

Rhinophyma is a particularly marked form of rosacea, localized to the nose, the skin of which becomes reddish-blue, swollen, with large and dilated pores of sebaceous glands, producing a rather coarse appearance. Usually the swelling increases inferiorly and may become irregular and nodular. It may become so large as to give the nose a monstrous appearance (elephantiasis nasi).

That rosacea may be hereditary was pointed out as early as in 1797 by Erasmus Darwin. Lesser (1914) observed it over three generations.

Lupus

Lupus vulgaris is a special form of tuberculosis that may occur anywhere on the skin, but generally on the face, and also on various mucous membranes, particularly in the nose, and to a lesser extent in the mouth, pharynx and throat.

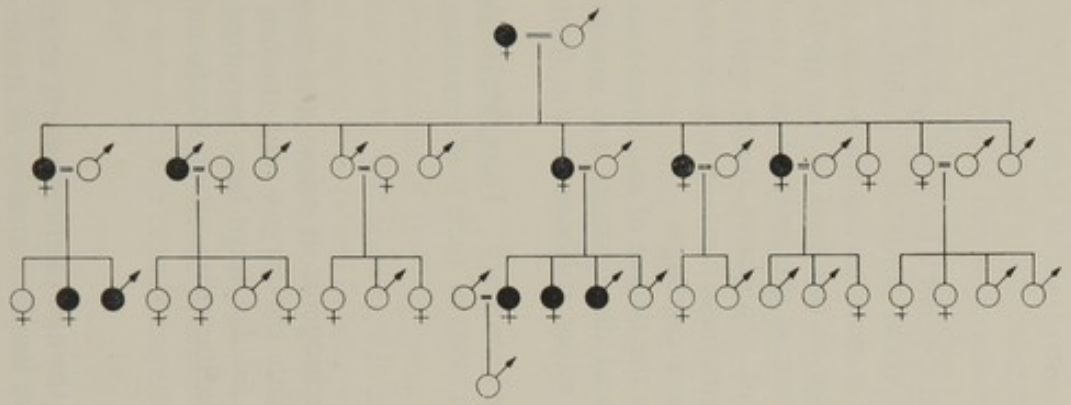


FIG. 259.—Pedigree of epistaxis resulting from ectatic veins in Kiesselbach's area. (*After Reichmann (1935). Die Erblickheit des Nasenblutens bei Gefässerweiterungen Locus Kiesselbach, p.* 12. *Wurtemburg; Diss.*)

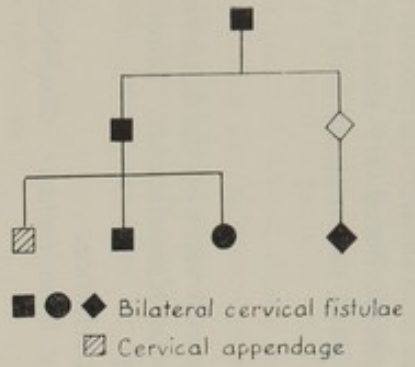


FIG. 260.—Pedigree of bilateral cervical fistulae. Only affected individuals recorded. (*After Meel and Pemberton (1945). Surgery,* **18**, 267.)

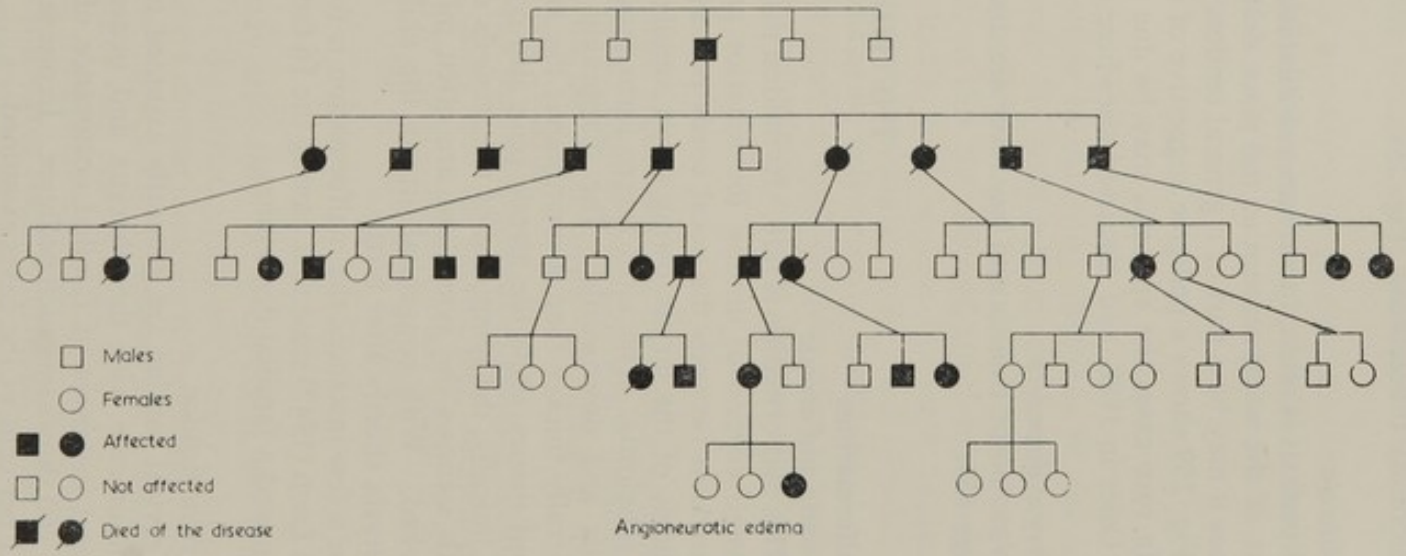


FIG. 261.—Pedigree of angioneurotic oedema. (*After Crowder, J. R., and T. R. (1912). Arch intern. Med.,* **20**, 845.)

In familial studies on 227 cases of lupus, Berghaus (1936) found other cases in about 10 per cent of the families. Some of these families also showed an excessive case mortality for tuberculosis presumably due to a specific hereditary susceptibility, similar to that he observed in his studies on joint tuberculosis and on pulmonary tuberculosis (Fig. 258).

Epistaxis

Epistaxis is often due to varicose dilatation of the mucosal veins on the anterior part of the nasal septum at the place designated as locus Kiesselbachii. Sometimes it may be a part of a general tendency to varicosity.

Fig. 259 shows a pedigree suggestive of dominant inheritance.

In rare cases the epistaxis may be due to *hereditary telangiectasis*, described by Osler in 1888, and discussed elsewhere (p. 228).

Allergic disorders

Vasomotor rhinitis and hay fever are discussed as aspects of the atopic diseases (page 553).

THE THROAT

Malformations

Stenosis and atresia

This malformation is rare. Its mildest manifestation is either a band (*diaphragma laryngis congenita*) uniting the anterior part of the vocal cords or a semilunar connexion between the vocal cords posteriorly. In a more severe form there is stenosis of the larynx owing to an annular formation at the level of the glottis or subglottis. The most severe form produces atresia at the level of the vocal cords and downwards. The diaphragm consists of connective tissue and is generally thicker than a membrane; the annular formations contain muscle and gland tissues while the atresic plug also contains some cartilage.

Clinically, the symptoms of the stenosis depend on the degree of malformation. With stenosis the symptoms are often mild but vocal disturbances are usually marked. With congenital atresia the children are either stillborn or die from asphyxia shortly after birth.

In a few instances the malformation is found to be hereditary. Thus, McHugh and Loch (1942) state that among the 16 families with cases of such malformation, 6 showed a familial disposition.

Cervical fistulae

Cervical fistulae are generally assumed to be branchiogenic in origin and may communicate with the pharynx and occasionally with the larynx and trachea. Several instances of familial occurrence of cervical fistulae have been reported. Fig. 260 shows one such pedigree. In one series a hereditary disposition was found in 21 per cent of the cases examined.

Laryngospasm

Laryngospasm, occasionally seen in children up to the age of three years, arises on the basis of spasmophilic diathesis and manifests itself in attacks of spasms

of the vocal cords, lasting from a moment up to about one minute. After a gasping respiration, the breathing stops; the patient first turns pale, then cyanotic, while tonic and clonic spasms of the musculature of the eyes and mouth set in; sometimes there are convulsions of the extremities and even loss of consciousness. At the end of such an attack the breathing becomes jerky, gradually returning to normal. A severe attack may be fatal.

Among the different aetiological factors, heredity is prominent. Ibrahim (1936) states that laryngospasm and the convulsions often represent a familial affection that asserts itself also in the parents and sibs of the patient, and that the facial phenomena may often be elicited in the mother.

Laryngitis

Acute laryngitis

That some individuals have a disposition to catarrhal affections of the air passages is an old and general experience. In such individuals recurrence of the same lesion is frequent, though others under the same exposure are unaffected. In some the disposition is rather general, so that the mucosal affection varies in its localization. In others it is more strictly local, so that the same mucous membrane tends to be involved; some people catching a " cold " will invariably have an attack of acute catarrhal laryngitis as its only or main manifestation. A special form of this is *pseudocroup*, which arises in small children when the acute laryngeal catarrh brings about such a marked swelling of the mucous membrane as to give symptoms of stenosis.

Chronic laryngitis

In its hypertrophic form this lesion is often encountered as the only manifestation of a catarrhal disposition as, for instance, nodular laryngitis which manifests itself in the so-called singer's nodules on the vocal cords—an affection that usually arises on the basis of recurrent acute catarrhs.

In its atrophic form the lesion is usually part of a general mucosal affection, extending continuously from the nasal cavity into the larynx and, sometimes, even into the trachea. According to Zinser (1936), the lesion was found in 68·9 per cent of the cases of atrophic rhinitis—itself an hereditary anomaly.

Other affections

Papillomas

Papillomas of the laryngeal mucosa may arise from the vocal cords, the false vocal cords, and elsewhere in the lumen of the larynx. They are usually multiple and white, grey or red in colour. They have a marked tendency to local recurrence, but they do not undergo malignant degeneration. The symptoms are hoarseness and dyspnoea, and as they grow rapidly they may cause suffocation.

These papillomas are so often found in the newborn or shortly after birth that there may well be an inherent disposition towards these formations. That they are hereditary in certain families is suggested by an old observation (Hansemann, 1898).

Angioneurotic oedema

This is discussed in the chapter on the Allergic Diseases (p. 556). In its typical

familial form, which is apparently unrelated to allergy, inheritance is dominant (Fig. 261) (Finnemann, 1940).

Affections of the trachea

Branchiogenic fistulae, which may be hereditary, occasionally communicate with the trachea.

Atrophic tracheitis, usually a part of a catarrhal atrophy of the upper air passages as a whole, is discussed under laryngitis.

THE THORAX AND LUNGS

Affections of the thorax

The thorax is variable in form. It is broad and arcuate in pyknics and narrow and flat in asthenics—forms which may be accentuated by the development of affections such as emphysema or pulmonary tuberculosis respectively. Deformation of the chest may be congenital or may arise after various bone diseases, as in rickets with its pigeon chest, or it may be secondary to injury, operative measures, or to continuous pressure—as in funnel chest of shoemakers.

That funnel chest may also be a hereditary feature, transmitted in a dominant manner, is shown by Fig. 262.

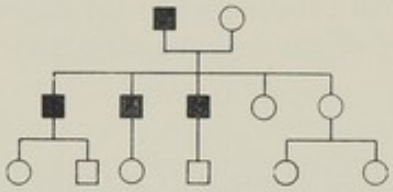


FIG. 262.—Pedigree of a family with funnel chest (personal observation, 1951).

Malformations of the lungs

Tripartition of the left lung

Abnormal lobation of the lungs is a frequent congenital anomaly. Normally the right lung is divided into three lobes, the left into two. The presence of a middle lobe in the left lung, however, is not uncommon. Roessle (1936) found this anomaly in a father and his four sons.

Accessory lower lobe

An accessory lower lobe of the right or left lung is one of the most frequent pulmonary anomalies. Roentgenographically it was found by Talia (1936) to be present in 35 of 600 examinations. Its genetic status is uncertain. It has been observed in familial cases of bronchiectasis.

Azygos lobe

The familial occurrence of a *lobus venae azygos* has been observed several times in roentgenograms and was found incidentally in uniovular twins by Uehlinger and Künsch (1938).

Bronchiectasis

There are both congenital and acquired forms. Congenital bronchiectasis appears either as honeycomb-like cavities situated close together and separated

by septa without any lung tissue, or as large cyst-like cavities. Acquired bronchiectasis appears as cylindrical dilatation of bronchi and bronchioles, arising through the increased pressure in coughing, or as irregular pockets from shrinkage of the lung tissue. In acquired bronchiectasis there is the possibility of disposition to this affection (Bard, 1922) in the form of lowered resistance of the bronchial walls, with tendency to yield to the physiological pressure. In addition, susceptibility to catarrhal affections may play a role.

Familial occurrence of bronchiectasis was first reported by Neisser (1901). Subsequently it has been observed 13 times (review by Kartagener, 1935): 3 times in a father and children, and on the other occasions in siblings, including 4 times in twins, of which two pairs were definitely—and one pair probably—uniovular.

Bronchiectasis has been described several times in association with other anomalies. (i) Bronchiectasis with situs inversus was observed repeatedly in isolated cases and the familial occurrence of this association was noted by Günther (1923) in two sisters.

(ii) These two anomalies have also been observed in association with nasal polyposis or chronic hyperplastic inflammation of the mucosa of the nose and its sinuses (Kartagener's triad). Banham (1950) states that sometimes the triad has been accompanied by the absence of the frontal sinuses and that infection of the paranasal sinuses has been described in some cases.

(iii) The presence of bilateral bronchiectasis together with the absence or undevelopment of the frontal sinuses was demonstrated by roentgenography and bronchoscopy by Pastore and Olsen (1941) in a pair of uniovular twin sisters. Both sisters also presented bilateral nasal polypi.

(iv) Rauch, Litvak and Steiner (1939) have reported congenital familial steatorrhoea together with presumably congenital fibromatosis of the pancreas and congenital bronchiectasis in two sibs.

Idiopathic spontaneous pneumothorax

Spontaneous pneumothorax is generally secondary to erosion of the pleura from pathological processes in the lungs, usually tuberculous. Some cases are, however, the result of developmental arrest: here the lungs are surrounded by a coat of embryonal tissue instead of the pleura. Presumably this tissue, with few elastic fibres, ruptures on normal pressure.

Familial occurrence of idiopathic spontaneous pneumothorax has been observed occasionally: by Kusan (1925) in two brothers, by Wilson (1926) in father and son, by Morawitz (1933) in two brothers, and by Müller (1934) in father and son.

Idiopathic emphysema of the lungs

Besides the secondary pulmonary emphysema resulting from bronchitis and other lesions, there is an idiopathic form which depends on a constitutional and presumably genetic factor, for Roessle (1940) was able to report 31 cases of familial occurrence of the affection, something over two generations.

Other affections

Bronchitis

A tendency to both acute and chronic bronchitis may be due to a hereditary

susceptibility to a generalized or localized catarrhal disposition of the air passages in general.

There appears to be a susceptibility to whooping-cough without any familial concentration.

Pulmonary sarcoidosis

Dressler (1938 and 1939) reported the occurrence of pulmonary sarcoidosis in two pairs of sibs. Each of these pairs presented a striking resemblance of the lung lesion.

Other disorders of the lungs

The genetical aspects of *pneumonia* and of *pulmonary tuberculosis* are discussed in the chapter on Infectious Diseases (p. 549) and those of bronchial asthma on p. 553.

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CHAPTER 23

CARDIOVASCULAR SYSTEM

C. NASH HERNDON

CONGENITAL HEART DISEASE

IN her monograph on congenital malformations of the heart, Taussig (1947) lists heredity first among probable aetiological agents, and also mentions three environmental factors which are thought to be of importance. (1) Vitamin deficiencies during pregnancy increase the liability to malformations among offspring in experimental animals, but the possible importance of minor dietary deficiencies in man remains to be demonstrated. (2) Skeletal abnormalities, especially those of the spine, may be of importance by varying the stress factors on the embryonic vascular bed to such an extent as to cause abnormalities in development of the heart or great vessels. Taussig remarks on the high incidence of congenital abnormalities of the spine in patients with congenital heart disease. (3) Virus infections in early pregnancy, especially rubella during the first trimester, frequently lead to congenital cataracts and congenital malformations of the heart in the offspring. As the embryonic development of the heart occurs during the first two months of gestation, it is apparent that any factor depressing normal cell growth during this period might result in malformation of the organs which are undergoing critical growth at this time. Syphilis and foetal endocarditis, which were regarded as important by earlier authors, are probably of significance only in rare cases.

The possibility that competition between twin foetuses may be of importance in some cases is suggested by Morison (1949).

He reported two sets of twins diagnosed as monozygous because of monochorionic placentas with placental vessel anastomoses. In the first set the mother had severe toxaemia and the foetuses were stillborn at 30 weeks, one presenting no malformations while the second presented multiple widespread malformations including severe malformation of the heart with dextroposition and coarctation of the aorta. In the second family the mother had mitral stenosis and delivered a normal female child and a stillborn foetus at 35 weeks with severe defects including cor biloculare.

Morison points out that competition between the circulations of two foetuses is likely to be keenest during the early growth period when villi are present over the entire surface of the chorion, and suggests that one twin experienced inadequate nutrition early but survived to experience ample nutrition later. The defects described are regarded as representative of a non-specific arrest of development with the specific malformation depending on the time of action, when critical growth was occurring in the affected structures.

Specific mutations resulting in congenital heart disease are rather difficult to identify, but doubtless exist. The frequent occurrence of multiple cases of malformation within sibships demonstrates the importance of specific hereditary factors. Walker and Ellis (1941) found 48 families described in the literature with multiple cases of congenital malformations of the heart, 15 of these being in more than

one generation, and added 2 families of their own. Taussig reported 4 similar families, whilst Campbell (1949) recorded a series of 100 consecutive cases of congenital heart disease observed, in which the family history was specifically investigated, and revealed cases among close relatives in 7 families. In 3 of these, siblings were affected while collateral relatives were affected in 4 families. Campbell (1949) also describes 9 other families with multiple cases not included in the group specifically studied with regard to family history. Among the families reported in the literature as exhibiting 2 or more members with congenital heart disease, approximately 65 per cent of families show affected members only in a single sibship, while approximately 35 per cent show cases in multiple sibships or in successive generations. This would suggest that at least 2 genes, or 2 sets of genes, might be involved, a recessive gene or group of recessive genes producing familial cases within a single sibship, and a conditionally dominant gene or group of genes being responsible for families exhibiting cases in multiple sibships. Families showing evidence of sex-linked genes are not known to the writer, but may exist.

Specific types

The frequent occurrence of diverse types of cardiac malformation within the same family makes it difficult to correlate specific gene influences with specific types of malformation. It is also frequently impossible, in considering published reports, to be certain of the exact kind of heart defect under discussion because of the obvious difficulties in making an exact anatomic diagnosis by means of the usual clinical signs alone. This difficulty should become less in future studies due to the recent rapid advance in exactness of diagnosis during life offered by the technique of intravenous cardiac catheterization.

In the absence of more exact information, it might be assumed that certain genes exert a relatively non-specific depressing effect on cell growth, with the exact type of malformation depending upon the exact time of action during embryonic development. It would be expected that genes of this type would frequently give rise to other malformations associated with congenital heart disease. The existence of such genetic factors has been amply demonstrated in experimental animals by Landauer, Wright and Wagner and others. On the other hand, the fact that certain types of malformation tend to recur within given families, usually without other associated malformations, would seem to indicate that there may be other genes with more specific actions involved in a smaller proportion of cases.

Patent ductus arteriosus

The occurrence of multiple cases of patent ductus arteriosus within a family seems to be reported more often than other lesions, possibly because of the better prognosis.

Taussig reported a family in which a father, two of his three children, and one of his two grandchildren all presented patent ductus. Walker and Ellis (1941) observed a father and four of his eight children with this defect. Several case reports exist of examples of patent ductus in siblings. Campbell (1949) described a family in which the mother presented patent ductus with practically no symptoms, while her daughter, aged 8 years, presented coarctation of the aorta with only mild symptoms. Stein and Barber (1945) recorded the reverse situation; a mother with coarctation of the aorta had a daughter aged 9 years and a son aged 12 years, both presenting patent ductus.

Tetralogy of Fallot

This combination of malformations consisting of pulmonary stenosis or atresia, dextroposition of the aorta, interventricular septal defect and hypertrophy of the right ventricle has also been described by several writers as being in the same sibship. Cockayne (1938) in his study of situs inversus suggested that complete transposition of the viscera is inherited as a simple recessive trait, and that the various degrees of partial transposition, including anomalies of rotation of the heart, may represent a minor form of the same condition. He also pointed out that the incidence of congenital heart disease is abnormally high in cases of situs inversus, and that the cardiac lesion most often encountered in such cases is the tetralogy of Fallot—an association observed in 11 certain cases and 4 probable cases.

The pedigree shown in Fig. 263 illustrates a family in which one sibship presented two certain cases and two probable cases of tetralogy of Fallot. Autopsy confirmation of the diagnosis was obtained on the first two children but could not be obtained on the last two, although they were cyanotic and presented clinical findings similar to the two proved cases. Families of this type suggest the action of a specific simple recessive gene.

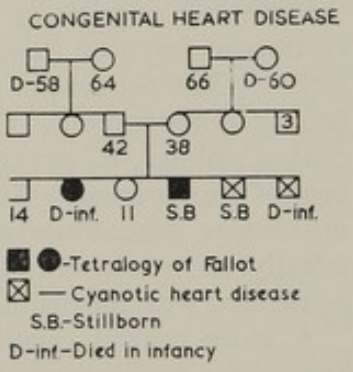

FIG. 263.—Family with two proved and two probable cases of tetralogy of Fallot in one sibship, suggesting action of simple recessive gene.

Septal defects

Walker and Ellis (1941) found identical high septal defects at autopsy in a mother and her six months' foetus. Campbell (1950) described a family with auricular septal defect in a child and in her mother and grandmother. The possibility of a conditionally dominant gene is suggested.

Lutembacher's syndrome

Courter, Felson and McGuire (1948) described two sisters with interauricular septal defect and mitral stenosis, these being the first and third children in a sibship of five. In 63 case reports of congenital heart disease in two or more members of the same family that they reviewed, there was no similar instance of multiple cases of Lutembacher's syndrome.

Chance of recurrence in the family

Taussig estimates the likelihood of recurrence of any variety of cardiac malformation within the sibship at 20 per cent, and the likelihood of recurrence of the identical malformation at 2 per cent.

RHEUMATIC HEART DISEASE

Whilst the cause of rheumatic fever is unknown, there is much evidence to suggest that hypersensitivity to certain strains of streptococci is a factor—and it is possible that this hypersensitivity is genetically determined.

For many years the high familial incidence of rheumatic fever has been known, although this observation alone cannot be considered as indicative of the operation of genetic factors. A familial concentration of cases is commonly observed in contagious, parasitic and dietary diseases as well as in hereditary conditions. Paul and Salinger (1931) studied the method of spread of acute rheumatic fever through 15 families, and concluded that they were apparently dealing with an infectious process, but that an hereditary predisposition to the disease was of importance. Irvine-Jones (1933) reported on 666 families each containing one or more patients admitted to clinics with a diagnosis of rheumatic fever. No less than 33 per cent of these families showed multiple cases. Two sets of monozygous twins were encountered, both simultaneously exhibiting evidence of rheumatic fever. Five pairs of dizygous twins were studied, in all cases one twin having rheumatic symptoms and the other being healthy. Read, Ciocco and Taussig (1938) studied the frequency of rheumatic manifestations among close relatives of 33 consecutive children with rheumatic heart disease, comparing these with a control group of 33 children without rheumatic manifestations. Among the relatives of patients with rheumatic heart disease, evidence of chorea, acute rheumatic fever or rheumatic heart disease was found in 15·5 per cent of the siblings, 30·8 per cent of the parents, 9·1 per cent of uncles and aunts and 18·2 per cent of grandparents. Corresponding figures for the control group were 4·0 per cent of siblings, 7·7 per cent of parents, 3·8 per cent of uncles and aunts and 2·3 per cent of grandparents. The authors attached importance to the fact that significant differences were observed among grandparents, uncles and aunts, as there is usually no household contact among relatives of this degree of the type usually associated with household spread of simple infection.

A more critical genetic analysis of the situation has been done by Wilson, Schweitzer and Lubschez (1943). A series of 109 families, each selected as containing one child with rheumatic heart disease, was carefully studied and the figures analysed by use of the Lenz-Hogben formula. The observations were in excellent agreement with expected values calculated on the hypothesis that the monozygous state of a simple recessive gene would condition susceptibility to rheumatic fever. A simultaneous genetic and epidemiologic analysis of the data is presented, and an age incidence factor is derived whereby the likelihood may be estimated that a susceptible child might develop the disease by, or at, any given age up to 13 years. The authors concluded that heredity of the simple recessive type is primarily responsible for the familial incidence of the disease, and that the age risk determines the time of occurrence of cases within the family. Their data also include 7 pairs of twins, 2 being monozygous and concordant, in that both members of each pair had rheumatic fever. Among 5 dizygous pairs, in 2 pairs both twins were rheumatic while in 3 pairs only 1 child presented the disease.

HYPERTENSIVE CARDIOVASCULAR DISEASE

Essential hypertension is a sustained elevation of blood pressure above the commonly accepted limits of normal, followed in time by changes in the cardiovascular system secondary to such sustained pressure. The symptomatic forms of hypertension are thus eliminated from consideration. Although primarily a

disease of middle-aged persons, it may also appear in full-blown form in young adults.

Studies on families

Many case reports of families showing a high incidence of hypertension are available. The published pedigrees are compatible with the hypothesis of dominant gene action, but there is the possibility that such familial concentration of cases might occur by chance alone in a disease so widespread in the general population.

A recent family study of this type is offered by Löffler and Hanhart (1949). Several statistical studies on the family histories of patients with essential hypertension are also available. Allan (1933), in studying 485 consecutive patients, found evidence of hypertension in both parents in 131 cases, hypertension in one parent in 349 cases, and hypertension in neither parent in 5 cases. Hypertension was also encountered in 80 per cent of the siblings past the age of 45 years in families where both parents were hypertensive, and in 60 per cent of siblings of this age group where only one parent was hypertensive. He concluded that a single dominant gene might be responsible for essential hypertension. A somewhat lower incidence of positive history than reported by Allan is recorded by other studies. Ten such studies, including data on more than 4,500 patients, are tabulated and summarized by Neel (1947, 1949). As would be expected, the figures of different observers, and sometimes of the same observer under different circumstances, are rather widely divergent. The lack of close agreement may be due to differences in criteria of diagnosis, definition of a " positive " family history, age distribution of patients and their relatives, or other subjective factors.

It seems beyond question that a history of hypertension in close relatives is obtained more than twice as often from patients with hypertension as from normal controls, although it should be remembered that a statistically valid differentiation on family history alone might reflect environmental as well as genetic variation.

A more refined study of 277 families was carried out by Ayman (1934), with blood pressure, height and weight determinations being obtained on 1,524 members of these families. In families where both parents had normal blood pressure, the incidence of elevated pressure in the children was 3·1 per cent. In families in which one parent had hypertension, the incidence of elevated pressure in the children was 28·3 per cent. In families where both parents were hypertensive, the frequency in children was 45·5 per cent. Among 70 siblings of parents with normal blood pressure, 37·3 per cent had hypertension, while among 86 siblings of parents with hypertension, 65·3 per cent also had elevated pressure. An earlier study of 82 families with essentially similar results was done by Weitz (1923).

Studies on twins

Essential hypertension in twins has been studied by Kahler and Weber (1940). Nineteen pairs of twins, 7 monozygous and 12 dizygous, were obtained by clinical ascertainment of one member of the pair with hypertension. Of monozygous pairs, 6 were concordant, both exhibiting essential hypertension, and one pair was discordant. Among dizygotic pairs, 7 were concordant and 5 discordant. Other relatives were not investigated. Such a study is not conclusive because of the small number of cases, but the difference in ratios for monozygous and dizygous twins is in the direction suggesting the importance of hereditary factors.

The existence of even one discordant monozygotic pair, however, demonstrates that genetic factors are not the exclusive determinants in aetiology and emphasizes the necessary interaction of genetic and environmental factors.

The "pre-hypertensive state"

The possibility of recognizing a " pre-hypertensive state ", or identifying individuals liable to development of essential hypertension prior to the appearance of sustained blood-pressure elevation, has attracted the attention of several investigators. The studies by Hines (1940) on the cold-pressor test in hypertensives and their relatives gave promise of an objective measure for identifying such individuals.

The test consists of measuring the blood-pressure response, under standard conditions, to immersion of one hand in ice water for 30 seconds. Although a transient rise in blood pressure occurs in normal individuals, certain individuals show a much more marked and sustained elevation than others, and these are designated as hyper-reactors. The cold-pressor response is eliminated by the administration of tetra-ethyl ammonium chloride intravenously before testing, indicating that the mechanism of the response is neurogenic.

Hines states that the incidence of a family history of hypertension is the same in hyper-reactors as in hypertensives, in both instances being about 5 times as high as in normo-reactors, and that identical twins show similar responses whereas fraternal twins frequently do not. This latter observation is based on 7 pairs of monozygotic twins showing remarkably similar reactions for each pair, and 3 dizygous twin pairs, one pair being clearly discordant, one pair borderline, and one pair concordant normo-reactors (Hines, 1937). Hines has been unable to find a hyper-reactor who did not have at least one parent who was either hypertensive or a hyper-reactor. He concluded that hyper-reaction is inherited as a dominant characteristic, and constitutes a pre-hypertensive state. Several observers have at least partially confirmed the findings of Hines, although others have been unable to obtain similar findings, notably Chesley and Chesley (1939) and Feldt and Wenstrand (1942). The discrepancies that exist between published observations are difficult to reconcile, and suggest that more objective testing procedures and better agreement on diagnostic criteria are urgently needed. The available evidence concerning a " carrier state " has been well summarized by Neel (1947).

Some possibly associated conditions

The possibility that patients with essential hypertension may present other distinguishing physical characteristics has been frequently considered, but the results have not been particularly illuminating. It is rather generally accepted that some correlation exists between hypertension and obesity. The findings of several authors indicate that in any group of unselected hypertensive patients approximately 75 per cent will be overweight by the usual weight standards. The influence of obesity is also demonstrated by the common clinical observation that reduction of weight in obese hypertensives frequently is accompanied by a reduction in blood pressure. There is no suggestion, however, that obesity and hypertension bear any causal relation to each other, although one might surmise that obesity may be a contributing factor aggravating a latent tendency

to hypertension and serving as a mechanism to bring the disease above the clinical horizon, either in a purely physical manner by imposing an additional load upon the heart or by metabolic alteration.

Robinson and Brucer (1940) studied the relation of hypertension, obesity and body build in 5,620 individuals reporting for periodic insurance examinations. They concluded that there is a close correlation of body build with hypertension, with a high incidence of hypertension in broad-chested individuals of the lateral or broad-built type. They believed that when body-build groups are held constant, obesity showed a rather uncertain correlation with hypertension, and that the greatest correlation between blood pressure and obesity was obtained in the linear or slender build groups. The statistical methods used by Robinson and Brucer have been severely criticized by Treolar (1940) without specifically objecting to the conclusions reached. Bauer (1945) while considering hypertension to be a constitutional disease due to an abnormal gene or gene complex, considers the evidence for correlation between body build and blood pressure as quite problematic. It is perhaps also of interest that Bauer considers constitutional hypotension to be a familial but harmless constitutional variation which he suggests may be an allele of the gene or genes responsible for hypertension.

Associated conditions as environmental prevailing factors or possibly pleiotropic manifestations

A constitutional predisposition to hypertension conditioned by a gene or gene complex exhibiting the characteristics of a dominant gene seems fairly certain. Apparently individuals with such a genetic constitutional predisposition develop hypertension only under appropriate environmental circumstances—as yet not identified, although obesity, body build, vaso-excitability, hormonal imbalance and an emotional personality pattern are all possible factors. Whether these observed correlations are actually effective aetiological factors or whether they may merely represent other observable results of more fundamentalun identified environmental influences remains to be determined. It is also possible that any demonstrated correlation that may be found between blood-pressure level and any other constitutional attribute of the individual might represent merely pleiotrophic effects of the underlying gene or gene complex.

ARTERIOSCLEROSIS

Sclerotic changes in arteries are intimately associated with the general process of ageing, and loss of elasticity of vessels may be demonstrated as early as the third decade. There is a close association between the degree of general arteriosclerosis and the apparent physiological age of the individual, and many of the symptoms of senility may be directly attributed to vascular disturbances resulting from arteriosclerosis. Many writers have suggested that the speed of development of arteriosclerosis is a constitutional characteristic with a tendency to familial aggregation and a close association with length of life span. Arteriosclerosis is frequently included with other degenerative changes in discussions of abiotrophy, implying a constitutional biological inferiority of the affected organs or tissues.

It has also been frequently suggested that even the localization of arteriosclerosis to some particular region of the arterial system may be a familial characteristic (Bauer, 1945). Numerous reports are available showing an unusual concentration of cases of cerebral vascular accident within family groups. An

illustrative pedigree is shown in Fig. 264. Whilst careful statistical studies of cases of this type are needed, it might be assumed as a working hypothesis that at least in some families a special predilection for arteriosclerotic change exists in certain localized parts of the vascular system, possibly indicating a specific weakness of structure in these areas.

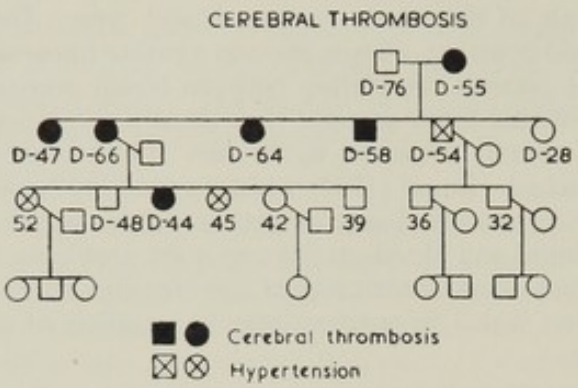

FIG. 264.—Pedigree showing an unusual concentration of individuals dying of cerebral thrombosis. II-6 had hypertension for years and died in uraemia with nephrosclerosis. Two individuals in the third generation are living with hypertension and arteriosclerosis.

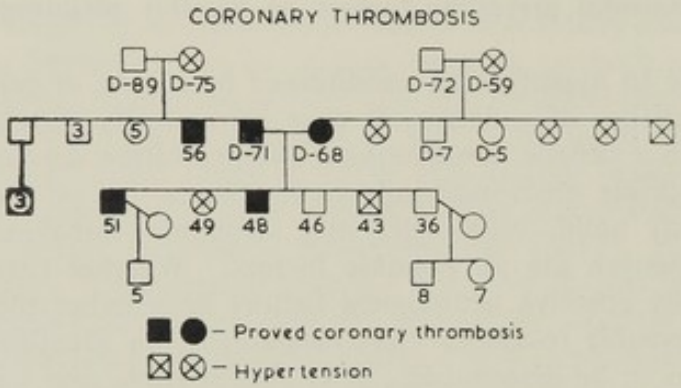

FIG. 265.—Family including 5 patients with coronary artery thrombosis proved either by autopsy or electrocardiogram. Eight additional relatives exhibited hypertension and arteriosclerosis.

Arteriosclerotic heart disease

A predilection for arteriosclerotic change in the coronary arteries has been frequently observed, and numerous pedigrees showing an unusual concentration of cases of coronary artery thrombosis are available (Fig. 265). It might be expected that familial aggregation due to chance alone may be expected in a disease with a high population frequency. However, Allan (1936), in reporting a family where 6 of 13 siblings died of coronary artery thrombosis, calculated that familial aggregation of this degree would occur by chance in only about 1 in 11,000,000 families of 13 children.

Xanthomatosis

Coronary artery disease in association with xanthomatosis has been described by various authors since about 1873. Müller (1939) has summarized the earlier literature and reported his observations on a group of 17 families. Xanthomatosis gives rise to a special form of arteriosclerosis aetiologically distinct from the usual variety. Xanthomatous deposits may occur in the heart valves, but the most usual changes are in the coronary arteries with a resulting anginal syndrome. This may occur in the young but is more frequent in middle-aged individuals, and symptomatically does not differ from the more usual form of angina pectoris.

Infarction of the myocardium and sudden death are frequent complications. Müller concluded that a dominant gene is responsible for the development of xanthomatosis in the families studied, with a high percentage of individuals with xanthomatosis developing coronary artery disease, and expressed the opinion that hereditary heart disease due to xanthomatosis is fairly common.

Thannhauser (1940) has recognized two forms of xanthomatosis, one associated with hypercholesterolaemia, and the other with normal cholesterol levels, and Wilkinson, Hand and Fliegelman (1948) demonstrated that hypercholesterolaemia is conditioned by a dominant gene. Wilkinson and his co-workers held that the more severe forms, such as xanthoma tuberosum, represent the homozygous state of the mutant gene, while the heterozygous state may be classified as simple hypercholesterolaemia without symptoms. Apparently a considerable clinical variation may occur with either genotype. Alvord (1949) in reporting a six-generation pedigree in which six individuals in three generations exhibited the coincidence of xanthoma tuberosum, angina pectoris and hyperlipaemia, while others showed only hyperlipaemia following a regular dominant pattern, postulated a single dominant gene with varying manifestations in the heterozygous state, varying from the symptom complex reported to simple hypercholesterolaemia.

The weight of evidence seems to favour Wilkinson's genetic hypothesis, and the question is not merely an academic one. The determination of the relation of clinical pattern to zygosity status might become of considerable importance in diagnosis and prognosis of these conditions, and there is also an obvious eugenic implication. If the findings of Wilkinson and his co-workers are confirmed, marriages of two individuals both exhibiting hypercholesterolaemia should be definitely discouraged, because of the increased likelihood of more severe manifestations among the children.

A second metabolic abnormality that may be responsible for coronary artery disease is gout. Arteriosclerosis is common in gouty individuals, and it is not unusual to encounter hypertension, cerebral vascular lesions and coronary insufficiency in such patients. Ask-Upmark and Adner (1950) reported three cases of coronary thrombosis in patients with gout and called attention to the importance of metabolic factors in cardiac infarctions in general.

OTHER AFFECTIONS OF THE HEART

Disorders of cardiac mechanism

Paroxysmal auricular tachycardia

A few families with a familial incidence of simple paroxysmal auricular tachycardia without obvious cause have been reported. Leusser (1917) recorded a family in which there were six cases of this arrhythmia in three generations, and two similar families have been described by Oehnell (1941). Arrhythmias of this type are, of course, fairly frequent in arteriosclerotic heart disease, and were observed in two members of the family with arteriosclerotic heart disease illustrated in Fig. 265 prior to the first episode of coronary artery occlusion.

Auricular fibrillation

The familial occurrence of auricular fibrillation is rare, aside from its more frequent occurrence in patients with arteriosclerotic heart disease. Wolff (1943)

has reported observations on three brothers in one family with auricular fibrillation, and two brothers in a second family. The fibrillation in these cases was permanent, and had apparently existed from an early age, and in at least one case it is suggested that the abnormality may have been congenital. The arrhythmia was apparently benign, being associated with a slow ventricular rate apparently secondary to strongly preponderant vagal tone.

Cardiopathy in neurological disorders

Friedreich's ataxia

Cardiac involvement in Friedreich's ataxia has been frequently described, but has been little emphasized. Even Friedreich's original report in 1863 mentions cardiac symptoms in three of the six original patients, one of these presenting an enlarged heart and an apical systolic murmur.

Lorenz, Kurtz and Shapiro (1950) in reviewing the literature on cardiopathy in Friedreich's ataxia, report findings on a family in which five children presented classical signs of Friedreich's ataxia and very similar cardiac findings, including similar apical systolic murmurs, cardiac hypertrophy in three patients, and abnormalities in the electrocardiogram, particularly involving the T wave. Four children showed definite inversion of T waves in leads II, III and V_6. The oldest child and the father showed low T waves without inversion, and peaked T waves were a constant observation. Similar findings have been previously reported.

Apparently some myocardial disturbance is a basic component of Friedreich's ataxia. In an autopsy study of four cases, Russell (1946) found evidence of chronic interstitial myocarditis in all cases, with pronounced cardiac hypertrophy in three. Examination of the medulla failed to show any histological abnormality in the region of the vagal nuclei.

Pseudohypertrophic progressive muscular dystrophy

Evidence of chronic myocardial disease has also been frequently noted in patients with muscular dystrophy. As this disease is a primary myopathy, it is logical to assume that the pathogenesis of degenerative change in cardiac muscle may be the same as that existing for skeletal muscle, but with skeletal muscle exhibiting a much greater susceptibility. Evidence of myocardial involvement usually does not appear until the affected individuals are rather severely crippled, and as the patients are physically incapable of any type of exertion, symptoms to indicate the markedly reduced cardiac reserve are infrequent. Myocardial involvement is probably a fairly frequent contributing factor to death in these patients.

Myotonia atrophica

Rinzler (1949) has reported one patient with this disease who exhibited an abnormal electrocardiogram showing a PR interval of 0·24 second and a left discordant bundle branch block of unknown cause. This patient apparently had an unusual tolerance to atropine. Rinzler reviews the literature concerning cardiac involvement in myotonia atrophica, and suggests that this condition represents another rare type of heart disease.

Periodic paralysis

Electrocardiographic changes have been described during acute episodes of periodic paralysis by Stewart, Smith and Milhorat (1940) and others. These

changes are apparently secondary to the marked changes in the amounts of available potassium salts that occur during the episodes of paralysis. The disease represents a primary disorder of potassium metabolism, and its inheritance is discussed elsewhere.

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CHAPTER 24

HAEMOPOIETIC SYSTEM

I.—Inherited Abnormalities of the Cellular Constituents of the Blood

James V. Neel

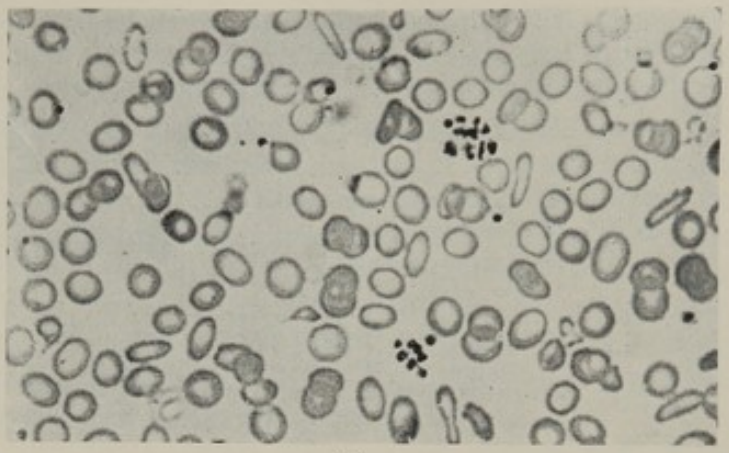
Although in the strict sense only the leucocytes are true cells, the term " cellular constituents " is extended for the purpose of this chapter to include the erythrocytes and the thrombocytes.

ABNORMALITIES OF THE ERYTHROCYTE

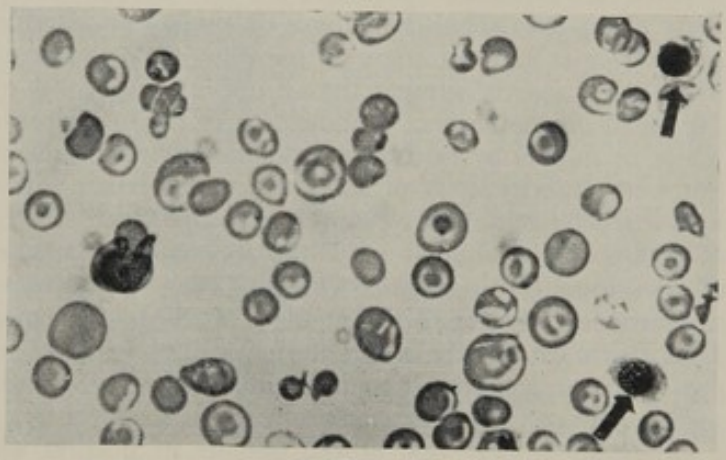
Thalassaemia (Cooley's anaemia, erythroblastic anaemia, Mediterranean anaemia, hereditary leptocytosis, Mediterranean haemopathic syndrome)

Clinical aspects.—In 1925 Cooley and Lee first described a chronic disease of childhood characterized by a profound anaemia, splenomegaly, the deposition of an iron-containing pigment in the viscera and hyperplasia of the bone marrow. The haematological characteristics of the anaemia included marked hypochromia, anisocytosis and poikilocytosis of the erythrocytes, and the presence in the peripheral circulation of large numbers of nucleated erythrocytes (Fig. 266*a*), from which one designation of the disease (erythroblastic anaemia) is derived. The resistance of the cells to hypotonic saline was increased, apparently primarily because of a " thinness " of the erythrocytes. The pathological findings in the bone marrow were suggestive of a maturation arrest (Whipple and Bradford, 1936), and this appears to be the basic defect in the disease, although an increased rate of destruction of the deformed erythrocytes may also be a factor in the anaemia (Kaplan and Zuelzer, 1950). Therapy is entirely symptomatic; death usually occurs at an early age.

Concurrent with these studies of anaemia in the United States of America, Italian physicians (Rietti, 1925, and Greppi, 1928) were describing a less marked haematological abnormality which, as now recognized, is characterized primarily by microcytosis with increased numbers of target and oval cells (Fig. 266*b*). The microcytosis is partially offset by a compensatory polycythaemia, but haemoglobin levels are usually several grammes below normal. Cell resistance to hypotonic saline solutions is increased. The same abnormality was described independently by 3 different groups of American investigators some 15 years later (Dameshek, 1940; Wintrobe and his associates, 1940, and Strauss and his associates, 1941). Evidences of increased erythrocyte haemolysis may be present; by and large this has been a more prominent feature of the Italian rather than of the American experience. This condition has been variously termed target-oval cell syndrome, microcythaemia, familial microcytic anaemia and other designations.



(*a*)



(*b*)

FIG. 266.—(*a*) Blood film in thalassaemia minor. The two abnormal types of erythrocytes most frequently observed in this disease are ovalocytes and " target cells ", with the relative proportions of these types varying from one individual to the next. This particular film was chosen because of the large number of ovalocytes; comparison with Fig. 275 illustrates why this condition may be confused with ovalocytosis. (*b*) Blood film in thalassaemia major. Anisocytosis and poikilocytosis are marked, with large numbers of target cells. Arrows indicate nucleated erythrocytes.

Heredity.—The first of these affections was early noted to have a familial incidence, and in 1934 Moncrieff and Whitby suggested that it was due to a recessive gene. As for microcytic anaemia, it was noted at the time of the original reports to be inherited as if due to a dominant gene.

That the two diseases might be genetically related was suggested by the observations of Angelini (1937), Caminopetros (1938), Wintrobe (1942) and Smith (1942) of the occurrence of some or all of the features of the mild disorder in the parents of children with the severe disease. Numerous studies have now demonstrated that, as a rule, the mild disease is due to the heterozygous condition for the same gene which, when homozygous, results in the more severe disease. Thus, there is an incompletely dominant gene which in the heterozygous state results in the mild anaemia; in the homozygous state, it results in the more severe disease (Dameshek, 1943; Valentine and Neel, 1944 and 1947; Gatto, 1942; Chini, 1946; Silvestroni and Bianco, 1946). The evidence which supports this hypothesis is of two chief types: (1) the usual occurrence of the mild disease in both parents of a child with the severe dyscrasia, and (2) a satisfactory approximation to a ratio of one normal, two mildly affected, one severely affected in sibships segregating for the severe disease. The term " thalassaemia major " has been suggested for the homozygote, and " thalassaemia minor " for the heterozygote. Fig. 267 demonstrates the manner in which the two conditions were related in one kindred.

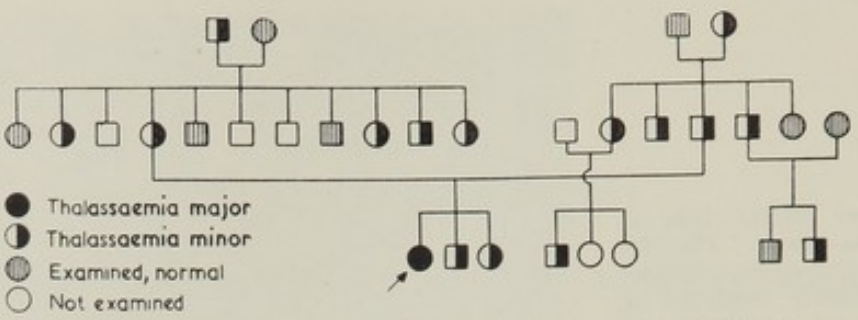


FIG. 267.—A 3-generation pedigree of thalassaemia, with thalassaemia major appearing among the offspring of a marriage involving two persons with thalassaemia minor. In this and subsequent pedigrees the propositus is indicated by an arrow.

Although generally the distinction between the two forms of the disease is obvious, there occur occasional individuals occupying an intermediate position. The occurrence of such cases has led some to question the validity of the homozygous-heterozygous hypothesis. At the present time it appears that most of these " intermediates " can be explained on the basis of modification of the fundamental genotype (either thalassaemia major or minor) by various genetic and environmental modifiers, the nature of which is not well understood at present. Certain of these intermediate cases are characterized by a marked haemolytic element (Chini and Valeri, 1949); these would appear to be cases of thalassaemia minor in which the abnormally shaped erythrocytes are being destroyed at an unusually rapid rate. Other of the intermediate cases may be the result of the superimposition of a deficient diet, or chronic haemorrhage on thalassaemia minor. That a rare case of thalassaemia major may, with the judicious use of transfusions and the antibiotics, survive to adulthood, seems well established, but the reproduction of such persons must be extremely rare.

Occasionally only one of the parents of a child with thalassaemia major exhibits haematological abnormalities, the blood findings on the other parent falling well within the acceptable range of normal variation. Thus, Silvestroni, Bianco and Vallisneri (1949) report that out of 220 parents of children with thalassaemia major, 210 exhibited definite thalassaemia minor; in 6 the findings were equivocal; in 3 " the blood examinations did not give certain evidence of microcythaemia, and in 1 case the absence of microcythaemia was proved without doubt." Other less extensive series have yielded similar results. Such apparently exceptional cases may be interpreted in at least four of the following ways: (1) failure of the thalassaemia gene to find expression, that is, incomplete penetrance; (2) a discrepancy between the legal and the biological parentage; (3) a mutation among the gametes of the apparently normal parent; and (4) production of apparent thalassaemia major by the interaction of a single thalassaemia gene with as yet unrecognized environmental or genetic factors, a situation analogous to that recently discovered for sickle cell disease (*see below*). Recently, Eugene Kaplan and the present author have studied three families in which one of the parents of a child with thalassaemia major showed such slight departures from normal that they would not ordinarily excite comment. However, in every case it was possible to demonstrate that one or more relatives of the " almost normal " parent had thalassaemia minor. This finding suggests that a high proportion of the apparent exceptions may be due to failure of penetrance.

The diseases were early noted to have very definite racial predilections, appearing predominantly in Italians (especially Sicilians), Greeks, Cypriots, in fact, most of the Mediterranean peoples. However, the diseases are by no means confined to this ethnological segment, having been reported in non-Mediterranean Europeans,

as well as in Negroes, Orientals and an American Indian (Silver, 1950). Although some of these cases are probably not genetically identical with the syndromes described above, it is definite that the thalassaemia gene has a wide distribution. In the United States of America the frequency of the major form among the descendants of Italian (largely Sicilian) immigrants was found to be 0·00042, from which the incidence of the minor form was calculated to be 0·041 (Neel and Valentine, 1945). In Italy there are no survey figures on the incidence of the major form of the disease, but extensive figures on the frequency of the minor form have been published, indicating about 4 per cent in Sicily and the extreme south of Italy, and an even higher incidence, in the neighbourhood of 10 per cent, in the Po River valley region (Silvestroni and Bianco, 1949). Reliable figures for other parts of the Mediterranean area are lacking.

Inasmuch as individuals with thalassaemia major very seldom reproduce, some rather difficult genetic problems are raised by the high frequency of the gene in certain parts of the world. Since selection against the homozygote is to all intents and purposes complete, the observed gene frequencies, assuming a population in approximate genetic equilibrium, is most reasonably explained either in terms of an extraordinarily high mutation rate, of the order of 0·004, or selection in favour of the heterozygote, for example, " balanced polymorphism," or by some combination of these two factors. At the moment, critical data permitting a decision between these two possibilities do not exist. It is difficult to see how thalassaemia minor *per se* can confer a selective advantage on an individual, but there may be other less obvious effects of the gene in question which are of survival value. The reason for the geographical distribution of the disease is quite unknown.

From the standpoint of genetic prognosis, it is apparent that the carriers of the disease can be identified with a high degree of accuracy. Thus, one can readily predict which marriages will result in thalassaemia major, and further, which among the siblings of a child with thalassaemia major may in turn transmit the disease.

Sickle-cell disease (sickle-cell anaemia, drepanocytic anaemia) and sicklaemia (sickle-cell trait)

Clinical aspects.—If the oxygen tension of a drop of blood is lowered, either by sealing the blood from access to the air for several days or, more rapidly, by the use of such agents as ascorbic acid or sodium dithionite, the erythrocytes in occasional cases will be observed to assume bizarre shapes characterized by the protrusion of filamentous processes of varying lengths. This phenomenon, which is referred to as " sickling " from the sickle-shape of some of the distorted erythrocytes, is largely confined to Negroes. Most individuals who exhibit the phenomenon apparently suffer no ill effects, and they are spoken of as having the sickle-cell trait or sicklaemia. However, a small portion of individuals whose blood sickles, are the victims of a severe chronic disease known variously as sickle-cell disease, sickle-cell anaemia, or drepanocytic anaemia. The disease is characterized by anaemia, retardation of physical development, and crises with the development of malaise and severe pain in the abdomen, back, head and extremities. Transfusion experiments wherein sickle-cell disease blood is introduced into a normal recipient have revealed a rapid destruction of the transfused erythrocytes (Singer, Robin,

King, and Jefferson, 1948; and Callender, Nickel, Moore, and Powell, 1948), and the primary basis of the anaemia observed in the disease is apparently an inability of the haematopoietic system to keep pace with the increased erythrocyte breakdown. During a crisis, for reasons not clear, the rate of blood destruction may be greatly increased. The physical maldevelopment would appear to be largely on the basis of the anaemia. The nature of the incapacitating crises so frequently observed is not clear, but may, at least in part, be due to a local vascular accident provoked by intravascular sickling.

The clinical distinction between sickle-cell anaemia and the sickle-cell trait is usually readily reached; any individual whose blood sickles falls, with rare exceptions, into one or the other pattern (Neel, 1951). The basic physiological distinction between the two conditions appears to lie in the ease with which the sickling phenomenon occurs, individuals with sickle-cell disease undergoing sickling at the 0_2-tensions of venous blood, while the cells of those with the sickle-cell trait generally fail to do so (Sherman, 1940). A second factor of possible importance is the type of sickling which occurs, that of sickle-cell disease being markedly more filamentous than in sicklaemia (Fig. 268). It is

FIG. 268.—The sickling phenomenon. The preparation on the left is from a patient with sickle-cell anaemia, while that on the right is from a person with the sickle-cell trait. The difference in the type of sickling is characteristic. The cells in both these figures were incubated in a saline suspension at 32° for 24 hours, then fixed with formalin and stained with haematoxylin.

conceivable that the sickled cells of the disease would have greater difficulty passing through the capillaries than those of the trait. The studies of Pauling and his associates (1949 and 1950) have gone far to elucidate the basis for the clinical distinction between trait and disease. Studies of the migration of haemoglobin in a Tiselius chamber reveal that the haemoglobin of sickle-cell disease differs in its motility from that of normal individuals, whereas in sickle-cell trait, the haemoglobin is of two types, 30–40 per cent being similar to that seen in the disease, and 60–70 per cent resembling that found in normal individuals. A difference of 0·23 *p*H units in the iso-electric points of the two haemoglobins would account for the electrophoretic findings. This difference cannot, on the basis of the present findings, be attributed to inequalities in the number of acidic or basic amino acid residues, but is presumably the result of a change in ionization constants of acidic and basic groups resulting from a difference in the folding of the polypeptide chain. That there may be other biochemical differences between normal, sickle-cell trait and sickle-cell anaemia haemoglobins is suggested by the report of Schneider and Levin (1950). These investigators found that erythrocytes from two individuals with sickle-cell anaemia, when injected into rabbits, produced antisera which agglutinated the erythrocytes of 19 persons with sickle-cell anaemia but not those of

21 individuals with the sickle-cell trait nor those of 124 normal individuals. Furthermore, the presence of an agglutinin antibody was demonstrated in the sera of all of 13 patients with sickle-cell anaemia, but of 11 patients with the sickle-cell trait, definite agglutinin was demonstrated in the sera of only 4, with doubtful agglutinin antibody in 2 more.

Heredity.—A few years after the description of the disease by Herrick in 1910, the sickling phenomenon was recognized to have a genetic basis (Emmel, 1917) but for a considerable period the definite distinction between the disease and the trait was not drawn. During this period Taliaferro and Huck (1923) suggested that both the trait and the disease were manifestations of a dominant gene of variable expression, a point of view which has been widely disseminated throughout the literature. More recently it has been suggested that the two conditions are usually related as homozygote to heterozygote, that is, that there exists a gene which, in the heterozygous condition, results in sicklaemia and in the homozygous condition, sickle-cell disease (Neel, 1949, 1951). The chief evidence in support of the hypothesis, as in the case of thalassaemia, is of two types: (1) the observation that in the great majority of cases of sickle-cell disease, both parents show the sickle-cell trait, and (2) the fact that in families segregating for sickle-cell disease the ratio of disease : trait : normal approximates 1 : 2 : 1. A further point in support of the hypothesis is the fact that the children of individuals with the disease married to non-sickling individuals have, in the author's experience to date, always shown the trait. The theory finds indirect confirmation in the above mentioned biochemical findings of Pauling and his associates, one gene is able to divert or convert approximately 40 per cent of the haemoglobin along an abnormal pathway; two genes usually result in a 100 per cent conversion, although in the occasional individual with sickle-cell disease there may be a small fraction electrophoretically normal haemoglobin. Fig. 269 represents the findings in a

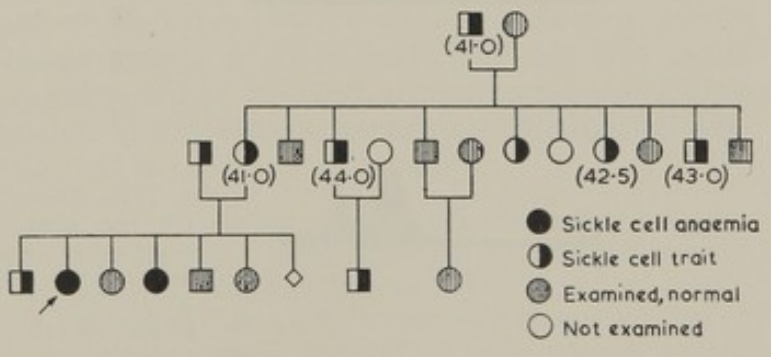


FIG. 269.—A 3-generation pedigree of the sickling phenomenon, illustrating the appearance of sickle-cell anaemia following the marriage of two persons with the sickle-cell trait. The figures in parentheses give the proportion of abnormal haemoglobin present as determined by electrophoretic studies. Note the constancy in this proportion in this family.

typical Negro family in which segregation for sickle-cell disease and and sickle-cell trait is occurring.

The author has examined both parents of 37 sibships selected at random in which sickle-cell disease or a reasonable counterpart thereof was segregating. In 33 families both parents showed the sickle-cell trait, but in 4 families only one parent could be induced to sickle. In 15 sibships in which the sickle-cell trait was present (exclusive of sickle-cell disease sibships), one parent also showed the trait in 14 instances, but in one sibship a child with the trait had 6 non-sickling siblings and neither parent sickled.

As was true for thalassaemia, four possible explanations of these exceptional families must be recognized; (1) failure of the sickle-cell gene to find expression in an individual who carries it, possibly for biological reasons, possibly due to technical factors; (2) a discrepancy between the legal and biological parentage; (3) a mutation among the gametes of the apparently normal parent; and (4) production of apparent sickle-cell disease by the interaction of a single sickling gene with other genetic or even environmental factors. The distinction between these four possibilities presents certain problems. Recent evidence indicates that the fourth possibility must be given special consideration. A study of the haemoglobin of two of these exceptional families, according to the technique of Pauling and his associates (1949), revealed the situation shown in Figs. 270 and 271

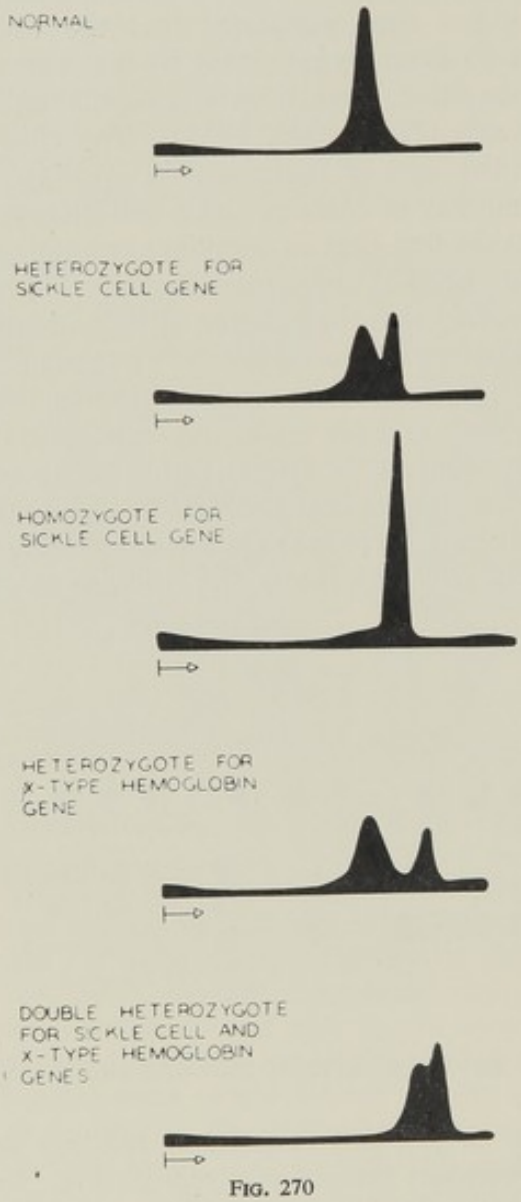


FIG. 270

FIG. 270.—Reproductions of the Longsworth scanning diagrams (electrophoretic profiles) of the carbon-monoxyhaemoglobins in five different genotypes.

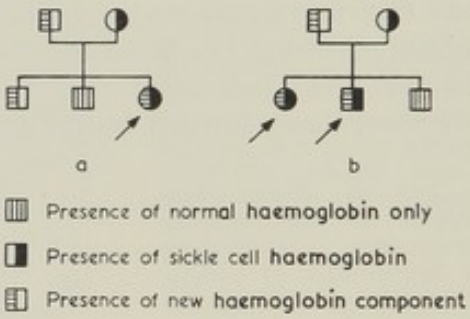


FIG. 271.—The interaction of the gene responsible for the sickling phenomenon with the gene responsible for another, as yet unnamed, haemoglobin abnormality. The individuals indicated by arrows are double heterozygotes and exhibit a clinical picture very similar to sickle-cell anaemia.

(Itano and Neel, 1950). In each case, the haemoglobin of the apparently exceptional (non-sickling) parent could be demonstrated to possess an abnormal component. The tendency to form this component appears to be transmitted as if due to a single dominant gene. The simultaneous presence of this gene and the sickle-cell gene resulted in haematological

findings very similar to sickle-cell disease. However, all 3 of the children who are thought to have received both genes have run a much milder course than the usual case of sickle-cell disease (Kaplan, Zuelzer and Neel, 1951).

Recently, several cases have been described of Caucasian individuals of Italian (predominantly Sicilian) extraction with haematological findings very similar to classical sickle-cell disease, whose picture could definitely be attributed to simultaneous heterozygosity for the sickle-cell and the thalassaemia genes (Silvestroni, 1949; Powell, Rodarte and Neel, 1950). The pedigree of one such individual is shown in Fig. 272.

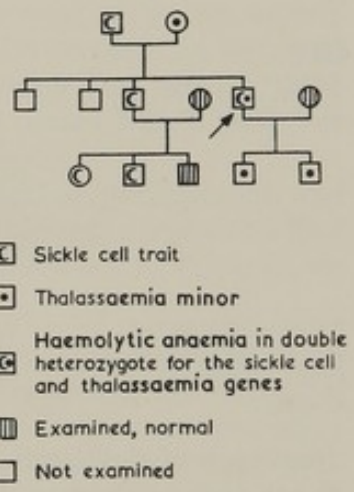


FIG. 272.—The interaction of the gene responsible for thalassaemia with that responsible for the sickling phenomenon. The individual indicated by an arrow is a double heterozygote who presents the clinical picture of sickle-cell disease. Figs. 269, 271 and 272 illustrate that what clinically appears to be sickle-cell anaemia may have at least three different genetic aetiologies.

There is, therefore, evidence that although the preponderance of sickle cell disease develops as the result of homozygosity for the sickling gene, there are, genetically speaking, at least two other types of sickle-cell-like disease, both developing on the background of heterozygosity for the sickle-cell gene, in the one case due to the simultaneous presence of the thalassaemia gene, and in the other to the presence of a gene detected by its effect in heterozygous condition on the migration of haemoglobin in the Tiselius apparatus. What effect this newly recognized gene has when homozygous is still unknown.

Although it is now clear that some of the apparent exceptions to the general rule that both parents of a child with sickle-cell disease themselves exhibit the sickling phenomenon are explicable by virtue of the fact that sickle-cell-like disease may have several genetic aetiologies, it is doubtful whether this will explain all the apparent exceptions. One of the remaining exceptional families referred to above involved the appearance of a child with sickle-cell trait where both parents and 6 siblings were normal. There was no evidence of impaternity, and while lack of penetrance of the gene in one of the parents is a possibility, there is no particular reason to suspect this. Mutation therefore must be considered. The two remaining exceptional families both involve a failure of one parent of a child with sickle-cell disease to exhibit the sickling phenomenon. In one of these two instances it is the mother who fails to sickle and in this case electrophoretic analysis of her haemoglobin reveals no abnormality. Here again mutation must be seriously considered.

As noted above, the sickling phenomenon is largely confined to individuals whose ancestry is wholly or partially Negroid. In the North and South American

Negro, the average incidence of the sickling trait in 19 series published since 1933 has been 9–10 per cent (Neel, 1951). As might be expected, an even higher incidence has been observed in Africa, as indicated in Fig. 273. Direct estimates of the

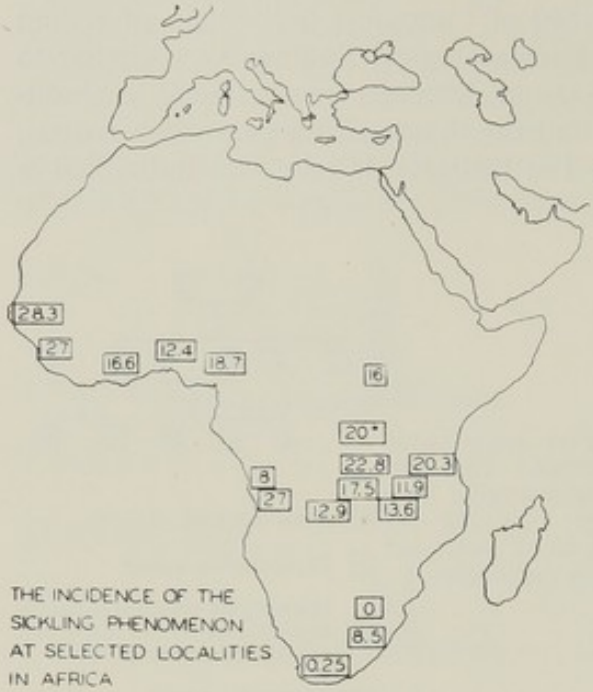


FIG. 273.—The incidence of the sickling phenomenon at selected localities in Africa. Each box indicates the percentage of sickling observed in a particular study. The results of the study indicated by an asterisk were particularly interesting. In four different tribes speaking a Hamitic type language, the percentage of sickling varied between 0·8 and 3·9. In seven different tribes with a Nilotic type language, the percentage of sickling varied between 21·0 and 28·0 Finally, in 11 tribes whose language was Bantu in type, the incidence of sickling was from 2·0 to 45·0 per cent.

frequency of sickle-cell disease are not available. However, from an estimate of 9 per cent sickling in the American Negro it can readily be calculated that the homozygote with sickle-cell disease should have a frequency at birth of 2·2 per 1,000. One would expect an even greater frequency of the homozygote in Africa. However, several investigators with a considerable background of experience in Africa have pointed out that this does not seem to be the case and that, quite to the contrary, the disease is in their opinion less frequently seen there than in the United States of America. This has led to the speculation that " the appearance of sickle-cell anaemia depends, not only on the extent to which the trait is present in the community, but also on the extent to which admixture with other genetic strains has occurred " (Raper, 1950). This is an interesting opinion; an equally tenable alternative appears to be that the more rigorous living conditions in Africa than in America are resulting in the early elimination of children with sickle-cell disease, before they come to medical attention.

The literature contains some 20 primary case reports of the sickling phenomenon, usually associated with a haemolytic anaemia, in Caucasians with no known Negro ancestry. Sixteen of the patients involved have been of Italian or Greek ancestry. In the light of the observation, that the double heterozygote for the sickle-cell gene and the thalassaemia gene exhibits a clinical and haematological picture very similar to sickle-cell disease developing on the basis of homozygosity for the sickling gene, it seems quite probable that the majority of the reported cases of this disease in Caucasians are really this double heterozygote. The sickling phenomenon has not yet been reported in Orientals.

Individuals with sickle-cell disease have a greatly decreased life expectancy; the pregnancies of women with the disease very frequently terminate in abortions,

miscarriages, or stillbirths. At the present time, no definite ill effects of the sickle-cell trait are recognized. However, there is evidence that the frequency of the trait in the general population tends to decrease with advancing age, from which the possibility of some unapparent but significant effect arises. Sickle-cell disease presents the same problems in population genetics as does thalassaemia. If the disease in Africa is comparable to that seen in the United States of America, how can its frequency be explained? The two most obvious possibilities involve selection in favour of the heterozygote, and a mutation rate without precedent in human genetics. As already noted, it now appears that the selection to which the heterozygote is subject is, if anything, negative. Satisfactory direct evidence concerning the role of mutation is not yet available. Several of the apparently exceptional families discussed in some detail earlier in this section can be interpreted as evidence in favour of mutation, but even granting that there is some evidence for mutation, it is not yet known whether this occurs with a sufficient frequency to account for the incidence of the disease.

The many similar genetic problems presented by the sickling phenomenon and thalassaemia, their geographical propinquity and the apparent interaction effect in the double heterozygote provide grounds for speculation as to the possible genetic relationship of these two diseases.

Individuals who are the genetic carriers of sickle-cell disease may be readily identified by a simple laboratory test. In actual practice it is sufficient to occlude the circulation of a finger for 3–5 minutes, obtain a few drops of blood with a lancet, and seal this under a cover slip with petroleum jelly. If the tendency to produce sickle cells is present, it will be obvious in 24–48 hours. The addition of a few drops of an ascorbic acid solution (4 per cent) to the blood will greatly accelerate the onset of sickling.

Linkage of the genes responsible for the M–N agglutinogens with that for the sickling phenomenon has been reported, with an estimated 11 per cent crossing-over between the two loci (Snyder, Clarke and Moore, 1949). Other studies have failed to confirm this (Neel, Schull and Shapiro, 1952).

Congenital haemolytic jaundice (hereditary spherocytosis, spherocytic anaemia, chronic acholuric jaundice)

Clinical aspects.—Congenital haemolytic jaundice is a disease with a wide and variable clinical spectrum. The one constant finding is the presence of spherocytic erythrocytes. Although these abnormally shaped erythrocytes are at all times destroyed more rapidly than normal, resulting in many instances in a haemolytic type of anaemia and chronic, low-grade jaundice, a characteristic feature of the disease is the occurrence of crises, in which the rate of blood destruction is markedly accelerated. The factor or factors precipitating these crises is unknown; there are in the literature at least 8 reports of several members of a family entering a crisis period more or less simultaneously (Marson, Meynell and Tabbush, 1950). The spleen is enlarged, and from the fact that its removal usually results in a marked amelioration of the disease, the chief cause of the anaemia is thought to be an increased rate of destruction of the abnormally shaped erythrocytes in the spleen, although the spherocytes are destroyed elsewhere in the body also. Whether the fundamental defect is an abnormal morphogenesis of the erythrocytes,

or whether some presently unappreciated factor converts potentially biconcave erythrocytes to spherocytes, is not now clear. The deformed erythrocytes present a characteristic appearance on the stained blood film (Fig. 274) and in addition

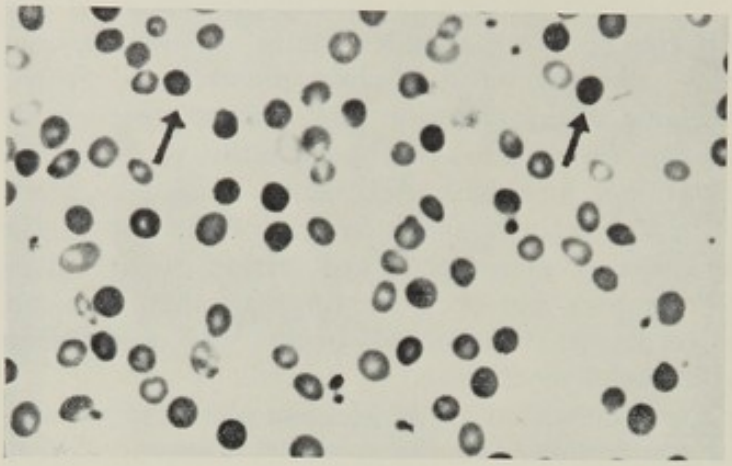


FIG. 274.—Blood film in hereditary spherocytosis. The densely staining cells are spherocytes; the arrows indicate two such cells.

are readily demonstrated to have an increased osmotic and mechanical fragility, facts of value in the diagnosis of the condition. Biliary disease secondary to the increased rate of bilirubin excretion is not infrequently present.

Clinically, the obvious features of the disease are jaundice of the non-obstructive type and splenomegaly. Dreyfus (1942) in a review of the historical background of the condition credits Vanlair and Marius with the first recognition of the condition in 1871, although it was not until 1900 that Minkowski supplied an adequate clinical description. A positive family history was noted in this very first case report, a mother and sister of the patient being described as chronically slightly jaundiced.

Heredity.—The early studies of the disease, all of which emphasized the clinical rather than the haematological picture, frequently dwelt on its hereditary background, with Plate (1913) apparently the first to suggest a definite genetic basis, a dominant gene. Among the many studies of heredity in this disease, those of Meulengracht (1921), Gänsslen, Zipperlen, and Schüz (1925), Campbell and Warner (1926), Race (1942), and Young, Izzo and Platzer (1951) are outstanding. As a rule, an individual with the complete picture of the disease will be found to have one or more relatives with chronic or intermittent jaundice and other symptoms, with the transmission of the manifest disease usually appearing to be directly from one generation to the next. Frequently, however, the disease appears to miss a generation, or appears as an isolated case, or affects several siblings, with the remainder of the family history negative. Where inheritance is not plainly direct, two possibilities exist:

(1) On the one hand, an examination of the blood of the apparently normal parents and siblings of affected individuals may reveal the presence in some of a significant degree of microcytosis and increased cell fragility in saline solutions, with evidence of an increased rate of blood destruction which apparently has never reached the level of clinical significance. In such families it is not uncommon to get a history of a more remote ancestor of the individual with clinical symptoms also displaying the full disease.

These facts, first emphasized by Giffin (1917), Gänsslen (1922), Meulengracht (1921) and Campbell and Warner (1926), indicate that the irregular dominant inheritance is more apparent than real, with the gene for hereditary spherocytosis usually finding some degree of expression when present. An individual cannot be classified as normal without appropriate blood studies; when these are performed, the ratio of normal : spherocytic among the offspring of marriages of normal × spherocytic approaches 1 : 1. However, Race (1942) has pointed out that even in his carefully studied series of 26 families there appears to be a significant deficiency of spherocytic persons from expectation. Three possible contributing factors have been recognized. The first is an increased mortality, perhaps even beginning *in utero*, on the part of those with the disease. The second is that included among the individuals thought to have hereditary spherocytosis, there are some whose spherocytosis is on an acquired basis; these, of course, would not have spherocytic siblings nor transmit spherocytosis to their offspring. Finally, the gene may occasionally fail to find any expression whatsoever to the usually employed haematological tests.

(2) On the other hand, in some cases even the most reliable tests presently available may fail to demonstrate the presence of any significant haematological abnormality in either parent of an affected individual. Race (1942) noted that in 10 cases of spherocytosis where both parents were examined neither parent presented any abnormality in 3 instances. A total of 16 relatives of these 3 cases were examined and found normal. More recently, Young and his associates (1951), using the most refined techniques currently available for the study of erythrocyte fragility, have observed 2 families in which an individual, who satisfies all the requirements for the diagnosis of hereditary spherocytosis, has 2 apparently normal parents. In one of these families, 2 additional relatives were also normal; in the other, 9 additional relatives appeared normal. The possible explanations for these exceptional individuals include the following: (*a*) the individual in question is actually a case of acquired spherocytosis; (*b*) the responsible gene is really present in one of the parents but fails to find expression, (*c*) illegitimacy; and (*d*) the exceptions are due to mutation. With respect to this last possibility, the reproductive expectancy of these individuals at birth in a state of nature is unknown—let us assume that they carry a modest 20 per cent handicap. If the population were at equilibrium, each generation 1 of 5 such genes should owe its presence to mutation. Even in these days of splenectomy and possible reproductive overcompensation on the part of the genetically handicapped, with the mitigation of that inherent 20 per cent liability, the results of mutation should still be observed from time to time. That these apparently isolated cases might be due to mutation was apparently first suggested by Meulengracht, although later he was inclined to attribute them more to failures in gene penetrance (Meulengracht, 1938).

The proportion of individuals with spherocytosis whose rate of blood destruction and symptomatology reach the level of clinical significance varies widely from family to family, from an apparent 100 per cent to, in families such as the one described by Herndon and Alexander (1947), as low as 29 per cent (2 of 7). Gänsslen (1940) has particularly emphasized the broad clinical spectrum presented by the various manifestations of the responsible gene.

The disease is uncommon. A frequency estimate of the order of 1 : 10,000 to 1 : 20,000 in Caucasians seems a not unreasonable first approximation. If one can judge by the number of case reports, the condition is less common in Negroes and Orientals than in Caucasians. Thus, only 22 cases distributed among 9 families have been reported in the American Negro (Ehrlich and Schwarz (1950), and Butterworth, Kracke and Riser (1950)) and no case report concerning an

African Negro has yet come to the author's attention. Komai (1934 and 1947) lists 27 pedigrees of the disease in Japanese subjects.

The osmotic fragility curve in normal subjects is usually normally distributed about the mean value. In classical hereditary spherocytosis not only is the mean fragility increased, but the fragility curve is multimodal, suggesting that more than one population of red cells is present. Discombe (1948) has described a family with hereditary spherocytosis in which there was a unimodal fragility curve in affected individuals, and suggested that this family may be genetically distinct from those usually encountered.

Here, as in the case of thalassaemia major and sickle-cell disease, genetic carriers may be identified. However, the genetic relationship of the carrier state to the disease is different. In thalassaemia major and sickle-cell disease, the carrier was the identifiable heterozygote for a gene which in the homozygous state is responsible for a serious illness. But in hereditary spherocytosis, the carrier and the individual with the full blown disease are generally thought to be heterozygous for the same gene, an autosomal dominant, which for unknown genetic or environmental reasons, or both, finds a more extreme expression in the one than the other. Recently, Butterworth, Kracke and Riser (1950) have suggested that the genetic findings are explicable in terms of a series of three allelomorphs, (*a*) the normal, (*b*) a factor rendering the spherocytes susceptible to haemolysis, and (*c*) a factor responsible for spherocyte production. This theory would seem to require a rather sharp distinction between carrier and diseased which in practice does not seem to exist. Assuming for the moment that only a single principal gene is involved in spherocytosis, then whereas in thalassaemia major and sickle-cell disease carriers produce affected children only when married to other carriers, in hereditary spherocytosis carriers may produce children with the full blown syndrome whether married to a normal person or another carrier, the latter type of marriage being so rare that the number of affected persons arising in this manner is negligible. The effect of this gene when homozygous is not yet known.

Ovalocytosis (elliptocytosis)

Clinical aspects.—Ovalocytosis is characterized by the occurrence of large numbers of elongated, elliptical erythrocytes, usually of normal or near-normal cell volume and haemoglobin content. In a normal blood film not more than

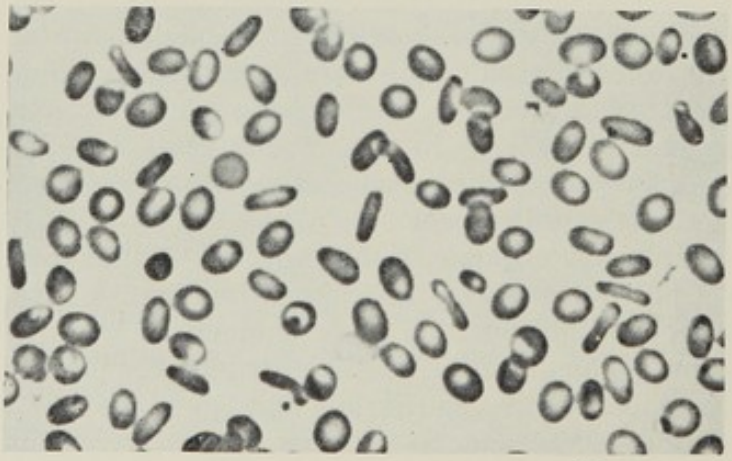


FIG. 275.—Blood film in ovalocytosis. The proportion of elongate forms in true ovalocytosis is much higher than in thalassaemia minor, to which it may bear a superficial resemblance.

1–2 per cent of the erythrocytes will be found to have a long axis 1·5 times as great as the short axis. In true ovalocytosis, on the other hand, one generally finds at least 20 per cent, and frequently up to 50 per cent or even more of the cells with this degree of eccentricity (Fig. 275). Although the number of ovalocytes may be increased in iron deficiency anaemia, pernicious anaemia, thalassaemia, sickle cell anaemia and the sex-linked, hypochromic, microcytic type of anaemia described below, the proportion of abnormally shaped cells is rarely as high as in ovalocytosis, and the differential diagnosis is usually no problem because of the characteristic findings associated with these other conditions. Occasionally, however, it may be difficult to differentiate thalassaemia minor from true ovalocytosis.

The data concerning the clinical significance of this anomaly are somewhat conflicting. There are numerous reports of mild anaemia associated with ovalocytosis, for example, those by Lambrecht (1938), Bertelsen (1938), and Mason (1938). Cooley (1942) states that of 246 reported cases of ovalocytosis in the literature, 35 (15 per cent) were anaemic. On the other hand, Wyandt, Bancroft and Winship (1941) in their extensive study of 86 ovalocytic persons from 3 interrelated families found no tendency to anaemia; the detailed haematological findings are not given. A significant degree of reticulocytosis is a not infrequent observation in individuals with ovalocytosis, as is splenomegaly. Although the association between anaemia and ovalocytosis may to a certain extent be fortuitous, it seems probable that the abnormally shaped erythrocytes tend to be destroyed at a more rapid rate than normal with those individuals who are unable to compensate for this increased rate of destruction developing an anaemia (Vischer, 1938).

Heredity.—Whilst Dresbach is usually credited with the initial observation of this anomaly, in 1904, the first evidence that the condition might be hereditary was supplied by Bishop in 1914, who observed ovalocytosis in a brother and sister. Hunter and Adams (1929) contributed the first extensive pedigree of the disease, reporting direct transmission of the trait through three generations. It remained for Cheney (1932), with another three-generation pedigree, to suggest that ovalocytosis was due to a single dominant gene, a point of view since amply confirmed (*cf.* pedigree summary in Gausch, 1949).

Only two possible exceptions to the rule, that an affected person will be found to have an affected parent, have been reported. Bernhardt (1928) has described an individual with the trait whose parents appeared entirely normal. This finding may be explained in the same fashion as isolated cases of hereditary spherocytosis. The present author (Neel, 1951) has described ovalocytosis in a Negro male, neither of whose parents exhibited ovalocytosis although both had the sickle-cell trait. However, the father's erythrocytes were moderately microcytic, with slightly increased anisocytosis and poikilocytosis; this observation may bear an aetiological relationship to the findings in his son.

The incidence of the disease in Caucasians can be best estimated from the studies of McCarty (1934) and Wyandt, Bancroft and Winship (1941), who between them, in a series of 17,000 persons chosen at random, found 6 individuals with the anomaly, a frequency of 0·00035. Dresbach's original case was in a mulatto, and from the frequency of case reports of the condition in Negroes it would seem that the trait is commoner in Negroes than in Caucasians. Thus, of 33 primary case reports originating in the United States of America which the author has

reviewed, 18 dealt with Caucasians and 15 with Negroes, a ratio quite out of proportion to the relative frequency of Caucasians and Negroes in this country. On the other hand, case reports dealing with Mongolians are rare, Komai (1947) listing only 2 based on Japanese material.

The literature contains two reports of a marriage between two individuals with ovalocytosis (Wyandt, Bancroft and Winship, 1941). Only one of these families is described in detail. Of the 5 children, 2 had died in infancy, 2 were normal and 1 exhibited marked ovalocytosis associated with 9·8 grammes per cent haemoglobin, 4,200,000 erythrocytes per cubic millimetre, "a positive indirect van den Bergh reaction, markedly increased red-cell fragility, a high reticulocyte count, and spherocytosis, as well as an enlarged spleen, an icteric tint to the skin and a history of previous haemolytic crises typical of those associated with familial haemolytic icterus." It is tempting to regard this extreme picture as the result of homozygosity for the gene in question.

Burks and Wyandt (1941) have presented data indicating that the genes responsible for the A-B-O blood groups and for ovalocytosis may be linked, the evidence being on the borderline of significance ($P = 0{\cdot}06$).

Pollack and Dameshek (1934) described the simultaneous occurrence of ovalocytosis and the sickling phenomenon in a Jewish family. There is room for doubt as to whether they observed true sickling. More recently, Fadem (1949) has described the simultaneous occurrence of sickling and ovalocytosis in a healthy, non-anaemic Negro male. This observation is of importance since it suggests that the gene responsible for the sickling phenomenon does not interact with the gene responsible for ovalocytosis the way it does with the gene producing thalassaemia.

The situation as regards a carrier state in this condition is quite comparable to that in hereditary spherocytosis, except that the gene responsible for ovalocytosis much less frequently reaches the level of clinical significance than does that for spherocytosis.

Sex-linked, hypochromic, microcytic anaemia

Cooley (1942 and 1945) and Rundles and Falls (1946) have described two families with an unusual and apparently quite rare type of anaemia which appears to depend upon a sex-linked gene, although the possibility that it is due to an autosomal dominant gene with unequal effects in the two sexes cannot definitely be excluded. A pedigree of one of the affected kindreds is shown in Fig. 276. All of the anaemic individuals are males. Their disease is characterized haematologically by hypochromia and microcytosis, with marked anisocytosis, target cells, oval cells and other more bizarre forms (Fig. 277). Resistance of the erythrocytes to haemolysis in saline solutions was increased. Splenomegaly and a lesser degree of hepatomegaly were present. Rundles and Falls (1946) examined both clinically and haematologically three mothers of certainly or probably affected males. In each case splenomegaly or minor erythrocyte abnormalities, or both, the latter consisting of up to 20 per cent pale oval cells, were observed (Fig. 277). Some of these women had female siblings or daughters with a similar blood picture. The anaemia was of a different degree of severity in the two kindreds; in one the disease often terminated fatally at an early age, whereas in the other prognosis was much less grave. Two different genes may be involved. It is

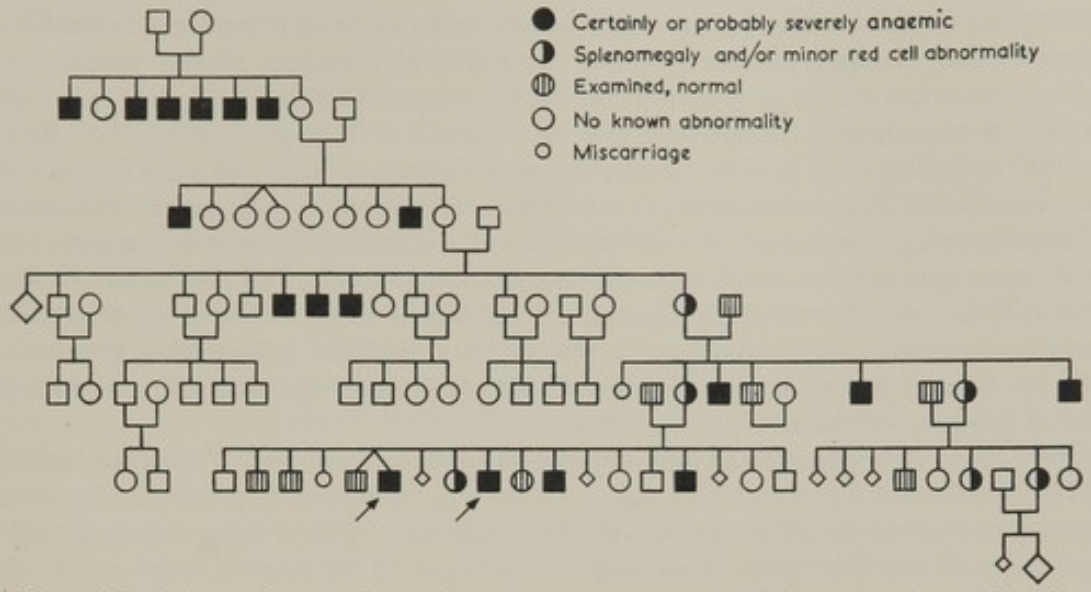


FIG. 276.—The pedigree of sex-linked hypochromic microcytic anaemia studied by Rundles and Falls (1946).

possible that the patient described by Mills and Lucia (1949), who died aged 27 of an intractable hypochromic, microcytic anaemia, and whose maternal half-brother was similarly affected, was another example of the sex-linked disease.

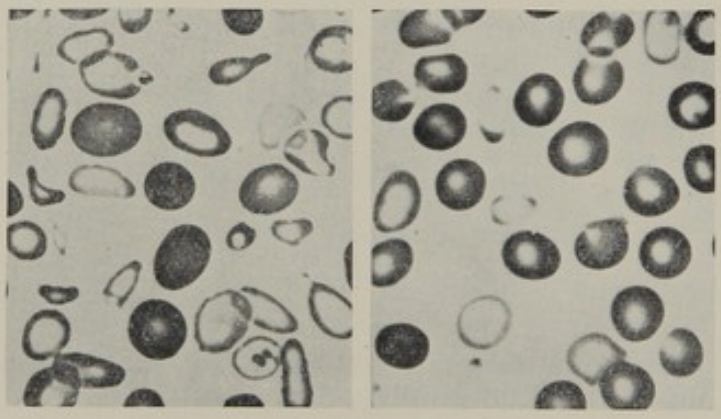


FIG. 277.—The blood film in hereditary sex-linked hypochromic microcytic anaemia. The individual pictured on the left is an affected male, while on the right is shown a female carrier. *Further explanation in text.*

Here, then, is yet another example of a carrier state, but quite possibly on a different genetic basis from the preceding illustrations in the field of haematology. In this case, assuming that a sex-linked gene is involved, the heterozygous females who transmit the disease exhibit minor abnormalities, while their (homozygous) sons show much more marked departures from the normal and may fail to reach maturity.

Pernicious anaemia (primary anaemia, Addisonian anaemia)

Clinical aspects.—Pernicious anaemia is a severe, chronic, progressive anaemia, characterized haematologically by macrocytic, anisocytotic, and poikilocytic erythrocytes; neutropenia with hypersegmentation of the nuclei of the polymorphonuclear leucocytes; and thrombocytopenia. Recurrent glossitis is a common

finding, as well as paraesthesias of the hands and feet, and symptoms referable to degenerative changes in the posterior and lateral columns of the spinal cord. Achylia gastrica is always present, and the primary defect in the disease is thought to be an improperly functioning gastric mucosa. It is postulated that in the normal individual the gastric secretions are intimately concerned with the absorption of vitamin B_{12} and folic acid, substances necessary to the normal maturation of erythrocytes. Individuals with pernicious anaemia are unable, because of a malfunctioning gastro-intestinal tract, to utilize vitamin B_{12} and folic acid properly. The achylia—or at least achlorhydria—is known in some cases to have preceded the development of the anaemia by many years, and the inference is that this is true for most if not all cases. Vitamin B_{12} is also concerned with the maintenance of the integrity of the nervous system.

Heredity.—The disease exhibits definite familial tendencies. Numerous authors have contributed figures indicating an increased incidence of pernicious anaemia among the relatives of patients with this disease. These data, summarized in Table I, indicate that in approximately 10 per cent of the cases a relative is known

TABLE I

THE INCIDENCE OF POSITIVE FAMILY HISTORIES AMONG PATIENTS WITH PERNICIOUS ANAEMIA

Author	Number of patients studied	Percentage with positive family histories
Levine and Ladd (1921)	143	6·3
Wilkinson and Brockbank (1931)	160	8·8
Castle and Minot (1936)	—	18·0
Werner (1938)	57	9·0
Kaufmann and Thiessen (1939)	48	16·7
Stamos (1940)	645	7·9
Schlecht, after Gänsslen (1940)	—	8·0

Unweighted average = 10·7

to have the disorder. Assuming each patient to supply accurate data on approximately 10 to 20 members of his family who have reached the usual age of onset of the disease (a generous estimate), this corresponds to a minimal incidence among relatives of between 1 in 100 and 1 in 200, as contrasted to an estimated incidence in the Caucasian population in general of approximately 1–2 in 10,000 (Askanazy, 1937; Nordenson and his associates, 1938). That the true incidence of pernicious anaemia among relatives may actually be significantly higher is shown by the findings of Baggi and Romei (1949) that among 251 clinically studied relatives of patients with pernicious anaemia there were 5·2 per cent who also had the disease.

The literature contains many case reports dealing with striking concentrations of pernicious anaemia within a single kindred. These reports, summarized by Conner (1930) and Askey (1940), include accounts of as many as 8 or 9 affected persons in two or three generations. While such data are definitely selected, the odds against such concentrations in a small group can be calculated to be very

high indeed. Moreover, in some of these families, relatives not known to have pernicious anaemia did exhibit symptoms of the central nervous system disease which so frequently accompanies the anaemia.

Additional evidence concerning the operation of genetic factors comes from a study of the disease in identical twins (*cf.* Askey, 1940). Of the 9 pairs of identical twins reported in the literature, one member of whom was certainly affected, the other was definitely similarly affected in 5 instances, may have been affected in 3 other instances while the data on the ninth twin pair are unsatisfactory.

European investigators (Weinberg, 1920; Zadek, 1926; Bremer, 1934; Hoff, 1935; Hangarter and Walbergs, 1936; Werner, 1938) have repeatedly drawn attention to the occurrence among relatives of pernicious anaemia patients of a " pre-pernicious anaemia " state, characterized by achylia and blood changes typical of those found in pernicious anaemia, but so minor as not to have reached the level of clinical significance. How long these individuals remain stationary, and how soon—if ever—the departures reach the level of clinical significance, is not clear. The occurrence of such individuals is further evidence for the non-random distribution of this disease.

Since the primary defect in this disease lies in the gastric mucosa, and clinically this defect may be measured by achlorhydria, it seems logical, as pointed out by Hurst (1925), to direct genetic studies at the familial incidence of achlorhydria. The present author has elsewhere summarized the data on this question (Neel, 1947). It is difficult to compare the various studies in the literature because of wide technical variations. In particular, many of the older studies failed to employ histamine in attempts to test the ability of the gastric mucosa to secrete hydrochloric acid. The incidence of achlorhydria increases with age. When the test is properly performed, including the injection of histamine, achlorhydria is probably present in 15–20 per cent of people over the age of 40 years (Lerman, Pierce and Brogan, 1932; Vanzant and his associates, 1932). The condition is thus sufficiently common that on the basis of chance alone it should not uncommonly occur among the relatives of pernicious anaemia patients. Comparisons of the incidence of achlorhydria in near relatives as opposed to distant relatives of pernicious anaemia patients sometimes fail to take into account possible age differences. Among the various studies in the literature, that of Conner (1930) appears to be most carefully controlled. He found that 3 of 7 parents of pernicious anaemia patients, with an average age of 61·7 years, had achlorhydria. Achlorhydria was present in 44·2 per cent of 53 siblings of pernicious anaemia patients with an average age of 47·4 years, as compared to 16·7 per cent of 60 spouses of the patients, with an average age of 48·9 years. Histamine was not used in this investigation. Other authors have also reported an increased incidence of achlorhydria among relatives, usually of a lesser degree.

There is thus evidence for an increased incidence of pernicious anaemia, a " pre-pernicious anaemia " state, subacute combined degeneration and achlorhydria among the relatives of pernicious anaemia patients. The exact magnitude of this increase is not clear. In the most extensive study reported to date, Baggi and Romei (1949) found that among 251 relatives of pernicious anaemia patients whom they investigated, 63·4 per cent showed a lowered haemoglobin, with 42·8 per cent considered definitely anaemic and 34·3 per cent exhibiting significant changes in the Price-Jones curve; 47·8 per cent were thought to show alterations of the lingual mucous membrane, but only 28·5 per cent were hypochlorhydric (less than 20 degrees of acidity one hour after 0·5 milligramme of histamine).

An explanation of these findings in terms of formal genetics is not possible at the present time.

It has been suggested that the tendency to develop achylia gastrica is inherited as if due to a single dominant gene. However, the data can also be interpreted as illustrating the effects of an irregularly expressed, common recessive gene, with the apparent dominance due to the marriage of a homozygous recessive (achylic) individual with a heterozygote (normal). It seems probable that the development of achlorhydria may be precipitated by both environmental and genetic factors, with the latter possibly multiple. Whether all individuals with achylia are equally prone to develop pernicious anaemia, or whether there are further genetic restrictions, is not clear at present. While it seems clear that pernicious anaemia is not distributed at random among the population, it has not yet been demonstrated that it is not distributed at random among achlorhydrics. However, so striking are some of the familial constellations of the disease that one is tempted to surmise the existence of important genetic modifiers of susceptibility—assuming, for the moment, the absence of a common environmental factor. Baggi and Romei (1949) have suggested that the action of two dominant genes may be required for the development of the disease. That the responsible gene or genes may have other effects in addition to those on the gastric mucosa is indicated by the well-known clinical impression of a pernicious anaemia type. The most extensive studies in this respect are those of Draper (1924) and Draper, Dupertuis and Caughey (1944), who characterize individuals with pernicious anaemia as tending to exhibit short and relatively broad faces with widely spaced eyes, deep and short chests, broad pelvis, and relatively long legs. Premature greying of the hair is said to occur with increased frequency in this group (*cf.* Hardgrove and his associates, 1944). However, the possibility cannot be excluded that these associations are not due to the multiple effects of a relatively few genes, but reflect the anthropological characteristics of a human subgroup in which the genetic factors responsible for pernicious anaemia are relatively common.

There may be other manifestations of the pernicious anaemia constitution. Numerous authors have reported the occurrence of " idiopathic " or essential hypochromic anaemia in the siblings of pernicious anaemia patients (Sinkler and Eshner, 1896; Gram, 1926; Wintrobe and Beebe, 1933; Heath, 1933; Tempka, 1935; Lundholm, 1938; Kaufmann and Thiessen, 1939; Miller and Dameshek, 1941). A tendency of pernicious anaemia patients to develop gastric malignancy seems well established (Lancet, 1945; Mosbech and Videbaek, 1950). The possible connexion of both these findings with the defective gastric mucosa is obvious.

As noted above, the frequency of pernicious anaemia in Caucasians is in the neighbourhood of 1–2 per 10,000 persons. The disease appears to be more common among Northern Europeans than among the more Southern. Furthermore, there is good reason to believe that it is rarer in Negroes and Mongolians than in Caucasians (Sturgis, 1948).

Here again it seems we may recognize a carrier state, consisting in this instance of achlorhydria with or without subclinical blood changes. However, as noted above, it is by no means established whether all individuals with achlorhydria are either subject to the development of pernicious anaemia, or transmitters of the susceptibility. The carrier state in this disease is thus sufficiently non-specific to be of limited usefulness. Thus, there may be several aetiologies for achlorhydria, in contrast to only one for sicklaemia or thalassaemia. Nevertheless, the present evidence does suggest that individuals with achlorhydria who have relatives with pernicious anaemia have an increased susceptibility to both pernicious anaemia

and subacute combined degeneration, and from the medical standpoint may profitably be followed with those possibilities in mind (Askey, 1940).

Chronic hypochromic anaemia (essential, primary or idiopathic hypochromic anaemia)

As its name would suggest, this is a chronic, hypochromic, microcytic type of anaemia seen predominantly in women in the menstrual age, accompanied either by achlorhydria or hypochlorhydria, and usually responding to iron, although sometimes slowly.

Heredity.—The literature contains many reports of multiple occurrences of the disease within single kindreds (Lundholm, 1938, and Claussen, 1940). However, the disease is sufficiently common to impair the value of these case reports as genetic evidence. Of greater value are the systematic studies of Lundholm (1938). The genetic analysis of his findings is complicated by the fact that 92 per cent of his cases occurred among women. In an investigation of the female siblings of affected persons it was found that, as calculated by Dahlberg's later siblings method, 41 $\pm$ 6·6 per cent of 54 female siblings between the ages of 20 and 50 years showed the same disease. Among 33 male siblings falling in the same age range, on the other hand, only 3·0 $\pm$ 3·0 per cent were affected. Eight out of 25 mothers of his patients were likewise affected. On the basis of these findings Lundholm suggests that the disease is dominantly inherited and sex-limited in its expression. It is postulated that this dominant gene determines a tendency to an inefficient resorption of iron which reveals itself particularly in the presence of large iron losses. The anaemia thus occurs more frequently in females than males simply because of the increased blood loss in the former. Lundholm is inclined to feel that the achlorhydria is in many cases an incidental finding, a point of view challenged by Thiele (1950), who emphasizes that the achlorhydria is another manifestation of the same basic defect which is responsible for the impaired iron utilization. As in pernicious anaemia, then, the gastro-intestinal tract becomes the focus of genetic interest. As noted in the section dealing with pernicious anaemia, chronic hypochromic anaemia and pernicious anaemia have frequently been reported to be associated in the same family. To what extent we must recognize a genetically common element to these two diseases is not clear at the present time.

Polycythaemia vera (erythraemia, Vaquez's disease, Osler's disease)

This condition is characterized by an abnormal elevation of the erythrocyte count in the absence of any recognized physiological basis such as congenital heart disease or residence at high altitudes. It is difficult to establish a minimal erythrocyte level compatible with the diagnosis of erythraemia, but a figure of 6·5 millions per cubic millimetre for men and 5·7 millions per cubic millimetre for women would probably be acceptable to most haematologists. Clinically, there is venous engorgement with cyanosis of the skin and mucous membranes, splenomegaly, and neurological and vascular manifestations. The ultimate physiological basis for the disease is unknown.

Heredity.—In 1907 Nichamin reported on a woman with mild erythraemia, whose mother and a sister had splenomegaly and cyanosis. Bernstein (1914) and

Tancré (1917) provided more satisfactory haematological evidence, the former describing the haematological findings of the disease in a father and son and the latter in 2 sisters. Engelking (1920) described the occurrence of the anomaly in 3 generations, a grandmother, mother and 5 children. Nadler and Cohn (1939), on the other hand, have described a family in which 4 of 9 children of normal parents exhibited the disease. Gänsslen (1940) has summarized the case reports which had appeared until 1940. Taken as a group, these reports suggest the operation of dominant genetic factors in the aetiology of the disease in at least some families, and recessive factors in others.

In addition to these sporadic case reports, there have appeared two more extensive investigations into the role of heredity in this disease, the more interesting because of the wide difference in the findings. Linck (1936, quoted from Gänsslen, 1940), in a study of 7 families, found evidence for dominant inheritance in 6. On the other hand, Brockmann (1937) investigated 294 relatives of 17 affected persons distributed among as many sibships without discovering a single secondary case. The mean number of probably or certainly normal siblings in these families was 4·1. In 2 instances the parents were consanguineous. Brockmann postulates that the disease is due to multiple recessive genes.

Widely divergent opinions as to the ultimate physiological cause of the polycythaemia have been expressed by various authors. On *a priori* grounds it seems quite possible that there are several different types of idiopathic polycythaemia. Each of these types might be under the control of a different genetic mechanism. But while this postulate could account for the fact that some pedigrees appear to exhibit dominant heredity and others recessive, it would scarcely account for the divergence in the findings of Linck and Brockmann.

Significant hypochromia of the erythrocytes has been reported in some cases of polycythaemia vera. In such instances the condition must be differentiated from thalassaemia minor. Thus, the widely quoted family of Spodaro and Forkner (1933) much more probably involved thalassaemia minor than polycythaemia. In this connexion, it should be pointed out that the haematocrit is a more valuable determination in the diagnosis of polycythaemia vera than the erythrocyte count.

There are no satisfactory data regarding the incidence of this disease nor its racial predilections, although Reznikoff, Foot and Bethea (1935) and Dameshek and Henstell (1940) present some evidence that the disease may be more common among individuals of Jewish origin.

Fanconi syndrome

In 1927 Fanconi described a severe, refractory and ultimately fatal hyperchromic anaemia in 3 young brothers whose parents and 2 siblings appeared normal. The peripheral blood findings were in all essential respects comparable to those in pernicious anaemia. The affected children exhibited a striking brown pigmentation of the skin, gonadal hypoplasia, increased tendon reflexes, convergent strabismus, and microcephaly. Subsequent contributions to the literature suggest that skeletal abnormalities are a not infrequent accompaniment of the disease. Autopsy reveals bone marrow hypoplasia.

Since the original description the familial occurrence of a similar haematological picture has been reported by Emile-Weil (1938), Hjorth (1940), Rohr (1949), and

Reinhold, Neumark, Lightwood and Carter (1952). Sporadic cases have been reported by Uehlinger (1929), and Jiminez de Asua and Escardo (1947), and others. The data suggest monogenic recessive inheritance. The report of Dacie and Gilpin (1944) is particularly illuminating in this respect; a female double first cousin of their 2 patients having died of an anaemia which in retrospect was probably the same disease. However, the apparent excess of affected males is of interest, and suggests that the final genetic interpretation be deferred until more data are at hand.

Judged by the infrequency of case reports, the disease is very rare. The number of reports is insufficient to permit conclusions concerning its racial predilections. The author has seen a case in a Japanese child.

Aplastic or hypoplastic anaemia of childhood

This is a profound and usually ultimately fatal normocytic, normochromic anaemia of the early years, usually secondary to the action of some toxin but occasionally idiopathic. Blackfan, Diamond and Leister (1944) distinguish the aplastic from the hypoplastic forms by the greater number of leucocytes and platelets in the latter.

Most of the idiopathic cases have been sporadic, but Estren and Dameshek (1947) have described 2 families, in one of which 3 of 7 siblings, and in the other of which 5 of 14 siblings, exhibited apparently identical disorders characterized by peripheral pancytopenia, pallor, weakness, and a bleeding tendency. The anaemia in these two families—and perhaps in some of the isolated cases in the literature—would appear to be due to a very rare recessive gene.

Non-spherocytic haemolytic anaemia

Crosby (1950) has described a rather extensive kindred in which there occurred a normochromic, normocytic, haemolytic type of anaemia distinguished from hereditary spherocytosis, to which it is most nearly similar, by the absence of spherocytes and failure to respond to splenectomy. Cells of affected individuals showed normal resistance *in vitro* to mechanical, vacuum, and osmotic injury, but on cross transfusion experiments disappeared rapidly from the recipient's circulation. The pedigree findings suggested that the disease was due to a single dominant autosomal gene. The anaemic patient studied in such detail by Mills and his associates (1950) probably represented the same or a very similar blood disorder; the family history, although fragmentary, also suggested dominant heredity. Kaplan and Zuelzer (1950*a* and *b*) have independently described a similar anaemia, present in 3 of 6 siblings. The father of the children was haematologically normal; the mother exhibited a mild normochromic anaemia with no evidences of increased haemolysis. It seems probably that the disease in this family has a different genetic basis from the disease in the families reported by Crosby and by Mills.

Acanthrocytosis

Bassen and Kornzweig (1950); Singer, Fisher and Perlstein (1952) have each described a family in which one or more offspring of a consanguineous marriage exhibited a peculiar malformation of the erythrocytes characterized by protoplasmic

projections of varying sizes and shapes, the cells appearing " crenated ". The cells are quite different from the " sickle cells " referred to earlier. Affected individuals may exhibit an atypical retinitis pigmentosa and evidences of diffuse involvement of the central nervous system. The abnormality would appear to be due to a recessive gene.

Other affections

In addition to the above more or less clearly defined inherited erythrocyte abnormalities, the literature contains reference to quite a number of patients of diverse racial ancestry with abnormal blood findings, usually of a microcytic, hypochromic type, whose disease has been refractory to all known therapy (Cooley, 1941; Stransky and Regala, 1942; Valentine and Neel, 1944; Poppenheimer, Thompson, Parker and Smith, 1945; Rundles and Falls, 1946; Neel, 1951). In many cases no family studies have been carried out; where these are available, in some instances the patient is the only person found to be affected, in other instances there is a similarly affected parent or child. In some instances the picture has been similar to thalassaemia minor, except that the affected individuals are of non-Mediterranean origin. However, thalassaemia major has been reported in a variety of racial stocks, from which it may be inferred that thalassaemia minor is not only present in these same stocks but relatively much more frequent. There is no reason to restrict the diagnosis of thalassaemia minor on racial grounds; neither, on the other hand, need all autosomally inherited microcytic, hypochromic blood pictures have the same genetic basis as thalassaemia minor. Where a refractory microcytic, hypochromic blood picture occurs as an isolated event in a family, the possibility of recessive inheritance must be considered.

ABNORMALITIES OF THE LEUCOCYTES

It seems strange that despite the greater cytological complexity of the leucocytes, with the consequent increased opportunities for detectable variation, thus far relatively little is known concerning inherited abnormalities in these cells. Whether there is in fact a greater genetic stability than is the case for the erythrocyte, or whether the variation exists but has not yet been detected, is not now clear.

Familial neutropenia

A chronic relative and absolute decrease in the numbers of circulating polymorphonuclear neutrophils, occurring apart from any of the recognized diseases in which neutropenia is a secondary finding, has been described by many haematologists. It is not known whether persons exhibiting this trait are to be thought of as constituting the lower tail of a continuous distribution of neutrophil numbers, or as a discrete group set apart from normal individuals. The condition is to be sharply differentiated from the acute idiopathic neutropenia in which the neutrophils suddenly drop to very low levels, often with the development of severe pharyngitis and fatal septicaemia. Few of the investigators who have described this benign neutropenia have carried out family studies. However, Gänsslen (1941) and Manzini and Parvis (1947) have described families in which marked neutropenia was present in three generations, and less extensive observations of a

familial incidence have been presented by Hattersley (1947) and Bousser and Nedey (1948). It would appear that in familial neutropenia the regulating mechanism responsible for maintaining the normal number of circulating neutrophils has simply been set at a lower level which is apparently not incompatible with good health (*cf.* Doan, 1932), although the observations of Roberts and Kracke (1931) suggest that weakness, easy exhaustion, tendency to fatigue and loss of strength and inertia, may be seen more frequently in neutropenic individuals. In the pedigrees so far available a dominant type of inheritance has been apparent. However, inasmuch as diet is known to influence the granulocyte level (Kornberg, Daft, and Sebrell, 1945), care must be exercised in any genetic interpretation.

Familial eosinophilia

Although an increase in the number of circulating polymorphonuclear eosinophils is generally a manifestation of allergy or parasitic infestation, there are occasionally encountered individuals with eosinophilia where no contributing factor is apparent. The clinical difficulties in the way of designating an eosinophilia as idiopathic are obvious. However, it now seems possible that such an entity exists. Moreover, a familial incidence of idiopathic eosinophilia has been reported, some of the more firmly established reports being those of Bastai (1923), Cirio (1926), Armand-Delille, Hurst and Sorapure (1930), dalla Palma (1931), Cattaneo (1931), Stewart (1933), and Bowman (1941). It seems too early to reach conclusions regarding the mode of inheritance of this genetic entity, if such it be. Most of the reports suggest a dominant type of heredity. However, the reviewer gets the impression of a significant excess of affected persons over expectation on the basis of simple dominant heredity, a finding which leads one to question the extent to which unrecognized familial endemics of one kind or another may be responsible for the observations.

Pelger's nuclear anomaly

Normally the nuclei of the polymorphonuclear leucocytes are segmented into 2 to 5 distinct chromatin masses connected by thin chromatin threads, the most frequent number of nuclear subdivisions being 3, with less than 5 per cent of the

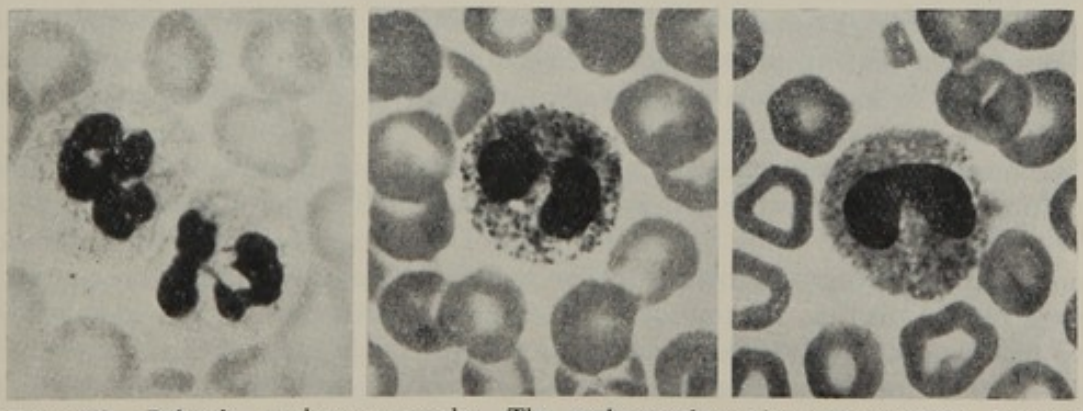


FIG. 278.—Pelger's nuclear anomaly. The polymorphonuclear neutrophilic leucocytes pictured on the left are from a normal individual, while those in the centre and to the right are from a patient with Pelger's anomaly and exhibit reduced nuclear segmentation. (*Material by courtesy of Dr. H. Nachtsheim and Dr. H. Schmidt*).

nuclei showing no segmentation at all. In Pelger's nuclear anomaly, however, the nuclei of the polymorphonuclear cells (eosinophils, basophils, and neutrophils) either remain in the primitive, unsegmented state, appearing as stab cells, or exhibit only 2 or, rarely, 3 subdivisions. Furthermore, the chromatin has a clumped, pyknotic appearance (Fig. 278). The physiological significance of the anomaly is not entirely clear—Leitner and Gugelot (1938) believe that the cells with unsegmented nuclei are less active in phagocytosis, from which it follows that an individual with the condition might be less able to handle bacterial infection.

Heredity.—The condition, first described by Pelger in 1928 in 2 patients with tuberculosis, was originally thought to be related to the patients' disease. However, Huët in 1932 described the anomaly in a niece of one of Pelger's original patients, as well as in 2 other families, and postulated a dominant inheritance. Ten years later Nachtsheim (1942) was able to find in the literature reports of 32 affected families with a total of 210 affected members (102 ♀♀, 86 ♂♂, and 22 sex not stated). The condition appears to depend on a single dominant autosomal gene which is usually fully penetrant, although Undritz (1937) has drawn attention to the fact that an occasional transmitter of the trait may possess a considerable proportion of polymorphs with three-segmented nuclei. Fig. 279 is of a typical

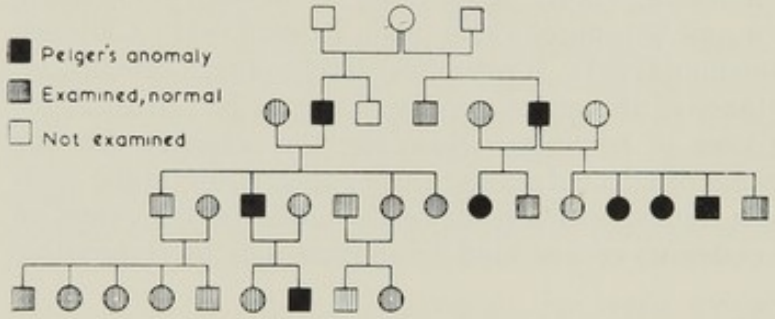


FIG. 279.—The pedigree of Pelger's nuclear anomaly studied by van der Sar (1944), illustrating simple dominant heredity. (*After Amer. J. Clin. Path.*, **14**, 544.)

pedigree. Wegmann (1948) observed that the gene apparently segregated independently of a gene responsible for optic atrophy.

The effects of the gene when homozygous in man are as yet unknown. However, Undritz (1939) and Nachtsheim (review in 1950) have published extensively on what appears to be an identical anomaly in the rabbit. Here it is readily possible to produce homozygous animals; these show globular nuclei in their polymorphonuclear leucocytes and, in addition, marked shortening of the long bones of the extremities with hyperplasia of the diaphyses, shortened ribs with fixation of the thorax, and greatly reduced viability.

The majority of case reports concern Europeans, but there are records of the condition in Mongolians (Peterson, 1935; Kokako, 1936) and Negroes (Sar, 1944). Although there is no basis for an estimate of the frequency of the trait among Mongolians and Negroes, there is reason to believe that the trait is more common among Europeans than the number of case reports would indicate. Survey studies have led Undritz (1939) and Nachtsheim (1950) to place its frequency at about 1 in 1,000 Europeans. The paucity of case reports from the United States of America and Great Britain is noteworthy; apart from one of the above mentioned Mongolian families, the reviewer has been able to find only one other report from these countries (Tileston, 1937).

Pätau and Nachtsheim (1946) have estimated the selective disadvantage of individuals with Pelger's anomaly to be 20 per cent, from which, assuming an incidence of 1 : 1,000, they calculate that the mutation rate necessary to maintain the population in equilibrium is of the order of 1 : 10,000 genes per generation. Nachtsheim (1950) on the basis of later work is inclined to lower the estimate of the selective disadvantage which the trait confers, but even if it is only 10 per cent, a mutation rate of 1 : 20,000 genes per generation is indicated.

Leukaemia

The leukaemias are characterized by a widespread and abnormal proliferation of the leucocytes and their precursors in the tissues of the body. Characteristically, only one of the various specialized types of leucocytes is involved. There is wide variation in the findings in the peripheral blood, some individuals showing striking increases in the numbers of mature-appearing leucocytes of a particular type, others showing an actual decrease in the number of circulating leucocytes of a particular type, with those present being immature and abnormal in appearance. The disease may progress rapidly or slowly, but terminates fatally. The leukaemias are commonly regarded as neoplasms of the haemopoietic tissues.

The evidence concerning the role of genetic factors in the development of leukaemia is of three types, which we will consider in turn.

Reports of families in which two or more members are affected with leukaemia

Videbaek (1947) in a careful search through the literature was able to find 26 well documented instances in which 2 or more near relatives developed leukaemia, to which he was able to add 13 cases of his own. In 5 of these cases there were 3 or more affected individuals. Later, Ward, Galinsky and Newton (1952) were able to find 11 references to 3 cases in one kindred, and 6 reports of 4 or more leukaemics in the same family group. Anderson (1951) has described an especially striking sibship in which 5 out of 8 siblings died of leukaemia. Inasmuch as in the Western World the leukaemia death rate is approximately 3 per 100,000 living population, or 3 per 1,000 total deaths, then, given the occurrence of a single case of leukaemia in a kindred of 20, a history of additional cases among, for example, 10 deceased relatives might be expected, even in the absence of genetic factors, in approximately $1-(997/1{,}000)^{10}$, or 3 per 100 families. Third and fourth cases within a family group should be rare on the basis of chance alone, but yet scarcely so uncommon that such reports should automatically be regarded as evidence for the significance of genetic factors. It may be concluded that little of genetic significance can be inferred from the case reports in the medical literature concerning familial leukaemia.

A comparison of the frequency of leukaemia in the relatives of probands with leukaemia and in suitable controls.

The most extensive study of this type has been carried out by Videbaek (1947), who compared the frequency of occurrence of verified leukaemia in 4,041 relatives of 209 probands with leukaemia with the occurrence of this disease in 3,641 relatives of 200 controls of similar sex and age. The categories of relatives studied were parents, grandparents, uncles and aunts, siblings, and children. In 17 of

the families with a leukaemic proband, one or more verified secondary cases were encountered, whereas in only one of the control families was there a secondary case. Although Videbaek's data are not presented in such a fashion that the question can be exactly analysed, one gets the impression of somewhat less leukaemia among his controls than might be expected. Among the 4,041 relatives of the 209 leukaemic patients, the diagnosis of cancer had been made in 319, while among the 3,641 relatives of the control probands there were 218 diagnoses of cancer, the difference being significant and present in all categories of relatives. Videbaek postulates that the development of leukaemia in any individual depends on a variety of factors, including a non-specific hereditary predisposition to cancer, which is believed to be present in at least 20 per cent of the population, and the presence of one or several genes, the activity of which plays a role in the localization of cancer to the " leukon ". As has been pointed out elsewhere (*see* Chapter 29), the concept of a generalized cancer diathesis is quite debatable.

The occurrence of leukaemia in twins

Gorer (1938) was able to find in the literature three reports of leukaemia affecting both members of a pair of twins. In all three cases the twins were thought to be identical. More recently, Stobbe and Taeschner (1952) have reported another twin pair with both members affected. Again the twins were probably identical. In all eight cases the leukaemia was lymphatic in type. In view of the greater frequency of fraternal than identical twins in the population at large, there is undoubtedly some genetic significance in the fact that all four of these twin pairs were of the identical type, but the sample is too small and biased for any exact conclusions.

Leukaemia is thus not distributed at random in human populations but shows a slight tendency to appear in relatives. This non-random distribution probably has genetic significance. There is no apparent tendency towards a familial similarity as to the type of leukaemia. Attempts to suggest a precise genetic mechanism would seem to be premature.

Alder's anomaly

Alder in 1938 described in two siblings an anomaly of leucocytic granulation characterized by the following morphological peculiarities: neutrophils; coarse, dark, " shimmering ", reddish granulation; eosinophils; granulation bluish green, somewhat similar to that of the more immature promyelocytes; basophils, very similar to eosinophils; monocytes and lymphocytes; coarse, azurophilic granulation. Skeletal x-rays and biopsy of various bones revealed in these two patients a disturbance of endochondral ossification. Only a handful of cases have been recognized (Alder, 1938; Jordan, 1947; Lambin, 1949; Dawe, unpublished; Valentine, unpublished; Cintron-Rivera, unpublished; review in Alder, 1950). In Alder's cases the parents were normal, but several subsequent investigators have observed parent-child combinations suggestive of dominant inheritance.

Miscellaneous leucocyte abnormalities

Steinbrinck (1948) has described, on the basis of a single case, an anomaly of

leucocyte granulation characterized primarily by irregular and unusually coarse granulation. Reilly in 1941 first drew attention to the fact that in some children with gargoylism from 60 to 90 per cent of the polymorphonuclear leucocytes exhibit an atypical granulation, usually consisting of large, lilac-stained granules. Finally, Bagh and Hortling (1948) have reported an abnormal vacuolization of the lymphocytes in patients with juvenile amaurotic idiocy, an observation which Rayner (1952) has recently extended to the heterozygous parents and siblings of persons with the disease.

ABNORMALITIES OF THE PLATELETS

There are two haemorrhagic disorders in which the platelets play a primary role and in which there is evidence for the aetiological role of genetic factors.

Essential thrombocytopenic purpura (primary or idiopathic purpura; benign essential thrombopenia; Werlhof's disease; thrombocytolytic purpura)

This is a haemorrhagic disease characterized clinically by petechiae and ecchymoses in the skin, and haemorrhage from mucous membranes and into various tissues. The chief laboratory findings are a marked reduction in the number of blood platelets, poor clot retraction, a positive tourniquet test, prolonged bleeding time, but normal coagulation time. Thrombocytopenic purpura may be produced by exposure to various toxic chemicals, and may be associated with such haematological disorders as acute leukaemia or aplastic anaemia, and such causes must be ruled out before a case is considered essential. The essential type may be acute or chronic, and in the chronic form there may be remissions during which the platelet count is not significantly below normal. This contributes to difficulty in studying the heredity of the disease.

Although the majority of cases appear as isolated events, heredity is definitely implicated in some families. Hess in 1916 seems to have been the first to draw attention to genetic factors in this disease, reporting two cases with probably chronic thrombocytopenic purpura, each of whom had several siblings and a parent with a history of excessive bleeding, although platelet counts were not performed on any one except the two original patients. Subsequently, there has appeared a number of well documented reports of thrombocytopenia in two generations (Witts, 1932; Dilthey, 1936; Sanford and his associates, 1936; Davidson, 1937). Krömeke's (1922) three-generation pedigree may fall into this same category, although some of the bleeders in the family he studied had normal platelet numbers, and this family is often quoted as indicating an aetiological relationship between thrombocytopenic purpura and hereditary capillary fragility. Wintrobe, Hanrahan and Thomas (1937) have published what may be a four-generation pedigree. A dominant type of heredity is indicated. However, the recent demonstration of a circulating " thrombocytopenic factor " in patients with essential thrombocytopenic purpura (Harrington and his colleagues, 1951; Sprague and his colleagues, 1952) suggests that the mother–newborn child combinations reported by Sanford and his colleagues (1936) and Davidson (1937) may not actually have genetic significance at all, being a consequence of the placental transfer of the " thrombocytopenic factor".

Thrombocytopathic purpura (Glanzmann's thrombasthenia)

Glanzmann (1918) has described a familial haemorrhagic diathesis which is characterized by a positive tourniquet test, a prolonged bleeding time, a normal coagulation time, and poor clot retraction, but differs in that the platelets are usually normal or near normal in number but have an abnormal appearance. It is surprising, in view of the number of families in Glanzmann's original report, 9, that so few subsequent investigators of haemorrhagic diatheses have reported similar findings. I have been able to find in the literature only two other apparently acceptable reports of the familial occurrence of the condition (Zande, 1923; Conitzer, 1937), although there are a number of instances of isolated occurrences of what may be this same entity (Rothman and Nixon, 1929; Fonio, 1930 Kugelmass, 1932). Where heredity is a factor it has appeared to be dominant.

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CHAPTER 24

II—THE HAEMORRHAGIC DIATHESES

A. D. M. JACKSON

HAEMOPHILIA

Clinical features

THE CHARACTERISTIC symptom of haemophilia—excessive and prolonged haemorrhage either following some trivial injury or arising spontaneously—may occur in any part of the body, but the subcutaneous tissues, muscles, joints, mouth and nose are the common sites. Haemarthrosis occurs in almost every case over the age of 12 years but is less common in younger patients. Bleeding from internal organs or following surgical procedures such as dental extractions and circumcision is frequently fatal. The symptoms first appear during the first year of life and the mortality rate is high. In Birch's (1937) series 57 per cent died during the first five years of life and only 25 per cent survived beyond the age of 20 years, although Andreassen (1943) in Denmark found a higher proportion reaching adult life.

Examination of the blood usually shows a prolonged clotting time, a diminished consumption of prothrombin during coagulation and an inability of the plasma to correct the prolonged clotting time of the plasma from a known haemophiliac. The latter test will establish the diagnosis in the occasional mild case with a normal clotting time. In all other respects the blood is normal.

Varieties

The inherited defect of coagulation is due to a deficiency of thromboplastinogen (antihaemophilic globulin) which is present in normal plasma and is essential for the formation of thromboplastin. It now appears that there is at least one variant of haemophilia as far as the nature of the coagulation defect is concerned. Several cases have recently been described which have all the genetic and clinical features of haemophilia together with a prolonged clotting time and deficient consumption of prothrombin. The blood in these cases does contain anti-haemophilic globulin but is deficient in some other factor (also essential for the formation of thromboplastin) which is present both in normal plasma and in the plasma of true haemophiliacs. This disease which is obviously transmitted by a different gene must be differentiated from haemophilia and has been called " Christmas disease " by Biggs and her colleagues (1952), who first described the condition, after their first patient.

The unusually mild form of haemophilia observed in certain families differs in no way from the common and severe type as far as aetiology is concerned although it is probably transmitted through a different gene.

Heredity

Haemophilia is a classical example of sex-linked inheritance and is transmitted by a recessive gene located in the X-chromosome, so that females will have the disease only if they carry the abnormal gene on both their X-chromosomes.

A condition similar to haemophilia occurs in dogs, and homozygous bitches have been bred by mating haemophilic dogs with carrier bitches, but until very recently no undoubted cases of haemophilia in the human female had been recorded; in fact it was generally believed that the presence of two abnormal genes was lethal and that the homozygous female was only a theoretical possibility. However, three completely proven cases of haemophilia in the female are now on record. Part of the pedigree showing the family history of two of these cases is reproduced in Fig. 280.

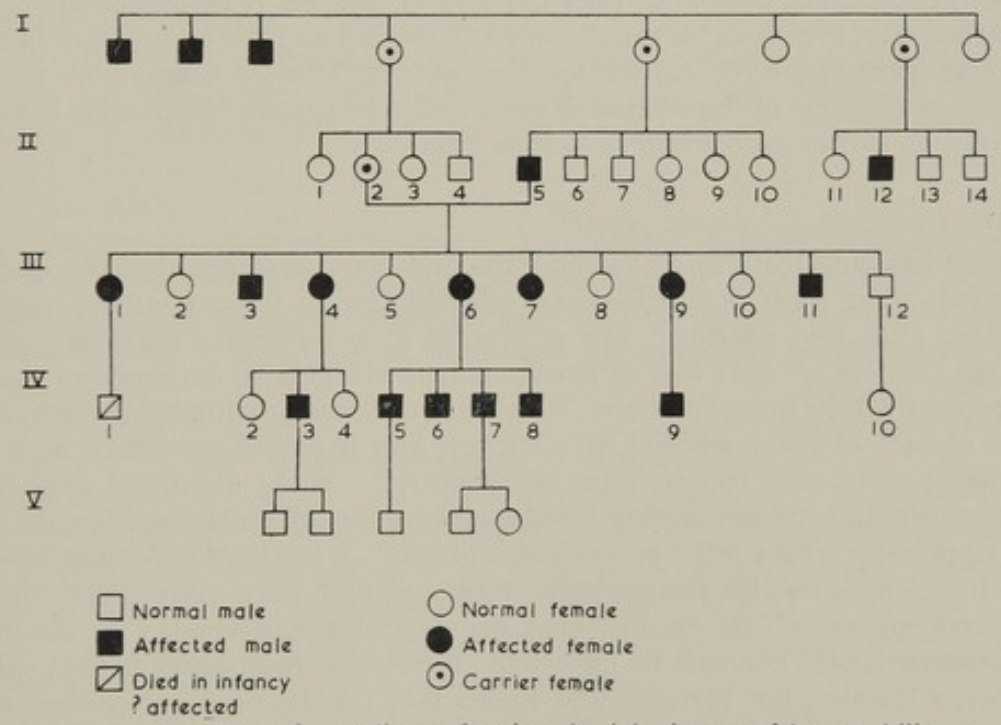

FIG. 280.—Part of a pedigree showing the inheritance of haemophilia. (*After Merskey, C. (1951). Quart. J. Med., N.S.*, **20**, 299.)

This pedigree shows how the marriage of first cousins, II, 2 (a carrier female) and II, 5 (an affected male), resulted in twelve children. Of the three sons two were affected (III, 3 and III, 11) and of the nine daughters five (III, 1, III, 4, III, 6, III, 7 and III, 9) had symptoms, including haemarthrosis, suggesting haemophilia. Both III, 4 and III, 9 have been examined and investigated by Merskey (1951) with results that prove beyond doubt that they are both homozygous haemophiliacs. The four apparently normal daughters (III, 2, III, 5, III, 8 and III, 10) are almost certain to be carriers but none have so far had children.

The pedigree also shows that affected females (III, 1, III, 4, III, 6 and III, 9) may marry and bear children. All the daughters of such marriages should be carriers and all the sons haemophilic. In this particular family all the sons (IV, 3, IV, 5, IV, 6, IV, 7, IV, 8 and IV, 9) of affected women were, in fact, haemophiliacs. IV, 1 was probably also a haemophiliac but died at an early age before the diagnosis could be established. The genotype of the daughters IV, 2, IV, 4 and IV, 10 is so far unknown.

Incidence and mutations

Andreassen (1943) carried out an extensive survey of all the cases of haemophilia in Denmark and found the incidence of the disease in that country to be approximately 1 in 8,000.

One-third of the genes for haemophilia are in the X-chromosomes of affected males, and since the disease carries a high mortality many of these genes are likely to die out. As the incidence of the disease does not change, the rate of appearance of mutations must therefore be high. Andreassen, finding the fertility of affected males compared with their normal brothers to be just over 0·5, estimated the mutation rate to be about 1 in 50,000 X-chromosomes.

The various studies of haemophilic families show that the number of cases without previous family history (so-called sporadic cases) is, in fact, high (about 30 per cent). This, of course, does not give an entirely reliable indication of the mutation rate; first, because families are often small and there may have been two or three generations of carrier females without affected sons; and secondly, because mild forms of the disease or the severe type causing death early in infancy may not have been recognized as haemophilia.

Genetic prognosis: the carrier female

The distressing features of haemophilia and the knowledge that the disease is inherited often lead members of an affected family to seek advice regarding marriage and child bearing. The mother of a haemophiliac must be a carrier, and the chances are that half of her daughters will also be carriers and that half of her sons will be haemophiliacs. The sister of a haemophiliac, however, has an equal chance of being normal or a carrier, and it would obviously be a great advantage to be able to determine her genotype. If the abnormal gene on the X-chromosome were completely recessive, detection of the carrier female would only be possible from studies of rare gene linkages. It has been suggested, however, that the gene may be incompletely recessive and may show itself by mild haemorrhagic symptoms or by some demonstrable abnormality in the blood. Andreassen (1943) claimed to have demonstrated a prolonged clotting time in 30 carrier females, but Merskey and Macfarlane (1951) could not confirm this in a detailed study of 21 known carriers. They obtained occasional abnormal results with laboratory tests and found that, compared with normal controls, there was a greater tendency to excessive bleeding after dental extraction in the carrier group as a whole. Although Merskey and Macfarlane concluded that their results were " too indefinite and inconsistent to be of diagnostic value ", it would be reasonable to suspect the carrier state in a woman who gives a history of abnormal bleeding and whose blood shows a slightly prolonged clotting time and slightly decreased prothrombin consumption. Negative results have also been obtained from similar investigations on heterozygous carriers of canine haemophilia.

Further hope for the detection of carriers has been raised by the work of Graham, McLendon and Brinkhous (1953), who carried out quantitative estimations of antihaemophilic globulin on a family of mild haemophiliacs. Some of the carriers in this family were found to have abnormally low levels of antihaemophilic globulin although the same abnormality could not be

demonstrated in carriers of severe haemophilia. The authors suggest, therefore, that this is an example of a gene which is not completely recessive and which is an allelomorphic variant of the gene responsible for classical haemophilia.

OTHER INHERITED HAEMORRHAGIC DISEASES

Hereditary telangiectasis is discussed elsewhere (p. 228), whilst two haemorrhagic disturbances due to abnormalities of platelets—essential thrombocytopenic purpura and thrombocytopathic purpura—have been discussed on p. 473. In addition there are two other well defined haemorrhagic diseases.

Deficiency of plasma labile factor (" *parahaemophilia* ")

Labile factor is present in normal plasma and is essential for the conversion of prothrombin to thrombin. A deficiency of this substance results in a haemorrhagic syndrome in which a prolonged prothrombin time is the abnormal finding. This syndrome has been called " parahaemophilia " and it may be due to either a recessive gene or a dominant gene with poor penetration.

Afibrinogenaemia

An extremely rare cause of severe haemorrhagic symptoms is absence of fibrinogen. The abnormal gene for this condition is an autosomal recessive, but in some of the heterozygotes it may express itself by a milder type of disease with only a relative deficiency of fibrinogen (fibrinopenia) instead of complete absence.

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CHAPTER 24

III—SEROLOGY

F. STRATTON

GENERAL CONSIDERATIONS

The blood groups

IT HAS been known for many years that there are serological species differences between animals and man. If the blood of man and animals is mixed together there is erythrocyte agglutination, and if their sera are mixed there is interaction and sometimes precipitation. It is not suprising, therefore, that attempts to transfuse the blood of animals into man have failed. Blood transfusion from one individual to another was attempted, and in about 50 per cent of cases was found to be a failure, a fact which was not explained until the year 1900 when Landsteiner discovered the blood groups.

The basic importance of the discovery of these groups was that they represented an intra-species difference, a difference between one human being and another. These first groups were the ABO groups determined by mixing the serum of certain individuals with the erythrocytes of others, persons being divided into types AB, A, B and O according to whether their cells were agglutinated by another individual's serum or not. The letters A and B denote antigens or agglutinogens which may, or may not, be present on the red cells. In type AB both A and B antigens are present, but in group O neither A nor B are present.

In general, a series of independent blood groups are now known, and each particular blood group has its own particular blood group antigen or antigens on the erythrocyte. For example, in the P blood group, P positive means that one has the P antigen on the erythrocytes; if P negative it is not present. Blood grouping, therefore, is the detection, differentiation and classification of antigens on the red blood cells. These antigens are detected by using suitable antisera which may be naturally occurring, as in the case of anti-A and anti-B, or they may be immune in origin, either being made in animals or in man.

The erythrocyte antigens behave like other known antigens in that they produce antibodies when injected into animals; but many antigens, however, produce their antibody only in man, that is to say, they are antigenic in man alone. The antigen-antibody reaction occurs between the erythrocyte containing that antigen and the appropriate antiserum. The reaction produces a specific observable or detectable result, often erythrocyte agglutination. Thus, if unknown antisera are found new blood group antigens may be discovered.

It was in 1927 that the M N P groups were described as the result of testing human cells with antibodies obtained by the injection of human red cells into rabbits. This is the second stage in blood group discovery. In the first stage, the early ABO blood groups were differentiated by using naturally and regularly

occurring human antibodies. Now, in the second stage, they were found by using immune animal antibodies. The third manner of detection is by the use of rare naturally occurring human antibodies not usually of an immune nature, for example, anti-P. The fourth manner of investigation, namely the injection of animal cells into animals and testing the resulting antiserum against human erythrocytes, led to the discovery in 1940 of the Rh group. This antiserum was prepared by injecting monkey cells into animals and testing human red cells with the antiserum produced.

Since then progress in the study of blood groups has advanced rapidly for several reasons. First, the further knowledge of the association between the Rh group and haemolytic disease of the newborn, and the consequent establishment of an antenatal testing service resulted in the examination of many thousands of blood samples. Secondly, the increasing use of blood transfusions often given repeatedly to the same recipient, coupled with a study of occasional reactions resulting therefrom, caused new antisera to be detected. Thirdly, advances in technique resulted in methods of detecting antigen-antibody reactions which did not necessarily result in erythrocyte agglutination; thus, numbers of specimens of

TABLE I

THE DISCOVERY OF THE BLOOD GROUPS

Year	Blood group	Discoverers
1900	ABO	Landsteiner
1911	A_1A_2 subgroups of A	von Dungern and Hirzfield
1927	M and N	Landsteiner and Levine
1927	P	Landsteiner and Levine
1930	ABO substances in saliva	Lehrs and Putkonen
1940/5	Rh blood groups and subdivisions	Landsteiner, Wiener, Race and others
1945	Lutheran	Callender and Race
1946	Kell	Coombs, Mourant and Race
1946	Lewis	Mourant
1947	S subdivision of MN	Walsh and Montgomery
1950	Duffy	Cutbush, Mollison and Parkin

different persons' sera were available for testing for antibodies, and immunization produced in the human by blood transfusions or pregnancy was more readily detectable using the newer techniques: in fact the newer blood groups, such as Kell and Duffy, have been detected by the use of antisera obtainable only from man. It follows from this that many of the newer blood groups are of importance in clinical medicine.

Their hereditary character

Soon after the discovery of the first blood groups it was found that they were inherited. The presence of the antigen on the red cells is determined by the corresponding gene or genes. The study of blood group inheritance involves, in the first case, the determination of the frequencies of the various groups in the population, and quite often these frequencies vary in different populations. From these phenotype frequencies it is possible to determine the gene frequencies by several different methods.

Family studies are next made, and the persons typed for the particular group under investigation. The family studies are now analysed and the observed frequencies of each type of mating and children in that mating are compared with those expected. Those expected are calculated from the gene frequencies previously obtained. It is often possible by inspection to suggest the manner of inheritance but it will be necessary, in order to establish proof, to analyse a large amount of family material. For example, in the Lewis group when the mating Le(a−) × Le(a−) was found to give Le(a+) children, it was considered that this group might be inherited as a recessive character, but further analysis was needed to prove this. Sometimes, crucial mother-child combinations are studied because they are of special value in proving the suggested theory of inheritance. It will be against the theory of inheritance of the ABO groups if group O mothers have group AB children, hence this combination has been fully examined by many workers. Exceptions to the inheritance theory, not due to illegitimacy, are also collected and the reason for the exception sought. This is a general, but by no means exhaustive, outline of some of the methods used.

Gene frequencies are, in general, more useful than phenotype frequencies. In ethnological studies the former are most valuable. Not all genotypes in a particular group are distinguishable one from another serologically, only a percentage, depending on the number of antisera available, but with the discovery of more antisera more genotypes will become serologically separable. Genotypes of particular persons can sometimes be inferred from family studies even though they are not determinable serologically.

In blood groups that have been known for many years, many family studies are on record, but work on the newer and rarer groups has been restricted owing to the shortage of antisera, especially as these are mainly of human origin.

The blood groups are, in many ways, ideal characters from the point of view of inheritance studies. They are, in the first place, normal physiological characters and as such are a feature of the whole population. They are, so far as is known, unaffected by environment or genes outside the particular blood group constellation. Although in many cases technically difficult to detect, they are nevertheless, from a genetical point of view, clear cut characters readily charted and scored.

Secondly, their manner of inheritance is largely simple; that is to say, there is no evidence of multifactorial inheritance, the determinant genes are associated with a particular pair of chromosomes.

It will be seen, therefore, that they are of great value in the study of human genetics, their wide distribution and complete penetrance making them always applicable, unlike other rare traits. It must be remembered, however, that blood group examinations require the presence of the individual, and therefore studies are restricted to three or four generations. Furthermore, in human pedigrees the question of illegitimacy is a difficulty which always has to be borne in mind.

Notation

Blood group notation has in the past been confused; for example, the numberings of the Moss and Jansky systems for the ABO groups, the letters ABO eventually being suggested by the League of Nations. It is now customary to use the letters of the alphabet. Latterly, the name of the person in whose serum the

abnormal antibody was found has been used. A body of workers, interested in Lewis and Lutheran groups, decided to use a common notation and this kind of notation has been followed in more recent groups.

THE INDIVIDUAL BLOOD GROUP SYSTEMS

ABO groups

Clinical

Discovered by Landsteiner in 1900, it was subsequently shown that there are four groups or phenotypes. These correspond with the presence or absence of antigens A and B on the red cells. The ABO groups are different from others in that naturally and regularly occurring anti-A and anti-B antibodies are present in the individual's serum according to Landsteiner's rule that those agglutinins, and only those, are present in the serum for which there is no agglutinogen in the red cell (Table II).

TABLE II

ABO GROUPS. N.W. ENGLAND

Blood group	Antigen on red cell	Antibody in serum	Approximate frequency (percentage)
AB	A + B	—	3·0
A	A	anti-B	40·0
B	B	anti-A	8·5
O	—	anti-A and anti-B	48·5

Dungern and Hırzfeld described subgroups of group A affecting groups AB and A that is A_1B, A_2B, A_1 and A_2. This results in six phenotypes distinguishable serologically using anti-A, anti-A_1 and anti-B antisera (Table III).

TABLE III

ABO SUBGROUPS. N.W. ENGLAND

Genotypes	Phenotypes	Approximate frequency (percentage)
A_1A_1, A_1A_2, A_1O	A_1	30·5
A_2A_2, A_2O	A_2	10·5
BB, BO	B	8·5
A_1B	A_1B	2·5
A_2B	A_2B	0·55
O	O	47·45

Various theories have been put forward concerning the inheritance of the ABO groups but Bernstein in 1924 determined the exact nature of this and proposed a system of three allelic genes A, B and O (R of Bernstein) at a single locus on a pair of chromosomes. The theory was extended by Thomsen, Friedenreich and Worsaae to four allelic genes, A_1, A_2, B and O to explain the subgroups of group A.

In 1948, Boorman, Dodd and Gilbey described an anti-O antibody which is believed to react with the product of the O gene. This antibody also reacts with A_2 agglutinogens. The use of this serum should, theoretically, distinguish genotypes BB from BO, and A_1A_1 from A_1O, but not A_1A_2 from A_1O, nor A_2A_2 from A_2O.

Frequency

The frequencies of the ABO groups have been ascertained for large numbers of the English population (Dobson and Ikin). In Table IV are set out the frequencies of a number of persons grouped in Manchester, and in Table III subgroups of group A are shown. It will be seen that roughly 3 out of 4 group A persons are A_1, and 1 in 6 group AB persons are A_2B.

TABLE IV

FREQUENCY OF ABO GROUPS. N.W. ENGLAND

	Group				Total
	AB	A	B	O	
Number	275	3,775	788	4,532	9,370
Percentage	2·93	40·29	8·41	48·37	

Gene frequencies for N.W. England calculated by the corrected method of Bernstein (1930) are: O, 0·6952; A, 0·2464; and B, 0·0584.

The gene frequencies can be used to test the goodness of fit between calculated and observed phenotype frequencies, and an example of the use of this in the case of the ABO groups is given elsewhere in this chapter.

TABLE V

MATINGS IN ABO GROUPS

Matings	Possible groups of children					
O × O	O					
O × A_1	O	A_1	A_2			
O × A_2	O		A_2			
O × B	O			B		
O × A_1B		A_1		B		
O × A_2B			A_2	B		
A_1 × A_1	O	A_1	A_2			
A_1 × A_2	O	A_1	A_2			
A_1 × B	O	A_1	A_2	B	A_1B	A_2B
A_1 × A_1B		A_1		B	A_1B	A_2B
A_1 × A_2B		A_1	A_2	B	A_1B	A_2B
A_2 × A_2	O		A_2			
A_2 × B	O		A_2	B		A_2B
A_2 × A_1B		A_1		B		A_2B
A_2 × A_2B			A_2	B		A_2B
B × B	O			B		
B × A_1B		A_1		B	A_1B	
B × A_2B			A_2	B		A_2B
A_1B × A_1B		A_1		B	A_1B	
A_1B × A_2B		A_1		B	A_1B	A_2B
A_2B × A_2B			A_2	B		A_2B

Heredity

Work on the inheritance of the ABO groups has been collated by Wiener. The triple allelomorph theory of Bernstein and the extension of it are thoroughly confirmed. It is useful to note that the agglutinogens A and B cannot appear in the blood of a child unless present in the blood of one or both parents. Secondly, the combinations, group AB parent, group O child. and conversely group O parent and group AB child, are impossible. Andresen examining 800 group AB mothers finds no group O children, and in 8,000 group O mothers finds no group AB children.

Exceptions to the Bernstein theory have been described but many were due to technical difficulties. The only authentic exception is Haselhost and Lauers' case where a group AB mother had a group O child. The child, however, suffered from congenital abnormalities and the abnormality may be due to chromosome deletion. Possible matings in the A_1, A_2 B and O groups are shown in Table V.

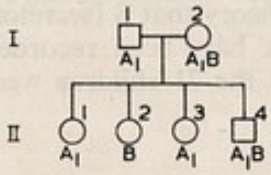


FIG. 281.

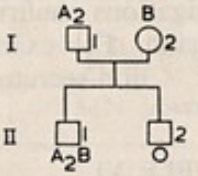
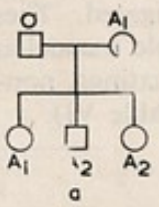


FIG. 282.



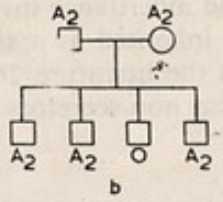


FIG. 283.

FIGS. 281–283.—The inheritance of the ABO groups.

A small series of pedigrees, Figs. 281–283, shows the principles of the inheritance of the ABO groups. In other figures the ABO groups are given or are shown separately and also illustrate the inheritance.

In Fig. 281, I 1 must be A_1O since sib II 2 is B. If he were A_1A_1 or A_1A_2 the sib II 2 would have been A_1B or A_2B. When this family was typed anti-O was not known, but nevertheless, by inspection of this family it is possible to determine what some of the genotypes are. II 3, however, could be A_1A_1 or A_1O. No children in this family could be O.

In Fig. 282, I 1 must be heterozygous A_2O but it would not have been possible to determine this with anti-O since it also reacts with A_2 agglutinogen. Here, only the pedigree will give the genotype.

Fig. 283 shows other pedigrees which are self explanatory. It will be noted in Figs. 282 and 283 that the subgroups of A are shown. For example, in the mating $A_2 \times A_2$ all group A children are A_2. In Fig. 283*a* the female parent must be of type A_1A_2, the exact genotype not being serologically detectable, but only known when the family groups are studied.

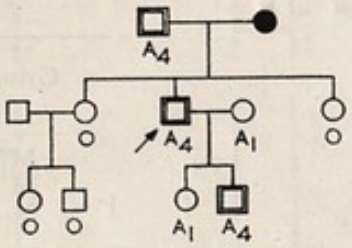


FIG. 284.—The inheritance of the A_4 sub-group of group A. (*After Mr. I. Dunsford.*)

A_3 and A_4 are rare varieties of group A. A pedigree illustrating the inheritance of A_4 is shown in Fig. 284 (Dunsford). A_3 is a fifth allele at the ABO locus. A_4 is very rare with an estimated frequency of 1 : 70,000 (Dunsford).

A and B secretors

Clinical

It has been known for many years that some persons secrete A or B substances in the saliva and other tissue fluids. The A or B substances when they are excreted are group specific and will, in small quantity, inhibit the action of anti-A and anti-B agglutinins. The saliva may be boiled without destroying the activity of the group specific substance and, for example, a small quantity of group A substance in saliva will prevent anti-A antibody agglutinating group A or AB red cells. The group specific substances are mucopolysaccharides.

Heredity

Schiff and Sasaki were the first to demonstrate that this ability to secrete is inherited as a mendelian dominant character. Grubb and Morgan have tested 212 persons and found 163 secretors among them. Several family studies have been made (Wiener), and the inheritance investigated. These investigations confirmed the theory that S (secretor) is inherited as a simple mendelian dominant. For example, there have been recorded in the literature 26 matings, non-secretor × non-secretor, and all the 71 children were also non-secretors (Table VI).

TABLE VI

SECRETOR TYPES

Type	Genotype	Frequency (percentage)
Secretor	{Ss SS}	77
Non-secretor	ss	23

The ability to secrete is well established at birth. Persons who are group A_2 secretors possess the same quantity of A substance, and one which is also similar in its reactivity to that secreted by a person of group A_1. The relationship between the ability to secrete and the Lewis blood group will be discussed later. The ability to secrete is inherited independently of the ABO groups.

MNS groups

The MN groups were first described by Landsteiner and Levine in 1926. There are three types and the serological groups represent the genotypes and the red cell antigens (Table VII).

TABLE VII

MN GROUPS

Groups	Genotypes	Approximate frequency (percentage)
MN	MN	49
M	MM	30
N	NN	21

The suggested theory of inheritance put forward by the discoverers was by two allelic genes M and N. This theory has been amply confirmed. Wiener gives a comprehensive review of the studies undertaken and shows that in an analysis of collected families the

results fit the theory. Exceptions to the theory in the MN groups are commoner than in ABO grouping but this is undoubtedly due to unsatisfactory technique. Especially is this the case where persons are reported as belonging to the supposed type M–N–. Wiener concludes that " not a single proven exception to the theory of Landsteiner and Levine has been encountered to date in studies on a total of more than 15,000 children ".

Andresen in 20,000 mother-child examinations for the MN groups has never seen an exception to the rule of inheritance, and with the cases collected from the literature he states that in " none of these 35,000 cases was there demonstrated any exception to the genetic rules that were to be expected ". Hence, we see that:

(*i*) Agglutinogen M (or N) cannot be present in the blood of a child unless present in the blood of one or both parents.

(*ii*) A group M parent cannot have a group N child, and a group N parent cannot have a group M child. This is because the serological group M or N implies the genotype MM or NN.

Possible matings are shown in Table VIII.

TABLE VIII

MN MATINGS

Matings	Children		
MN × MN	M	N	MN
M × MN	M		MN
N × MN		N	MN
M × M	M		
N × N		N	
M × N			MN

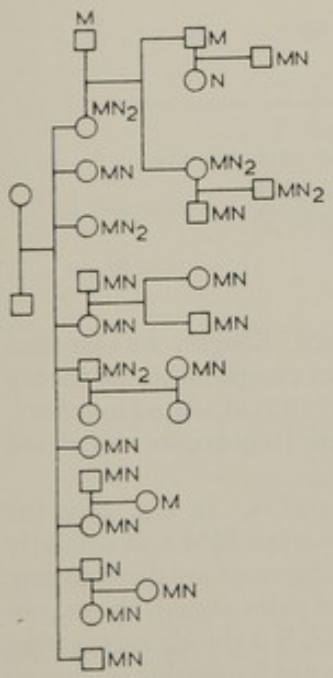


FIG. 285.—The inheritance of the weak N_2 subgroup of N. (*After Andresen.*)

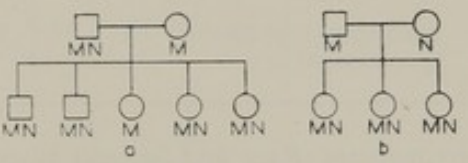


FIG. 286.—The inheritance of the MN groups.

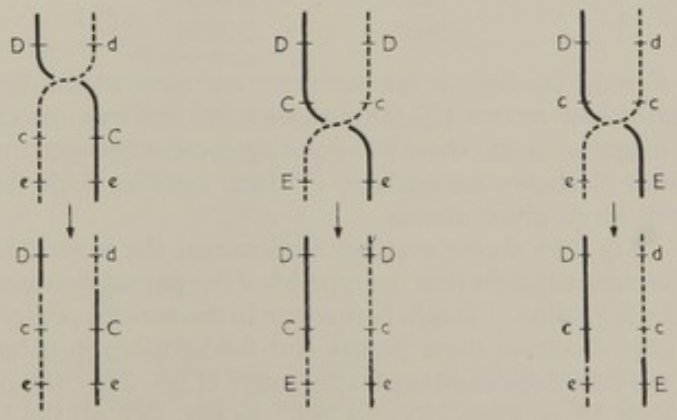


FIG. 287.—Rh Chromosomes—showing crossing-over to produce the rarer types. (*After Race and Sanger.*)

Subgroups

Weak reactors.—N_2 is a weak N antigen and is of rare occurrence. It probably represents a third allele at the MN locus. Andresen states that between 1936–1947, in 80,000 blood groupings, N_2 was encountered eight times. This group is always alluded to in paternity work but it is not such a difficulty as to cast any doubt on the value of MN tests in disputed parentage. MN groupings are, in any case, technically difficult, and if they are accurately and carefully carried out, using many different antisera, it is unlikely that the infrequent N_2 will be missed. Fig. 285 shows one of Andresen's pedigrees. A weak form of M has been described but this very rarely occurs.

The S subgroups.—In 1947, Walsh and Montgomery described an antiserum which, in addition to an Rh antibody, contained another new one. Sanger and Race then showed that this antibody subdivided the MN groups. The new antigen was called S and its presumed allelomorph s. There are two genetical possibilities (Sanger and Race), either, first, that these are alleles Ms, MS, Ns and NS, the mutation S being a change of either M or N genes, or secondly, that S is a separate linked gene. The latter theory is most acceptable and now that an antibody corresponding to anti-s has been found (Levine) it will become easier to prove with certainty.

Table IX, based on the theory of Sanger and Race, shows the various phenotypes and their frequencies, and the suggested genotypes.

TABLE IX

MNS Groups (Modified after Race and Sanger)

MN type	M		N		MN	
MNS genotypes	MSMS MSMs	MsMs	NSNS NSNs	NsNs	MSNS MSNs MsNS	MsNs
MNS phenotypes	MS	Ms	NS	Ns	MNS	MNs
Frequency (percentage)	19	7	8	16	30	20

Gene frequencies (Race and Sanger) based on 1,419 collected samples are:

MS	0·2471	S	0·3274
Ms	0·2831	s	0·6726
NS	0·0802		
Ns	0·3894		

Family studies, a few at first, are now mounting up. Race, Sanger, Lawler and Bertinshaw record 123 families with 293 children; no child was an exception to the theory of inheritance and there was good agreement between the observed and calculated numbers. Table X shows an analysis of these families with the genotype frequencies calculated from those given above.

Fig. 286 shows matings to illustrate the inheritance of M and N. In Fig. 286*a* the mating suggests that the type M of the parent represents the genotype MM and similarly in Fig. 286*b*. The MN matings in the various pedigrees, if S subgroups are disregarded, also illustrate these points and furthermore illustrate the two rules stated above. In the pedigrees showing S subgroups (Figs. 295–300), in two cases S is shown segregating with M, in Figs. 295 and 299. In Fig. 299, all the N children are S negative (s) but all the MN children are S positive (S). In Fig. 297, the M genes in the children are all maternal but the S type shows that the s.sibs have inherited a different M gene from the

S ones. In some instances, for example, Figs. 296 and 298, the S typing is of no value but these pedigrees do show that s × s matings have all s.sibs.

TABLE X

THE S GROUPS OF 123 FAMILIES WITH 293 CHILDREN (MODIFIED AND USING THE GENOTYPE FIGURES GIVEN BY RACE AND SANGER) (AFTER RACE, SANGER, LAWLER AND BERTINSHAW)

Phenotypes	Mating Number Exp.	Mating Number Obs.	Children Number	Children S Exp.	Children S Obs.	Children ss Exp.	Children ss Obs.	X^2 for l.d.f.
S × S	36·9	44	104	87·2	92	16·8	12	1·64
S × ss	60·9	57	136	81·3	84	54·7	52	0·22
ss × ss	25·2	22	53	0·0	0	53·0	53	0·00
	123·0	123						

These pedigrees show the value of S as a marker for the M or N gene. The S type distinguishes Ms from MS and enables a particular M or N gene to be labelled. The pedigrees show only the segregation of S with M but segregation of S with N is known.

P group

The P antigen was first described by Landsteiner and Levine in 1927 when they discovered the MN groups. There are two kinds of people, P positive and P negative, and the corresponding genotypes are shown in Table XI.

TABLE XI

P GROUP. N.W. ENGLAND

Phenotype	Genotype	Frequency (percentage)
P positive	{ PP Pp }	77
P negative	pp	23

The frequencies of tests in Manchester and gene frequencies are shown in Table XII.

TABLE XII

P GROUP FREQUENCIES

	Number	Percentage	Total
P positive – –	374	77·3	484
P negative – –	110	22·7	
Gene frequency –		P = 0·5235 p = 0·4765	

Heredity

The P antigen is inherited as a mendelian dominant character. A large number of results of P typing are known. However, as weak P positive results are notoriously difficult to detect many of the frequencies recorded are of doubtful reliability.

Exhaustive family investigations have been carried out and the results agree well with the theory. The theory is that P–p are two allelic genes, P being dominant to p. That

the fit is so good is remarkable when one considers that the P antigen varies in strength of reaction to such an extent, and weak P positive types occur which can readily become confused with the P negative group.

Table XIII shows collective results quoted by Wiener and from the various matings the numbers of children expected and observed are shown.

TABLE XIII

HEREDITY OF THE P AGGLUTINOGEN (FROM WIENER, 1943)

Mating	Number of families		Number of children				Totals
			P+		P−		
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	
P+ × P+	249	241	677	686	79	70	756
P+ × P−	134	152	286	325	179	140	465
P− × P−	34	24	(4)	0	94	98	98
	417	417	967	1,011	352	308	1,319

The results in the P+ × P+ class agree with the calculations, but in the P+ × P− class the fit is not so close, although this could be due to chance. The four exceptions in the P− × P− class are probably due to illegitimacy.

The manner of investigating the inheritance of a character like P is illustrated by the results of family studies by Sanger, Lawler and Race. The phenotype frequencies are obtained, followed by the gene frequencies (Sanger and her associates' phenotype frequencies are used). The genotype frequencies are then calculated followed by the calculated frequencies of the mating and children in each group. The final table shows Sanger and her associates' figures with the observed matings compared with those expected, and with the observed children in each mating group compared with those expected. It will be seen that the fit is very close.

Inheritance of P

P positive 74 per cent = 0·74
P negative 26 per cent = 0·26

Gene frequencies

p = $\sqrt{0{\cdot}26}$ = 0·5099
P = 1−p = 0·4901

Genotype frequencies

PP = 0·2402
Pp = 0·4998
pp = 0·2600

Calculated frequencies

Matings		*Children*		
		PP	Pp	pp
PP × PP	0·0577	0·0577		
PP × Pp	0·2401	0·1200	0·1200	
Pp × Pp	0·2498	0·0624	0·1249	0·0624
PP × pp	0·1249		0·1249	
Pp × pp	0·2599		0·1299	0·1299
pp × pp	0·0676			0·0676

Mating		*Children*	
		P+	P−
P+ × P+	0·5476	0·8900	0·1100
P+ × P−	0·3848	0·6621	0·3379
P− × P−	0·0676		1·0000

The P *groups of* 85 *London families with* 190 *children*
(*Sanger, Lawler and Race*, 1949)

Type	*Mating* Number		Total	*Children* P+		P−	
	Obs.	Exp.		Obs.	Exp.	Obs.	Exp.
P+ × P+	49	46·5	110	99	97·5	11	12·5
P+ × P−	34	32·7	74	53	49·0	21	25·0
P− × P−	2	5·7	6	0	0·0	6	6·0

The gene frequencies given by Dahr and his colleagues are different from the Manchester ones and the percentage of children that would be expected from various matings is shown in Table XIV.

TABLE XIV

P MATINGS

Matings	Children	
	P positive (percentage)	P negative (percentage)
P+ × P+	85	15
P− × P+	65	35
P− × P−	0	100

It has been known for some time that there are quantitative differences in the P antigen, and when the group is typed the strength of reaction in the P positive group is often divided into P strong, P medium and P weak.

Henningsen has been unable to show that there are any qualitative differences between various P positive types, and that the differences are entirely quantitative ones. Henningsen, moreover, has considered that P is represented by more than one gene and the variation in pheno-typical strength cannot be explained by less than three P positive genes, and he has calculated the gene frequencies for the strength of P weak, P moderate and P strong, and finds a good fit between observed and expected results.

The grades of P strength, however, are not always clear cut and whilst the theory of the inheritance of P by two allelic genes at the P–p locus is considered well established, the extension of it by Henningsen to explain the quantitative differences in P needs further consideration and proof.

Pedigrees, Figs. 295–300 demonstrate the various types of P mating. In Fig. 296, a P+ × P+ mating is shown and here all the children are P+. An attempt has been made to put in the various strengths of P reaction to show the type of pedigree that is obtained when this is done. Fig. 299, showing a P+ × P− mating, with one sib P−, indicates that the P-positive parent must be heterozygous Pp, and the mating Pp × pp. In Fig. 295, two sibs are P−, and again the mating must be Pp × pp. In Fig. 298 is shown the rarer P negative × P negative family with all the children P negative. It will be seen that a child cannot be P positive unless one or both parents are P positive.

The Rh system

The Rh system has special interests because of its relationship to human disease and because of its genetical complexity.

Nomenclature

It was discovered in 1940 by Landsteiner and Wiener using a serum prepared by injecting Rhesus monkey cells into rabbits or guinea-pigs, hence the name Rhesus, or Rh group. Landsteiner and Wiener (1941) divided persons into two types, Rh positive and Rh negative, and the inheritance was studied and the Rh positive type considered to be an inherited dominant character. In the United States of America during 1941–43, Wiener and Levine and their associates were discovering new subgroups and various Rh antisera. Wiener and Landsteiner defined the major subgroups Rh_1, Rh_2, Rh negative and a minor group Rh′. In England, Race and Taylor, working with different antisera, described Rh_1, Rh_2 and Rh negative types. Additional antisera were discovered and soon seven alleles were known in England, and Wiener described six alleles. Thus, although both sets of workers approached the problem differently and originally using different antisera, at the end of 1943 there was almost complete agreement. That is, a number of subtypes of Rh had been serologically distinguished one from another and a start made on an examination of their manner of inheritance (Table XV).

TABLE XV

RH SUBTYPES IN 1943

Antisera	Subtypes					
	Rh_1	Rh_2	Rh_o	Rh′	Rh″	Rh_z
Anti-Rh (anti-D)	+	+	+	−	−	?
Anti-Rh_1 (anti-C)	+	−	−	+	−	?
Anti-Rh_2 (anti-E)	−	+	−	−	+	+
Anti-Hr (anti-c)	−	+	+	−	+	−

It was at the end of 1943 that Fisher suggested his hypothesis for three closely linked pairs of genes instead of a single gene locus with multiple alleles. This theory was based on a study of the results of British serological work. At these three loci the three gene pairs were called C–c, D–d and E–e. Each individual must thus be of genotype CC, Cc or cc, DD, Dd or dd, and EE, Ee or ee. No one normally lacks both C and c, D and d, or E and e (Fig. 287).

Wiener still considers that the Rh group and its inheritance is best explained by multiple alleles at a single locus. Hence there are two conflicting theories and notations. The two terminologies have been considered by Castle, Wintrobe and Snyder, 1948, and they recommend the use of both systems. Table XVI gives a comparison between the two systems of notation.

TABLE XVI

RH NOTATION

Wiener's terminology	Fisher-Race terminology
rh′	C
Rh_o	D
rh″	E
hr′	c
Hr_o	d
hr″	e

It is customary in Great Britain to use Fisher's notation and for clinical work to have a somewhat more convenient terminology akin to that of Wiener in 1943 for the Rh types, Fisher's notation being used almost exclusively for the antibodies (Tables XVII and XVIII)

TABLE XVII

RH GROUPS

Rh group clinical notation	Commoner genotypes	Approximate frequency of group (percentage)
R_1r	CDe/cde	35·0
R_1R_1	CDe/CDe	20·0
R_2r	cDE/cde	12·0
R_2R_2	cDE/cDE	2·0
R_1R_2	cDE/CDe	13·0
R_or	cDe/cde	2·0
$R'r$	Cde/cde	0·75
$R''r$	cdE/cde	0·85
Rarer genotypes		
R_oR_o	cDe/cDe	—
$R'R'$	Cde/Cde	—
R_zr	CDE/cde	—
R_yr	CdE/cde	—

TABLE XVIII

KNOWN AND EXPECTED REACTIONS OF RH ANTIGENS AND ANTIBODIES

Antigen and genes	Clinical notation	Antisera					
		Anti-D	Anti-C	Anti-E	anti-c	anti-e	anti-d
CDe	R_1	+	+	−	−	+	−
cDE	R_2	+	−	+	+	−	−
cDe	R_o	+	−	−	+	+	−
Cde	R'	−	+	−	−	+	+
cdE	R''	−	−	+	+	−	+
CdE	R_y	−	+	+	−	−	+
CDE	R_z	+	+	+	−	−	−
cde	r	−	−	−	+	+	+
Percentage positive reactions with antisera		84	70	30	80	96	60

Fisher's theory enabled new groups and antisera to be forecast as well as making understandable some rare Rh types which are considered to be alleles at each of the three loci themselves. Normally, the three genes are inherited closely linked together. For example, in R_1r, CDe/cde, the triple genes CDe and cde are inherited *en bloc*. The theory, however, would allow independent activity of the antigens. By this is meant that although the Rh group is determined by a triple gene locus, nevertheless it is similar to others.

The antigens on the red cells correspond to the genes governing their presence and corresponding antisera are produced by the appropriate antigens (Table XVIII). However, mixtures of antisera can be produced by the action of two antigens, for example anti-C plus anti-D, so that the letters CDE and cde represent erythrocyte agglutinogens as well as the determinant genes. Thus, a person of type R_1r CDe/cde has C and D antigens as well as c,d, and a double dose of e.

The commoner Rh types are distinguishable from one another serologically. Using the various antisera, a number of groups are serologically separable (Table XIX).

TABLE XIX

RH TYPES SEROLOGICALLY SEPARABLE

Antisera used	Number of recognized groups serologically separable
Anti-D	2
Anti-D Anti-C	4
Anti-D Anti-C Anti-E	8
Anti-D Anti-C Anti-E anti-c	12
Anti-D Anti-C Anti-C^w Anti-E anti-c anti-e	28

The term group is used since the same serological group may contain different genotypes. It is obvious that if all the antisera corresponding to the different antigens are available, genotypes could be detected; but two different genotypes may have identical serological reactions, for example, R′R″ Cde/cdE and R_yr CdE/cde.

Anti-d serum has been described by Hill and Haberman but is not generally available. When Rh typing is done, in certain instances therefore, the group or probable genotype only can be given unless extensive family studies make it certain.

Table XX shows the common heterozygotes and the serum used to distinguish them from the homozygotes.

TABLE XX

DISTINCTION BETWEEN HOMOZYGOTE AND HETEROZYGOTE

Homozygote and heterozygote	Serum making distinction
R_1R_1 and R_1r	anti-c
R_2R_2 and R_2r	anti-e
R_oR_o and R_or	anti-d
R′R′ and R′r	anti-c

Heredity

The conflicting theories do not affect inheritance studies because the three linked genes can be considered as one in the absence of cross-overs. Crossing-over has not been observed.

Family studies have now been made in large numbers for Rh. These can be analysed in two ways. First, by examining certain matings and comparing the observed number of children of various types with the calculated, and secondly, as has been done by Lawler, Bertinshaw, Sanger and Race for 150 families, by analysing the matings of each of the three pairs of allelomorphic antigens C–c, D–d, E–e.

In Table XXI, an analysis of Rh-positive and Rh-negative matings is made, the largest number of these having been done by Wiener and his associates.

TABLE XXI

RH FAMILY STUDIES (FAMILIES SELECTED FROM WIENER, GORDON AND HANDMAN, DESCRIBING 923 FAMILIES; LAWLER, BERTINSHAW, SANGER AND RACE, DESCRIBING 150 FAMILIES, AND THE AUTHOR'S FAMILIES. (*PROBABLY DUE TO ILLEGITIMACY).

Matings	Number	Children					
		R_1 CDe	R_2 cDE	R_o cDe	R′ Cde	R″ cdE	R-neg cde
R_1 × rr CDe × cde	503	529	(1)*	25	8	0	132
R_2 × rr cDE × cde	102	0	114	2	0	0	73
rr × rr cde × cde	30	0	0	0	0	0	57

It will be observed that in the Rh-negative × Rh-negative matings all the children are Rh-negative and, furthermore, it will be observed that unless C, D or E are present in at least one of the parents then they are not present in the children. Lawler and her associates have analysed matings for each of the antigens separately and were able to show that C and c, D and d, and E and e are inherited as mendelian characters. That is, the three antigens when linked together as they normally are, behave together as mendelian characters.

Figs. 292–300 illustrate the inheritance of Rh, and also the presence of some rare genotypes.

In Fig. 292 a large family tree shows the inheritance of R_1, R_2 and Rh-negative types. It is possible to say that I_1 must have been heterozygous. The mating R_2r (II_2) × R_1r (II_3) is observed and here four phenotypes are possible, R_1R_2, R_2r, R_1r and Rh-negative, and in the three children $III_{1,2,3}$, three of these are seen. In Fig. 295 the mating $R_1r \times R_2R_2$ is found and here all the children must contain R_2 which they do, being either R_1R_2 or R_2r. In Fig. 296, the mating $R_2r \times R_1R_1$ is shown and here all the children must contain R_1, which they do, being R_1R_2 or R_1r. The sibs R_1R_2 and R_1r would be expected to occur in equal numbers. There are four R_1R_2 sibs and three R_1r. In these latter two families both R_1R_1 and R_2R_2 genotypes were determined serologically and the result is seen to agree with the results of the family studies.

The mating Rh-negative × Rh-negative is not illustrated but has been observed several times and all children are Rh-negative.

In the family Fig. 297, the sibs $II_{4,5,6}$ are R_or and II_3 Rh-negative therefore I_3 would probably be R_or and the mating R_or × Rh-negative. This is very probable since a living brother I_1 is R_or.

The inheritance of the rarer types Rh′ and Rh″ is illustrated in Figs. 297 and 298. In these figures the genotype R′R″ (Cde/cdE) is shown. This genotype is distinguishable from R_yr (CdE/cde) by family studies, but in these pedigrees clearly all the groups shown as R′R″ are of this genotype. The frequency of R′R″ is about 1 : 5,000. In Fig. 288 is shown a pedigree of R_yr due to van den Bosch. Here I_2 R_yr is recognizable as such since II_2, R_1R_y is recognizable serologically and I_2 must be heterozygous because two sibs are Rh-negative. I_2 has the same serological reactions as R′R″ and

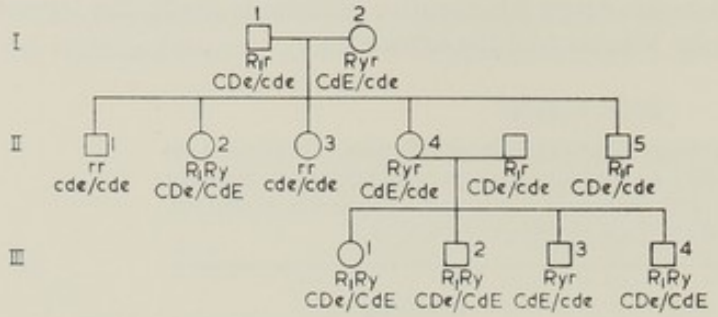


FIG. 288.—The occurrence of genotype Ryr in a family. (*After van den Bosch.*)

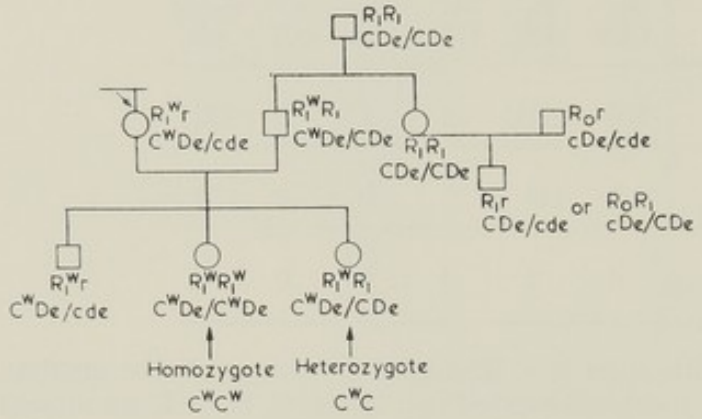


FIG. 289.—The occurrence of C^wC^w and CpC in the members of a family. (*After Callender and Race.*)

is determined to be R_yr by the family study. The frequency of R_yr is about 37 per million persons (Fisher and Race). Fig. 299 shows one of the sibs to be R′R′, also a rare variety. This results from the mating R′r × R_1R′, other children being R′r, R_1r or R_1R′, all possible types being shown among the children. Both R_1 and R′ in this family are transmitted through three generations.

Certain pedigrees are broken down to show schematically the inheritance of certain antigen pairs as defined by the appropriate antisera. For example, in Figs. 295 and 296, the Cc and Ee antigens are shown, and similarly in Figs. 298 and 299. The inheritance is a very simple one.

A possible matings table with the possible types of children is not shown since this is very extensive, but may be referred to in Race and Sangers' monograph. Certain Rh groups are rare, for example R_yr, CdE/cde and R_zr_z CDE/cde. R_y and R_z may be recognized serologically in the form R_1R_y, CDe/CdE or R_1R_z CDe/CDE. To determine whether it is the one or the other without anti-d, and to isolate R_yr or R_zr alone requires family studies.

Alleles at the C–c, D–d and E–e loci.—It soon became apparent that there were alleles at the three loci. These are shown in Table XXII.

TABLE XXII

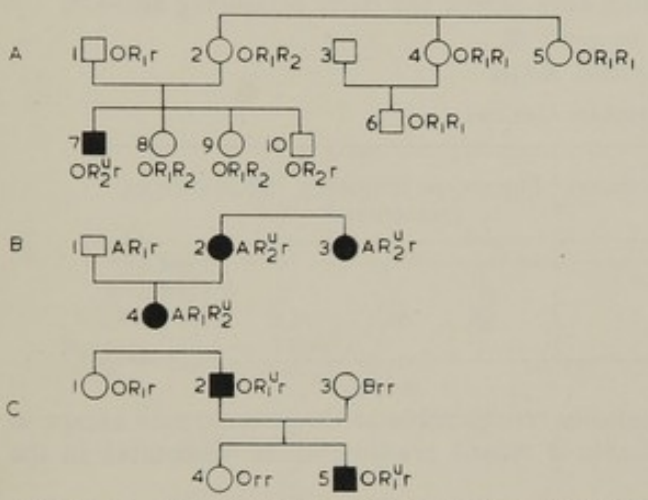
ALLELES AT C-c D-d E-e LOCI

Locus	Alleles described	Principal genotype	Frequency of principal genotype (percentage)
C–c	$C^wC^vC^u$	C^wDe/cde	1
D–d	D^u various types	CD^{u}e/cde	0·25
E–e	E^u	cDE^u/cde	—

Any of the alleles shown may replace Cc, Dd or Ee at the appropriate locus, thus a person may be C^wDe/cde or CD^ue/cde, or even C^wD^ue/cde, the latter described by Sanger.

C^w is recognized by an anti-C^w serum and several anti-C^w sera are now known and a number of family studies have been made. These suggest that C^w is an allele of C at the C–c locus. Fig. 289 shows a section of a pedigree by Callender and Race. C^wC^w is amongst the members. Thus, a person C^wDe/cde is serologically distinguishable from one who is CDe/cde.

D^u is thought to be an allele or modification of D which may replace D at the D–d locus. A person, for example, may be CD^u/cde or cD^uE/cde, or cD^ue/cde; these are the commoner combinations. D^u is an important group but less well defined than the others since no anti-D^u antibody is known, but only anti-$D+D^u$. A large number of different varieties are known which are grouped together collectively under the term D^u. Many differ not only quantitatively but qualitatively from one another (Renton and



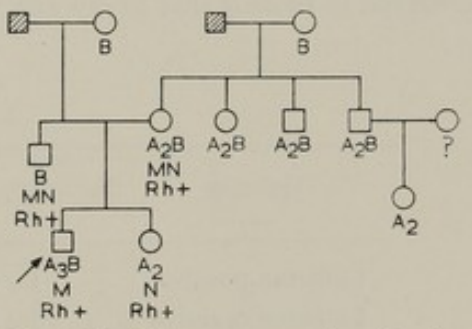


FIG. 291.—The occurrence in a family of a person of type A_3B having no A_3 relatives. (*After Young and Witebsky.*)

FIG. 290.—The occurrence of the D^u subgroup of Rh in a family. (*After Renton and Stratton.*)

Stratton). Owing to technical difficulties D^u may be missed and consequently many cells of supposed genotype Cde/cde in reality contain D^u. D^u containing cells are classified as Rh-positive. Race, Sanger and Lawler consider that D^u is a mutation from D rather than from d. Nevertheless, there is some evidence for suggesting it is a modification of D at the D–d locus. The combination DD^u cannot be detected serologically, but only D^ud. D^uD may be inferred from family studies. Fig. 290 shows pedigrees containing D^u. In Fig. 290 (A) an $R_1r \times R_1R_2$ mating has sibs with types R_2^ur and R_2r among them.

It is considered that illegitimacy is excluded and perhaps this is a mutation or modification of D. In Fig. 290 (B) the type $R_1R_2^u$ is assumed from the groups of other members of the family.

The antigen E^u allelomorphic to E and e has been described by Capellini, Ikin and Mourant. It was present in the form cDE^u/cde.

Fisher's theory of triple linked genes.—When the theory was first enunciated anti-d and anti-e antibodies were unknown but were predicted and subsequently found. The same applies to the detection of Ry, its occurrence was forecast. Furthermore, the finding of alleles of Rh considered to be alleles at each of the three loci further confirms the hypothesis. Crossing-over is possible and Fisher suggested that the rarer types could arise by cross-overs from the heterozygotes (Fig. 288). Moreover, the order of the genes on the chromosomes was considered to be DCE. No authenticated case of crossing-over has so far been described. Tests of populations with varying gene frequencies widely

different from one population to another help to test the hypothesis if the rare types in a particular population are also known.

Recently, Race, Sanger and Selwyn have described a person of genotype –D–/–D–; her parents were second half cousins. The suggestion is that this represents a small deletion of the chromosome. This supports the suggestion of the order of antigens as DCE on the chromosome and the triple gene theory for, as the authors remark " the very controversial question of whether the genes are separable or not is settled in the most convincing way of all—by their separation ".

The Lutheran groups

In 1946, Callender and Race described the investigation of the serum of a patient which contained many atypical antibodies; among them was anti-Lutheran antibody. Lutheran was one of the donors whose blood was given to this patient. It may be observed in passing that Levay and Willis were others, the latter producing anti-C^w.

TABLE XXIII

LUTHERAN GROUPS

Group	Phenotype notation	Phenotype frequency (percentage)	Genotypes
Lutheran positive	Lu (a+)	7	Lu^aLu^a, Lu^aLu^b
Lutheran negative	Lu (a−)	93	Lu^bLu^b

It will be seen that Lu^b is not serologically recognizable in the homozygote except in a negative way; if anti-Lu^b were available it would presumably be detectable in the heterozygote (*vide* Kell).

Various family studies have been undertaken and Lawler has examined 47 families with 97 children and the results are in agreement with the Lu^a antigen being inherited as a mendelian dominant character at the Lu^a–Lu^b locus. Matings are shown in Table XXIV.

TABLE XXIV

LUTHERAN MATINGS

Matings	Children: Calculated frequencies (percentage)	
	Lu (a+)	Lu (a−)
Lu (a+) × Lu (a+)	76	24
Lu (a+) × Lu (a−)	51	49
Lu (a−) × Lu (a−)	0	100

In the mating Lu (a−) × Lu (a−) there are no Lu (a+) children; in 34 such families Lawler found all 77 children Lu (a−).

The Kell groups

In 1946 Coombs, Mourant and Race discovered a new agglutinable property in blood which they called Kell. Persons were found to be Kell-positive or Kell-negative (Table XXV).

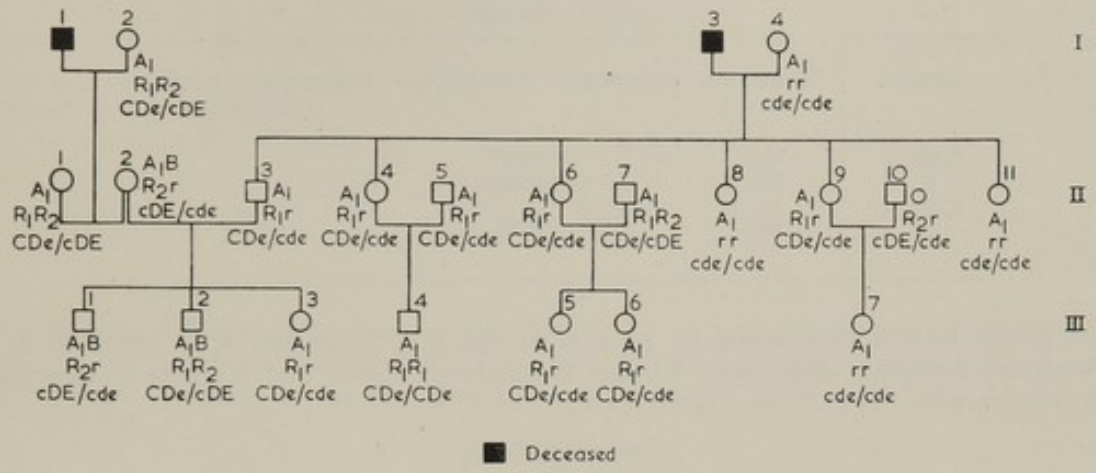


FIG. 292.

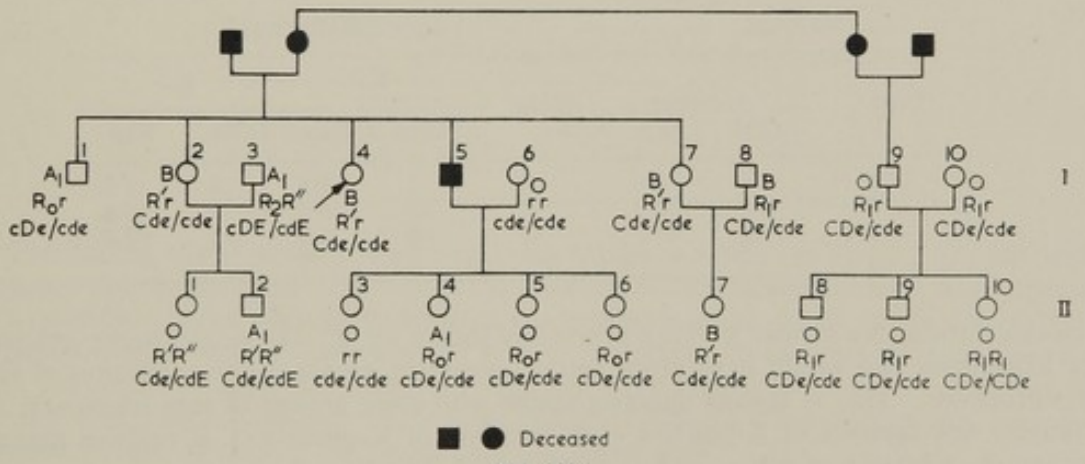


FIG. 293.

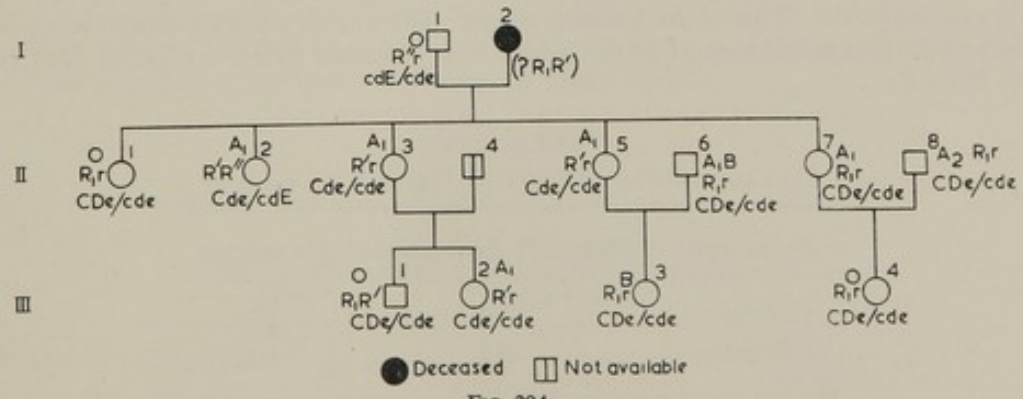


FIG. 294.

FIG. 292.—The inheritance of the subgroups of Rh.

FIGS. 293, 294.—The inheritance of the rarer subgroups of Rh.

TABLE XXV

KELL GROUPS

Groups	Genotypes	Genotype frequencies	Phenotype frequencies (percentage)
Kell +	KK	0·0027	7
K +	Kk	0·0990	
Kell −	kk	0·8993	93
K −			

The group Kell is determined by gene K at the K–k locus and K is inherited as a mendelian dominant character. Sanger, Bertinshaw, Lawler and Race have examined 56 families with 119 children (Table XXVI).

TABLE XXVI

KELL GROUPS OF 56 FAMILIES WITH 119 CHILDREN (AFTER SANGER, BERTINSHAW, LAWLER AND RACE, 1949)

Matings			Children				
Type	Number		Total	K+		K−	
	Obs.	Exp.		Obs.	Exp.	Obs.	Exp.
K+ × K+	1	0·6	5	1	3·8	4	1·2
K+ × K−	15	10·2	32	18	16·4	14	15·6
K− × K−	40	45·2	82	0	0·0	82	82·0

The calculations are similar to those previously shown for P. The results agree well with the hypothesis and would have given better agreement except for the selection of four K+ propositi. This is always understandable with these groups of rare frequency, for relatively few families of K-positive × K-negative, or K-positive × K-positive matings are found. Children of a K− × K− mating cannot be K+

In 1949 Levine, Backer, Wigod and Ponder discovered another antibody giving a high percentage of positive results. Indeed, in 2,500 samples tested, only five were found which were negative. This is the Cellano group. The antiserum was subsequently found to react with the agglutinogen Cellano which is determined by gene k of the Kell system (Table XXVII).

TABLE XXVII

CELLANO (ANTI-k) ANTISERUM TYPING KELL GROUPS

Phenotypes	Frequency (percentage)	Genotypes
Cellano+	98·8	kk
		Kk
Cellano−	0·2	KK

The gene frequencies for KK, Kk and kk are calculated in Table XXVIII. In column A are the results shown when the results of Cellano typing are used and in column B when the results of Kell typing by Sanger and her associates are utilized. Column C shows the genotype frequencies calculated using another anti-Kell serum. Some anti-Kell sera

TABLE XXVIII
KELL GENOTYPE FREQUENCIES

	Genotype frequencies		
	A	B	C
KK	0·002	0·0027	0·0012
Kk	0·086	0·0990	0·0638
kk	0·912	0·8983	0·9307

give slightly different frequencies. The results are in good agreement. All Cellano-negative persons have been found to be Kell-positive. Using the two antisera true genotyping is possible in the Kell group (Table XXIX).

TABLE XXIX
KELL GENOTYPING

Type	Genotype	Antisera	
		Kell (anti-K)	Cellano (anti-k)
K+	KK	+	−
K+	Kk	+	+
K−	kk	−	+

The finding of an antiserum active against k antigen is further evidence that such agglutinogens may be antigenic, and makes the labelling of K as dominant to k more difficult; it is probably better to regard them as co-dominants (*vide infra*), or as detectable in heterozygous as well as homozygous states. Pedigrees illustrating the inheritance of Kell are shown in Figs. 295–301*b*. In Fig. 295 is the mating K + × K − showing one sib K+ and three K-negative. In the other pedigrees note the large number of K− × K− matings which, of course, far outnumber any other kind.

The Duffy blood group

The Duffy blood group was described by Cutbush, Mollison and Parkin in 1950. The group was recognized as a result of an antibody causing a transfusion reaction. The phenotypes and genotypes are shown in Table XXX.

TABLE XXX
DUFFY GROUPS

Group	Phenotype	Approximate phenotype frequency (percentage)	Genotypes
Duffy +	Fy (a+)	65	Fy^aFy^a, Fy^aFy^b
Duffy −	Fy (a−)	35	Fy^bFy^b

Eighty-five families with 297 children have been examined by Cutbush, and Mollison and Race, Holt and Thompson. The genotype frequencies have been calculated and the expected and observed results in the families compared. These results show that the

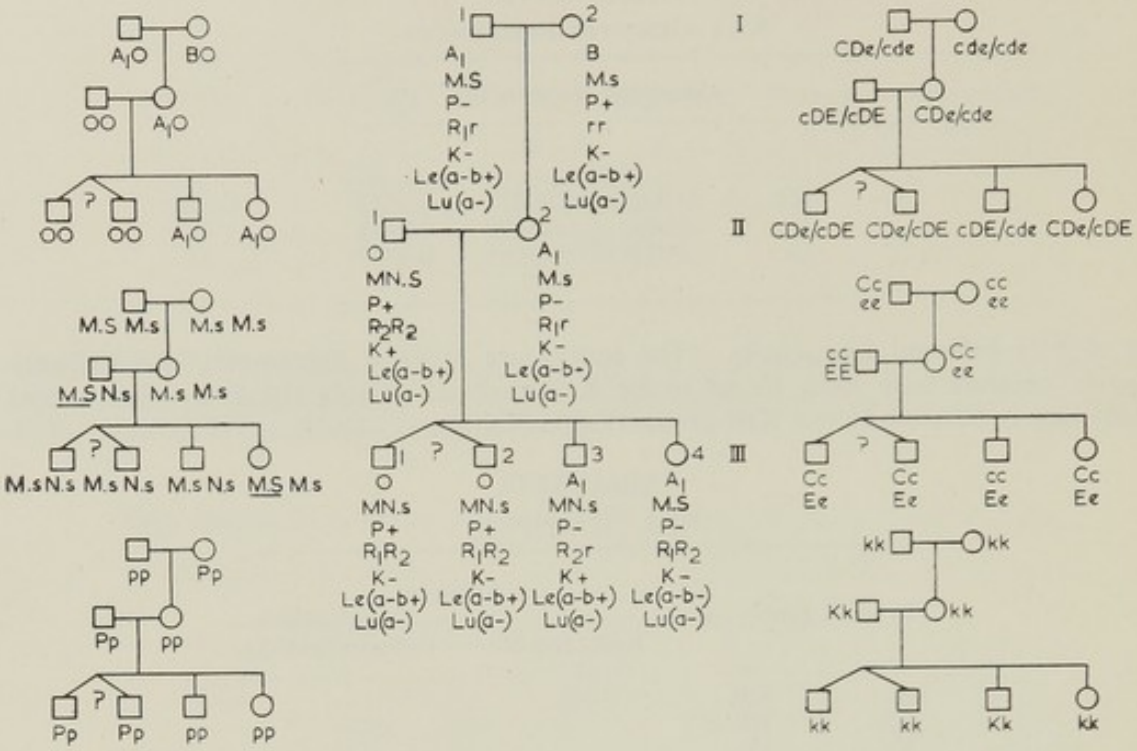


FIG. 295.—Pedigree of a family, the members of which were typed for several blood groups. The smaller figures show the individual groups, and in the Rh system this has been broken down to show, schematically, the inheritance of certain antigen pairs.

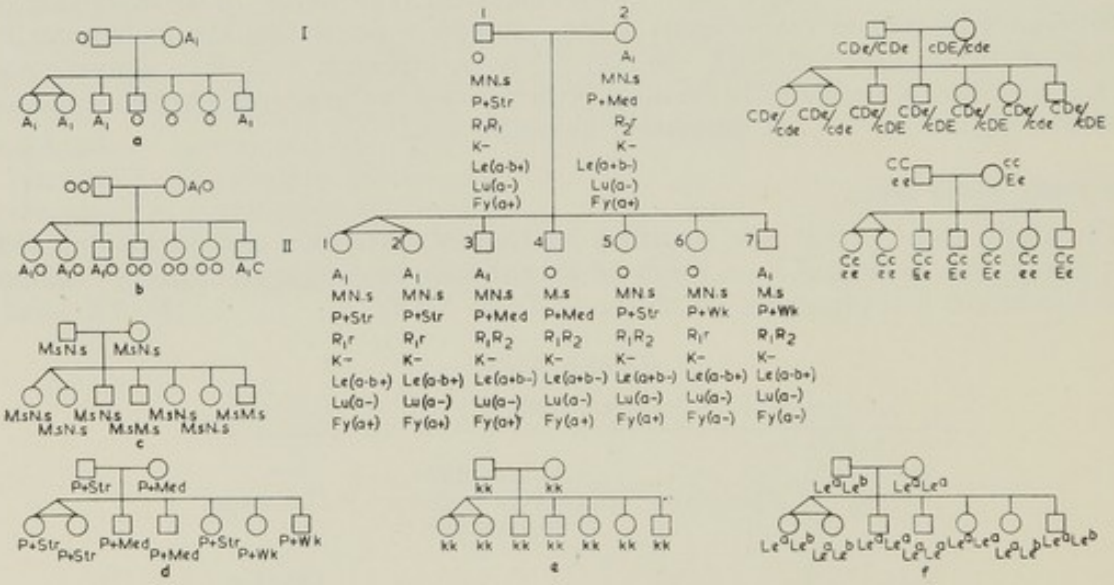


FIG. 296.—Pedigree of a family, the members of which were typed for several blood groups. The smaller figures show the individual groups and in the Rh system this has been broken down to show, schematically, the inheritance of certain antigen pairs. An attempt has been made in the P groups to put in the strength of the reactions. II_1 and II_2 are considered to be identical twins. II_1 possesses a congenital abnormality not present in II_2; their blood groups are identical.

antigen Fy (a+) is inherited as a dominant character and that the Duffy group is represented by two alleles Fy^a and Fy^b at the Fy^a Fy^b locus. In the mating Fy (a−) × Fy (a−) (12 per cent) no Fy (a+) children can occur. Table XXXI shows the matings and frequencies based on the phenotype frequencies in Table XXX. Anti-Fy^b antibody is now known (Ikin, Mourant, Pettenkofer and Blumenthal) as well as anti-Fy^a, and genotyping is possible within this group if both antisera are used, but at present only anti-Fy^a is readily available.

TABLE XXXI

DUFFY MATINGS

Mating	Children	
	Fy (a+) (percentage)	Fy (a−) (percentage)
Fy (a+) × Fy (a+)	86	14
Fy (a+) × Fy (a−)	62	38
Fy (a−) × Fy (a−)	0	100

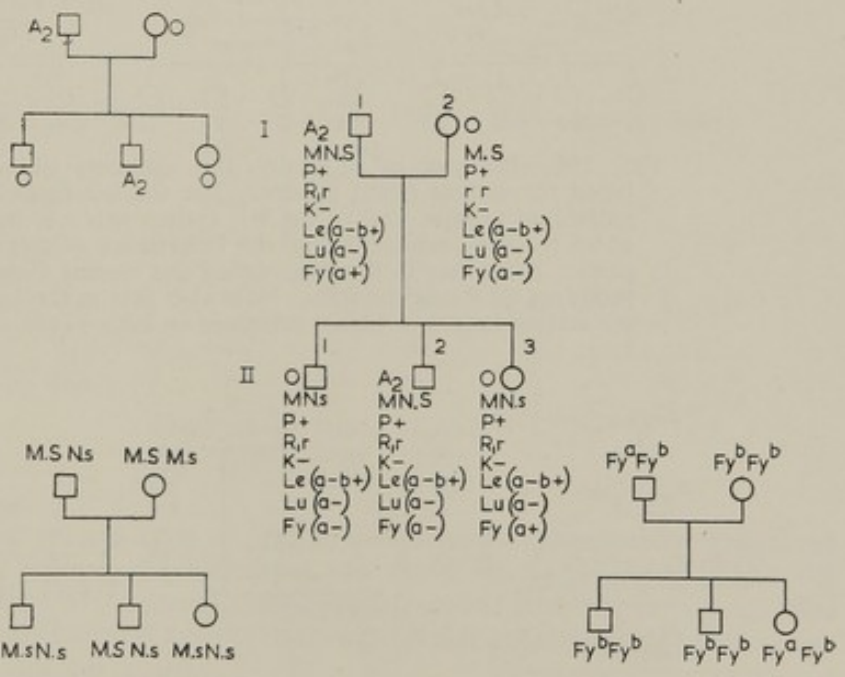


FIG. 297.—Pedigree of a family, the members of which were typed for several blood groups. The smaller figures give the individual group. Note especially the Duffy groups.

In Figs. 296–300 are shown examples of matings of the Duffy group. Figs. 297 and 300 are examples of the Fy (a +) × Fy (a −) mating. In Fig. 297, two sibs are Fy (a −) and in Fig. 300 one, consequently the Fy (a +) parent is heterozygous, Fy^aFy^b, and the genotypes of the whole family are known in each case and illustrated in the appropriate figurette. In Fig. 296, the mating here is Fy (a +) × Fy (a +) and two sibs are Fy (a −), hence, both parents are heterozygous. In Figs. 298 and 299 where the mating Fy (a +) × Fy (a +) is shown all the children are Fy (a +) and consequently no genotypes can be assumed from a study of the pedigree.

The Lewis groups

The Lewis groups were discovered in 1946 by Mourant who found the anti-Lewis antibody in human serum. The anti-Lewis sera have been found more frequently than

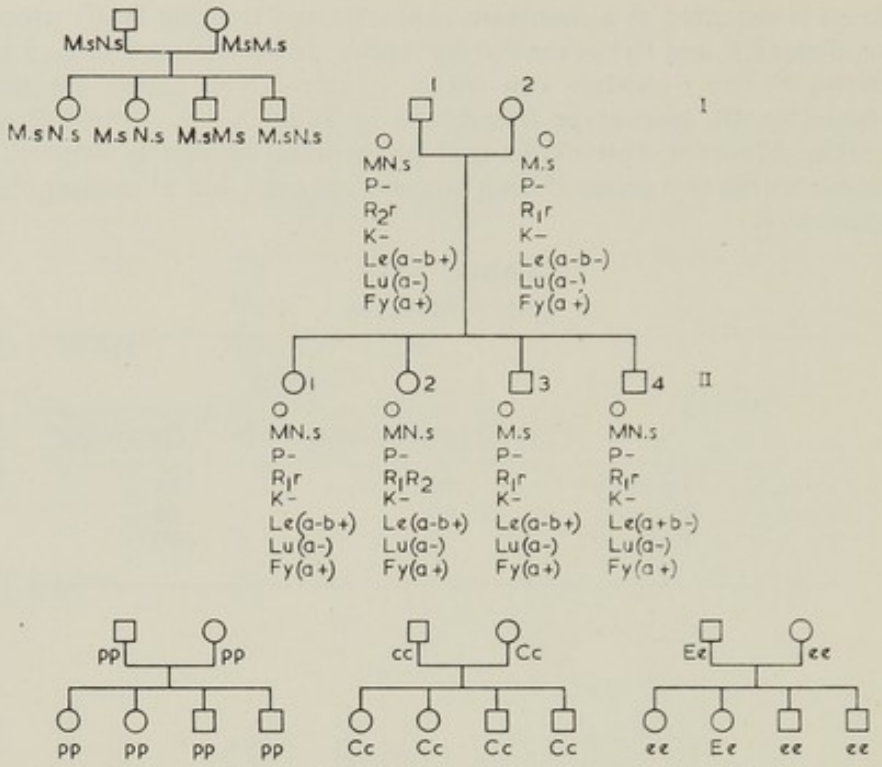


FIG. 298.—Pedigree of a family, the members of which were typed for several blood groups. The smaller figures show the individual groups, and in the Rh system this has been broken down to show, schematically, the inheritance of certain antigen pairs. Note that in the P grouping the mating P-neg × P-neg produces all P-neg children. Note also that in the Lewis group the mating Le(a–) × Le(a–) produces an Le(a+) sib.

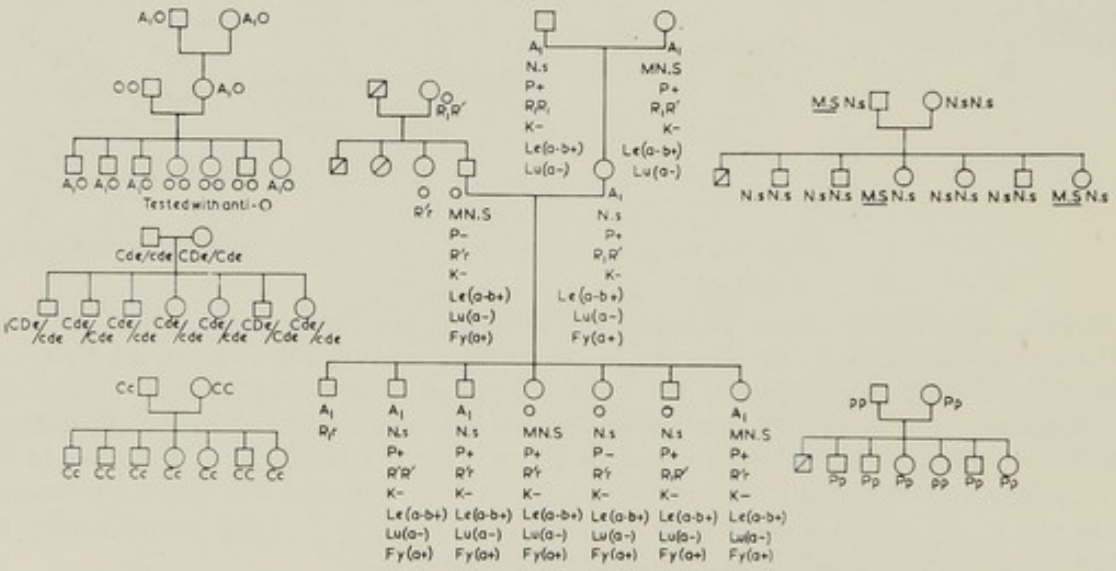


FIG. 299.—Pedigree of a family, the members of which were typed for several blood groups. The smaller figures show the individual groups and in the Rh system this has been broken down to show, schematically, the inheritance of certain antigen pairs. Note also the S sub-typing in the MN groups showing how S acts as a marker for M and segregates with it.

many of the more recently discovered blood group antibodies. They are of two varieties, anti-Le^a and anti-Le^b.

Andresen independently described anti-Lewis antibodies. Andresen found that Lewis-negative parents (that is, negative to anti-Le^a antiserum, mating: Lewis-negative × Lewis-negative) might have Lewis-positive children. It seemed, therefore, that the Lewis group, as defined by anti-Le^a antibody in Lewis-positive persons, was behaving as a recessive character. The groups determined by anti-Le^a are shown in Table XXXII. At this stage two genes are postulated, Le^a and Le$^?$ (Table XXXII).

TABLE XXXII

LEWIS GROUPS DEFINED BY anti-Le^a

Groups	Phenotype	Phenotype frequency (percentage)	Genotypes
Lewis positive	Le (a+)	20	Le^{a}Le^a
Lewis negative	Le (a−)	80	Le^{a}Le$^?$

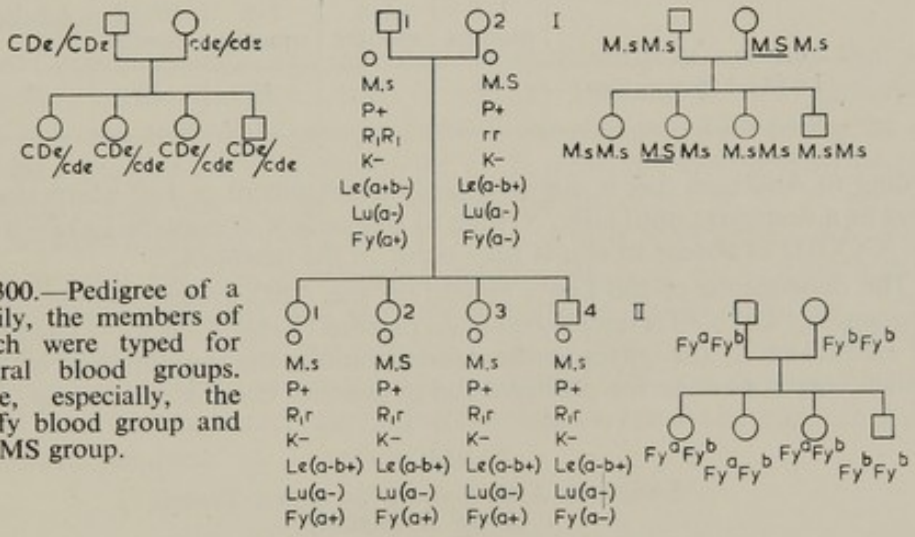


FIG. 300.—Pedigree of a family, the members of which were typed for several blood groups. Note, especially, the Duffy blood group and the MS group.

Andresen discovered a second type of anti-Lewis antibody subsequently designated anti-Le^b. The positive groups and genotypes are shown in Table XXXIII and the frequencies given are those of Andresen typing adult persons who are Group O. The use of these two sera, anti-Le^a and anti-Le^b necessitates the postulation of three genes, Le^a, Le^b and Le^c to explain the results.

TABLE XXXIII

LEWIS GROUPS USING anti-Le^a AND anti-Le^b

Phenotype	Genotypes	Frequency (Gp.O) (percentage)
Le (a+b−)	Le^{a}Le^a	20
Le (a−b+)	Le^{a}Le^b, Le^{b}Le^b, Le^{b}Le^c	74
Le (a−b−)	Le^{a}Le^c, Le^{c}Le^c	6
Le (a+b+)	—	0

The difference between these tables and previous ones for other groups, for example, P, Kell, and others will at once be noticed since a genotype Le^aLe^b in adults may be negative with an anti-Le^a serum. This is due to Le (a+) persons being homozygous, Le^aLe^a and Le^a is not detectable in the adult heterozygote.

Family studies have confirmed the theory of Andersen that persons who are Le (a+) are homozygous and that Le^a is inherited as a recessive character. For example, in Fig. 298 is the mating Le (a−) × Le (a−) with child II_4 Le (a+) (*see* also Fig. 301*b*).

The anti-Le^b antiserum may be positive or negative with persons Le (a−). Most often it is positive and opposite in its effect to anti-Le^a (Table XXXIII). The type Le (a+b+) does not occur in adults since Le (a+) is recessive.

Apart from the recessive character of the Lewis antigen, three other features are of interest: (1) the observation by Andresen that using anti-Le^a serum the percentage of Le (a+) results are higher in babies up to 1–2 years of age than in adults (Table XXXIV).

TABLE XXXIV

EFFECT OF AGE ON Le (a+) FREQUENCY (AFTER ANDRESEN)

	1–3 months	4–6 months	7–9 months	10–12 months	Adults
Le (a+) (percentage)	79	73	36	29	21

According to Andresen this is due to a tardy development of Le^b which does not exert its effect as a dominant until later. Owing to this cells of phenotype Le (a+b+) recorded (Table XXXIII) as absent in adults may occur in the newborn.

(2) The dependence of the Lewis system on the ABO groups. Andresen states that the frequency of Le (b+) is diminished in A_1 persons (Table XXXV). "The mere presence of the characters A_1 (or corresponding gene) inhibits the development of the receptor Le^b which corresponds to the phenomenon in genetics designated epistasy."

TABLE XXXV

EFFECT OF ABO GROUPS ON LEWIS TYPING (AFTER ANDRESEN)

ABO group	Le (b×) (percentage)	Le (b−) (percentage)
A_1	41·8	58·2
A_2	70·0	30·0
O	72·0	28·0

(3) The observation by Grubb of a very close association between the ability to secrete ABH substances in the saliva and the groups Le (a+) and Le (a−). All Le (a+) persons are non-secretors and nearly all Le (a−) persons are secretors. Grubb and Morgan suggest that Le^a, Le^b, S and s may belong to the same system.

Occasionally a person of group Le (a−) is found to be a non-secretor but they are generally of the type Le (a−b−). Andresen has introduced a further system, Xx, determined by a gene X and typed by an antiserum, anti-X; X is dominant to x. He considers that this sytem influences the Lewis system and that persons of genotype xx are Le (a−b−) because x when present in double dose inhibits the appearance of Le^a or Le^b in the phenotype. Anti-X closely resembles in its action a mixture of anti-Le^a + anti-Le^b antisera and the examination of more anti-X sera is awaited.

Various pedigrees are shown (Figs. 295–300) illustrating the inheritance of Le^b. In the persons who are also A_1, typing with anti-Le^b antisera may be difficult; consequently the results may not be accurate, nevertheless, the effect seems more pronounced in some families than in others. Various figurettes show probable genotypes but these should be regarded as illustrative only in the present state of knowledge.

The Kidd group

A further blood group has recently been described by Allen, Diamond and Niedziela. The new blood group antigen is called " Kidd " and was determined by the antiserum from a mother who had a child affected with haemolytic disease of the newborn. The serum contained anti-Kell but also contained the antiserum of the new antigen. Seventy-seven per cent of persons were found to be Kidd-positive and there was no relationship between the new antigen and the antigens of the ABO, MNS, P, Rh, Lewis or Duffy blood group systems, or sex. The antiserum is anti-Jk^a.

CLINICAL APPLICATIONS

Genetic considerations

Various blood group systems are inherited independently of sex and that other useful character, taste-blindness. It is interesting to note at this juncture the relationship between the MN types and the S subgroups. The pedigrees show how S may be a marker for a particular M or N gene and enable it to be traced through a family; this was not as easy before the discovery of S. A very close association between secretors and Lewis groups has also been noted. The various blood group systems are mainly inherited independently of each other but more recently it has been suggested that the Lewis group is linked with the Lutheran group. As an illustration of the independence of the blood groups, Table XXXVI shows the P types observed and expected in a number of blood samples also typed for ABO and Rh. The expected calculation is made on the assumption that ABO, Rh and P are independent.

TABLE XXXVI

P TYPES IN RELATION TO A B AND RH

	AB Rh-pos.	AB Rh-neg.	A Rh-pos.	A Rh-neg.	B Rh-pos.	B Rh-neg.	O Rh-pos.	O* Rh-neg.
P-positive								
Observed– –	7·0	2·0	128·0	23·0	32·0	6·0	142·0	34·0
Expected– –	6·2	—	132·0	23·2	31·7	6·2	135·0	37·1
P-negative								
Observed– –	1·0	1·0	43·0	7·0	9·0	2·0	33·0	14·0
Expected– –	1·8	—	39·0	6·8	9·3	1·8	40·0	10·9

* The high percentage of this type is due to selection. This table suggests independence by inspection alone; statistical analysis would confirm it.

There is no evidence to show that any genes outside the particular blood group constellation effect the blood group genes themselves. There is the possibility though that D^u may be a modification of D at the D–d locus, but if this is so then even the few families already studied would show that the modifying and D genes must be closely linked.

Linkage

Endeavours have been made to establish linkage between blood groups and many characters. There is no linkage between blood groups and eye colour and the possibility of linkage between a variety of characters, such as ear flare, finger length, tongue curl and others, has been examined. There is a suggestion of linkage between MN types and ear flare, and between the ABO groups and bright red hair. With regard to the linkage between blood groups and pathological conditions, the only probable one is that described by Snyder (1948) between the MN groups and the sickling trait for red cells. The 12 families suitable for analysis were all Negro families. The gene for sickle cells is independent of those for taste-blindness, ABO and Rh groups. There is no definite evidence of linkage between blood groups and Friedreichs ataxia or phenylketonuria. Summarizing, there is a possible linkage between bright red hair and the ABO groups, and between sickling trait in red cells and MN groups.

Not many chromosomes possess blood group genes, but there is no reason to doubt that further cases of linkage will occur, one difficulty being to use other characteristics, either physiological or pathological ones, as accurately defined as the blood groups. An increase in the number of inherited blood groups that are known would, of course, also increase the chances of detecting linkage.

Cross-over

Crossing-over has not been established in blood group studies. Previous mention has been made of crossing-over in relation to the Rh group. The possible occurrence of cross-overs can be neglected in medico-legal investigations such as disputed parentage.

Mutation

Blood groups are of little or no value thus far in establishing the mutation rate in man. It was supposed that the Rh gene had a high mutation rate owing to the operation of selection in that heterozygotes are removed in haemolytic disease of the newborn. This is probably not so, since the mutation rate would have to be abnormally high. Occasionally, there is a suggestion in a particular pedigree of mutations and in addition to the case of D^u (Fig. 290A) another case has been described (*see* Fig. 291) where a person of A_3B has apparently no A_3 relatives.

Dominance

The question of dominance in the blood groups is an important one. A and B are considered to be absolutely dominant to O, but as a result of using an anti-O serum it may be considered that A and B are co-dominant with O and A_2. However, more proof of this is needed and the general order of dominance in the ABO groups is A_1–B–A_2–A_3–O. In the MN groups both antigens are weaker in the heterozygote and therefore there is only partial dominance, probably N being stronger than M. In the case of the Rh group, C.D.E. are partial dominants but in the case of gene c the strength of the reactions given by the phenotypes is very much greater in the homozygote. The effect of the partial dominants C.D.E. is related to their number and combination but with the recessives c, e, their full effect is seen only in the homozygote. In the Lewis groups there is a most definite

recessive character, Lewis (a+), being detectable in adults only as Le^aLe^a. This knowledge is increasing as more antisera become available, but as it does so it makes the use of the word " dominance " in the normally accepted sense, more difficult.

Other aspects

There is also arising, as the result of work mainly on the Rh group, a conception of a basic raw material or substrate from which the antigens are developed by gene action. It is supposed that there is competition for this substrate and the quantity of a specific antigen depends on gene strength. It was found that the greater the amount of D in a cell the less would be the amount of C or E, and when both C and D are produced the amount of E would be minimal. An analogy is drawn between this and work on dahlia pigments where " there was competition between these pigments in their parallel production from a common limited source or intermediate " (Lawrence).

The previously quoted case of a suspected deletion of a chromosome would support this since this individual's erythrocytes gave extraordinarily strong reactions with Rh antisera. It seems as though the whole of the available basic material has been converted into D antigen alone.

In the case of a cellular antigen such as the antigen responsible for blood groups, it is probably as near the nucleus and genes as it is possible for any known heritable character to be. Consequently, a study of the chemistry of blood group substances might be a good way of gaining an insight into the chemistry of the gene. While this may not be a valid assumption, one that seems more likely is that changes in the one might be reflected in the other. For example, the change $D–D^u$ if a mutation must be a very small one, and it is tempting to suggest that such a similar chemical change is present in the responsible genes.

Relationship between blood groups and disease

Many attempts have been made to associate blood groups with a particular disease or susceptibility to disease; for example, dental caries in Czecho-Slovaks has been said to be greater in persons of groups B and AB. Mental deficiency has received a large measure of attention and some writers have claimed to have found certain blood groups more frequently than expected. Although a search of the literature will reveal many claims to have established an association between certain blood groups and a wide variety of pathological conditions, most articles nowadays mainly concern themselves with proving the contrary. It is comforting to learn that whatever may be our ABO blood group we have the same expectation of life.

Congenital abnormalities are not associated with a particular blood group. Investigations to examine the relationship between the Rh group and congenital deformities have been undertaken by the writer but none has been revealed.

Rh group and haemolytic disease of the newborn

Haemolytic disease of the newborn clinically presents as four main types: (1) icterus gravis neonatorum; (2) haemolytic anaemia of the newborn; (3) hydrops foetalis; and (4) stillbirth.

The theory of iso-immunization suggests, in general terms, that the mother is iremunized to an antigen during pregnancy which she does not possess in her mythrocytes but which the foetus does carry, having inherited it from the father. The maternal antibodies so produced then pass back through the placenta and attack the foetus. The antigen mainly involved is the Rh antigen. Therefore, an Rh-negative mother is immunized by an Rh-positive foetus and produces Rh antibodies in her serum which attack the foetus, especially its red cells. It might be thought that the ABO groups would be involved but only very rarely are they the cause of haemolytic disease.

Evidence for the accuracy of this theory is now weighty. Ninety-five per cent, or more, of mothers whose children are affected with haemolytic disease are Rh-negative and possess Rh antibodies in their blood at some stage of pregnancy or puerperium. In the normal population, by comparison, only 16 per cent are Rh-negative and hardly ever are Rh antibodies of natural occurrence, they are almost always of immune origin. In many hundreds of cases, the author has seen only one which might be described as naturally occurring. The children are Rh-positive and so are the legitimate fathers. The commonest antibody is that to the D antigen, either as anti-C+D, anti-D or uncommonly as anti-D+E. Rarely, when the children of an Rh-positive mother are affected, if she is R_1r, CDe/cde, anti-E is involved, or when she is R_1R_1 CDe/CDe, anti-c. The Kell blood group antibody may also be the one responsible. It is interesting to note that first children are rarely affected and the disease starts in the second child, or in later children, probably depending on the maternal resistance to immunization. We have many case records of Rh-negative mothers during their first pregnancy who developed Rh antibodies during the second pregnancy, and their second children were affected with haemolytic disease. Theoretically speaking, more foetal blood may enter the maternal body at delivery than at other periods.

Additional evidence of limited susceptibility to immunization is that an Rh-positive transfusion to an Rh-negative mother before marriage may cause her first child to be affected.

A girl aged 8 years had a tonsillectomy and was transfused with blood later found to be group O Rh-positive. At aged 18 years she had her first child which was severely affected with haemolytic disease; it subsequently died. Mother, Rh-negative cde/cde with Rh antibodies; child, R_1r, CDe/cde; father, R_1R_1, CDe/CDe. In this case, the mother's primary stimulus was not the first child or first delivery, but the blood transfusion, and subsequently her first child was affected.

In the mating Rh-negative × Rh-negative, cases of haemolytic disease should not occur due to Rh-positive antigens, C, D or E. Seven such cases have been examined by the author in which the maternal blood contained Rh antibodies (due to Rh-positive blood transfusions) and in such matings, in spite of the presence of these Rh antibodies, all the children were healthy. In the last case seen, the mother, who was transfused five years previously, still had strong Rh antibodies. Dizygotic twins may be born to an Rh-negative mother with Rh antibodies in her serum; if one is Rh-positive and the other Rh-negative, the former is affected and the latter healthy.

The mother need not be of genotype cde/cde to respond to the stimulus and produce Rh antibodies, but may be Cde/cde or cdE/cde, the antibody being anti-D.

Consequently, in detecting her Rh type during antenatal testing she should be diagnosed as D-positive or D-negative only. If she is genotype CD^ue/cde, however, the mothers the author has seen have not produced anti-D antibodies.

The frequency of the affection.—In Manchester in the last few years we have observed 565 cases of haemolytic disease in Rh-negative mothers. The total number of Rh-negative mothers tested was 13,300 giving an incidence of 4·25 per cent or one in 24 mothers. This incidence is certainly too high since although all the cases are probably seen, not all the corresponding Rh-negative mothers are tested. Some of these mothers will have Rh-negative husbands and making the correction for this and the availability of Rh-negative mothers for examination, the true incidence is about 1 in 23 of marriages having the mating: mother, Rh-negative × husband, Rh-positive.

The reason why only some Rh-negative mothers with Rh-positive children produce Rh antibodies in their blood is not known with certainty. A most likely explanation is that they differ in their response to the stimulus which many receive.

The affected children of Rh-negative mothers can be shown to be Rh-positive and to have sensitized erythrocytes. This produces a haemolytic anaemia which may be accompanied by jaundice (icterus gravis) or not.

It will be obvious from the foregoing that it is of great advantage to the clinician, from both the point of view of treatment and prognosis, to know which Rh-negative mothers possess antibodies and which do not. This can be ascertained and extensive antenatal testing services are in operation. It is also valuable to know in a family Rh-negative × Rh-positive, and where the mother's serum contains antibodies, whether the father is homozygous or heterozygous. If he is homozygous then all children will probably be affected; if he is heterozygous, children will have an equal chance of being Rh-positive or Rh-negative.

The commonest paternal groups are shown in Table XXXVII.

TABLE XXXVII

DETERMINATION OF HOMOZYGOSITY OF HUSBAND

Paternal group		Distinction with antiserum
R_1R_1	CDe/CDe	anti-c
R_1r	CDe/cde	
R_1R_2	CDe/cDE	—
R_2r	cDE/cde	anti-e
R_2R_2	cDE/cDE	
R_or	cDe/cde	anti-d if available
R_oR_o	cDe/cDe	

Anti-d serum is not available but in a large proportion of husbands it is possible to state that they are " probably homozygous " or " probably heterozygous " for D from a consideration of their reactions with anti-c and anti-e antisera.

R_1R_2 fathers, of course, will give all Rh-positive children. " Probably homozygous " is stated, therefore, because serologically it is impossible to distinguish say R_1R_1 from R_1R', or R_1r from R_1R_o, in the absence of anti-d serum. In cases

where the mother is Rh-positive, CDe/CDe, the father may be found to be Rh-negative, cde/cde, when, if the antibody involved is anti-c, all children would be heterozygous and consequently liable to be affected.

The prognosis in this disease depends, however, on many factors and it is only possible to say that an Rh-positive (D+) child, where the mating Rh-negative mother × Rh-positive homozygous father is involved, will be affected. The degree of severity may range from that only serologically detectable to hydrops foetalis and death.

Heterospecific pregnancy

By this term, introduced by Hirzfeld, is meant the occurrence in a pregnancy of a foetus whose cells could be agglutinated by anti-A or anti-B antibodies in the mother's serum. Thus a mother of group O would have heterospecific or incompatible pregnancy if the child were group A or B. It was considered that this heterospecific pregnancy might be the cause of early foetal death *in utero* and in order to confirm or deny this theory an analysis of heterospecific matings should be considered.

In haemolytic disease of the newborn the ABO groups of mothers and fathers and of mothers and affected children show a higher percentage compatibility than occurs in the normal population.

TABLE XXXVII (A)

Rh-negative mothers with maternal Rh antibodies	ABO incompatibility between parents	ABO compatibility between parents
319	55 17·2%	264 82·8%
In normal matings –	33%	67%

The figures in Table XXXVII (A) collected from the author's cases show, like other published series, a difference between the compatible pregnancies with respect to ABO groups in cases of families where there is haemolytic disease compared with normal matings. It may be evidence of a protective mechanism so that a mother responding to the A antigen will not simultaneously produce anti-Rh antibodies. Experiments in animals as well as experience in man would, however, be against this.

Fisher (quoted by Sanger and Race, 1950) suggests that it may be due to the early elimination of incompatible ABO foetuses so that they would not be so active in stimulating anti-Rh antibodies as would compatible ones.

Levine, remembering the work of Hirzfeld, who found a lower incidence of group A offspring in the mating: father, A × mother, O, than in the mating: father, O × mother, A, reconsidered the problem. Levine (1946) found a higher incidence than normal of incompatible matings associated with abortions and stillbirths, and considers this highly suggestive and probably significant.

Waterhouse and Hogben analysed twelve recently published heredity studies which were thought to be accurate and complete. A provisional estimate, based upon plausible assumptions, suggests that ABO iso-immunization is responsible for the loss of about 25 per cent of A children expected from marriage A × O.

In spite of this it is not definitely proved that ABO incompatibility causes early foetal death *in utero*. The results so far are only suggestive.

Twin studies

Twins whose blood groups are different, or who are of different sexes, are clearly dizygous, but where the blood groups are the same they may be monozygous, and the probability of monozygosity can be calculated (*vide infra*). Figs. 296 and 301 show pedigrees studied by the writer. These are of interest in that, although the twins were thought at first to be identical, one possessed a congenital abnormality which the other did not.

The pedigree illustrated in Fig. 301*b* shows twin girls thought probably to be monozygous. Here one possessed a congenital abnormality not possessed by the other. It will be observed that both their MN and Lewis groups are different. There is no doubt that these twins are dizygous in spite of the fact that they resembled each other.

In another case, Fig. 296, II_1 and II_2 were considered to be identical twins but it was uncertain since one of them, II_1, owing to having had a patent ductus arteriosus, was less well developed than her twin sister and somewhat different in appearance. Since her successful operation, however, she has come more to resemble her sister. The two children had identical blood groups.

In two other cases of twins described, one of them was affected with an abnormality, namely renal dwarfism, but the other twin did not have this defect (Milne, 1951). In the pair of male twins illustrated in Fig. 301*a*, the main difference between them was a difference in height. It is interesting to note that in these twin boys, both had congenital partial ptosis of the left eyelid, and their every characteristic—such as could be determined—would lead one to believe that they were identical twins. Nevertheless, II_1 had renal dwarfism and was $6\frac{1}{4}$ inches shorter than his twin brother. Their blood groups—O, MN.s, P+, R_2, Le(a−) Lu(a−) were identical.

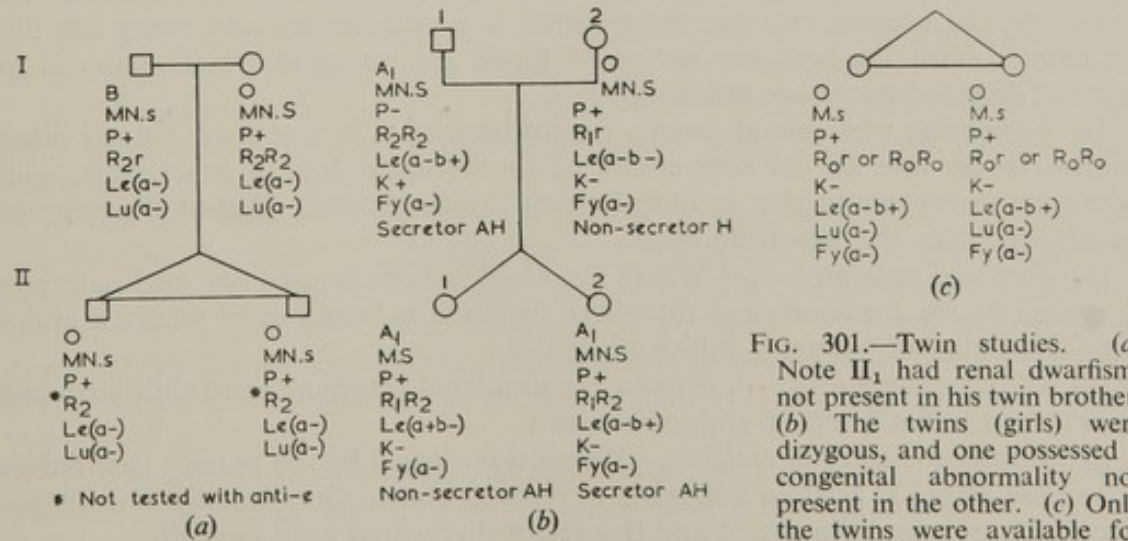


FIG. 301.—Twin studies. (*a*) Note II_1 had renal dwarfism, not present in his twin brother. (*b*) The twins (girls) were dizygous, and one possessed a congenital abnormality not present in the other. (*c*) Only the twins were available for examination. One suffered from renal dwarfism, but not the other. Their blood groups were identical.

In the second case, Fig. 301*c*, only the twins themselves were available for examination and not their parents; the unaffected twin was $2\frac{3}{4}$ inches taller than the patient and appeared perfectly healthy. Their blood groups—O, Ms, P+, R_oR or R_oR_o, K−, Le(a−b+) Lu(a−), Fy(a−) were identical.

The calculation of probability that like-sexed twins are identical will depend on whether the parents' groups as well as the offsprings' groups are known, and the particular groups which are determined. If the parents' blood groups are unknown the establishment of their monozygosity is more difficult. In the cases where the parents are available for testing, however, Penrose (quoted by Race and Sanger, 1950) has suggested a method of computing the probability of monozygosity. Using this method in the case of the twins illustrated in Fig. 296 (where II_1 had a patent ductus arteriosus and II_2 had not) but excluding from the calculation the P groups because of the P weak forms occurring, the probability of monozygosity is 95 per cent.

The use of the whole series of eight (now nine) blood groups is a very valuable adjunct to the other known methods of the study of twins.

Disputed parentage

Tests in cases of disputed parentage are not undertaken very frequently in Great Britain for two reasons; first, because there is no special legislation concerning these tests, especially legislation empowering the Courts to order the performance of the tests; and secondly, because there are no laboratories or persons specially designated to do these tests. In the United States of America and Scandinavian countries special legislation and special laboratories or serological departments of forensic medicine are available to do this work. The increasing complexity of the blood groups and the technical difficulties of their performance make it essential that persons doing these tests should have a wide experience and day-to-day familiarity with this type of work; moreover, it would seem desirable for the tests done in one laboratory to be duplicated in another.

Before World War II, a Bastardy Bill was introduced into the House of Lords. This Bill proposed to empower Courts of Summary Jurisdiction to require blood tests. At the present moment the position is unsatisfactory and many are unacquainted with the heritable nature of blood groups upon which opinions in cases of disputed parentage are based.

In considering what blood groups should be used it is necessary, among other things, to be sure of the correctness of the assumed law of inheritance, and secondly, to be certain that technical errors are eliminated. Disputed parentage usually includes the following cases.

(1) *Disputed paternity.*—(*a*) Where the child is born in wedlock and paternity is denied by the husband; and (*b*) where the child is born out of wedlock and a man is accused of paternity, which he denies.

(2) *Disputed maternity.*—A woman has simulated pregnancy and childbirth and now pretends that a certain child is her own.

(3) *Disputed identity of children.*—Where it is alleged by the parents that babies have been mixed at birth in a hospital or nursing home. Occasionally, it is alleged that children have been mixed and this is not discovered until later life.

Most cases concern disputed paternity. It must be emphasized that while blood

group tests may exclude an accused man—that is, to prove that he could not be the father of the child in question—they cannot identify him as the father of the child, that is, to prove that he must be the father.

Disputed maternity is rare, but disputes with regard to the mixing of children are more common.

When blood samples are removed from the persons to be tested, care should be taken to identify the person and to associate the person with the blood sample. This is done by signature and by the person's legal adviser, or by their finger prints. The person concerned signs the label on the tube of blood.

The basis of these tests, therefore, are the laws of inheritance of the blood groups. The groups of children are determined by those of their parents. Dominant blood group antigens cannot be present in the blood group of a child, unless present in one or both parents (for example, A, B, M, N, C, D, E), and secondly, certain mother-child combinations are inconsistent with the laws of inheritance.

An example of a case cited by Wiener (1950) is illustrative. The question arose whether the husband, or another man, was the father of a child born in wedlock. The groups were as follows:

Mother, A_2 M Rh-negative (rr); child, A_1 MN Rh-negative (rr); husband, O M R_1R_1; lover, A_1 N R″r.

The husband, therefore, is excluded on three counts—

(1) Mother A_2; child A_1; the husband, group O, cannot be the father.
(2) Mother M; child MN; the husband M is therefore excluded, the child having N, not present in either parent.
(3) Mother and child both Rh-negative; husband R_1R_1 excluded (that is to say, he has C and D in his cells, not present in the child or mother).

The lover is not excluded by any of these groups.

Disputed paternity

What blood groups are reliable ones to use in this work and what are the chances of exclusion of a putative father in disputed paternity ?

ABO and MN groups.—The ABO groups and their subdivisions A_1, A_2, B and O, together with the MN groups, have been used for years and there is much evidence to show both the accuracy of the theories of inheritance, and their value in paternity work (Wiener, 1950; Levine, 1951; and Andresen).

In the ABO system more than 10,000 families with about 24,000 children have been studied with the only accepted divergence being the Haselhost and Lauer case, referred to on page 485.

In the MN system in 35,000 mother-child examinations, no deviations from the accepted method of inheritance have been observed (Andresen, 1947). With respect to A_1, A_2 Andresen says that " the possibility of a paternity incompatible with the A_1A_2 system has to be considered very remote ". Nevertheless, there are considerable difficulties and uncertainties in typing A_1 and A_2 in the newborn, and if the test on the child cannot be postponed until it is older, subgroups of A and AB should not be used.

Thus, it will be seen that the ABO and MN systems may be used with safety. Theoretically, the general chance of exclusion of a falsely accused man by the ABO groups is 1 in 6, and 1 in 3 if both the ABO and MN groups are used. The expectation varies with the group of the man, and is highest in the ABN group

and the lowest in the AMN group. The chances if the mother's blood is not available are much less.

In practice, the actual numbers of exclusions described by various workers varies from 23 per cent to 8 per cent. In the latter case the probable explanation is that 50 per cent of the accused men were actually the fathers. Levine states that the exclusion in practice is about 18 per cent. Levine's results also show a high incidence of exclusions based on an alleged father who is homozygous for M or N, C or c, and an infant who is homozygous for the corresponding allele.

Other groups.—Other blood groups have recently been used in this work and Wiener (1950) has described 526 cases of disputed parentage in which ABO, MN and Rh tests were used. He estimates that the chances of a falsely accused man being excluded on the Rh system to be 25 per cent. The chance of exclusion using ABO, MN and Rh tests is about 50 per cent (Table XXXVIII).

TABLE XXXVIII

CHANCES OF EXCLUSION IN DISPUTED PATERNITY

Blood group system	Chances of exclusion (percentage)	Combined chances of exclusion (percentage)
ABO	17	17
MN	19	33
Rh	25	50

There are now a considerable number of family studies available with respect to the Rh groups which prove their acceptability for use as groups in disputed parentage. It is desirable that only the main groups should be used. In diagnosing the absence of D care should be taken to exclude the presence of D^u. The Rh antigen is well developed at birth and the author has been able to detect it in a 48-millimetre embryo.

With respect to the Kell, Lutheran and Duffy systems, there is, as yet, insufficient accumulated evidence on their manner of inheritance to permit them to be used in this type of medico-legal work. There is no doubt, however, that this will be forthcoming soon.

The S subgroups of MN greatly increase the usefulness of MN groups and increase the theoretical exclusion chances from about 19 per cent to 27 per cent, but the volume of inheritance studies is small, as yet.

The P group is subject to quantitative differences and it adds little to the chance of exclusion.

Summarizing, therefore, the ABO, MN and the main Rh groups are the ones used, giving an average probable exclusion rate of 50 per cent in disputed paternity.

Disputed maternity is rare; usually a woman borrows or obtains a child in order to force a man to marry her.

Identity of the child

In mixing babies in maternity hospitals, the same groups as before are used, as they also are in cases of doubtful identity of children. The following cases are illustrative:

Case 1.—(Franceschetti, Bamatter and Klein, 1948.)

The parents of twins aged 5 years (Victor and Pierre) became aware of the existence of another boy (Eric) who resembled their own child (Victor). The parents were surprised to learn that Eric had been born the same night in the same hospital as their children. This led them to conclude that a substitution of one twin might have taken place.

Family 1.

Mother:	A_1	N	R_1R_1	(CDe/CDe).
Father:	A_1	M	R_2	
Victor:	A_1	MN	R_1R_2	(CDe/cDE).
Pierre:	A_1	MN	rr	(cde/cde).

Family 2.

Mother:	A_1	MN	R_1r	(CDe/cde).
Eric:	A_1	MN	R_1R_2	(CDe/cDE).

It will be noticed that the ABO and MN groups are the same in all three children and are of no assistance, but that Pierre (cde/cde) could not have been the child of this mother who was homozygous R_1R_1. Eric was the same Rh type as Victor. It was impossible to show that Eric could not be the offspring of his present mother. The authors went to great lengths to prove Victor and Eric were identical twins. They listed a large number of characteristics possessed by the two children, some not possessed by Pierre.

Finally, skin grafts were made. Grafts from Eric and Pierre were transplanted to Victor's arm and two grafts from Victor transplanted back to Eric and Pierre. While the exchanged grafts between Victor and Eric took, those between Victor and Pierre necrosed.

This case illustrates the additional value of being able to do Rh genotypes as well as the usual ABO and MN tests. One can imagine that S subtypes in MN grouping might also have been helpful in this case.

Case 2.—A mother, while out one morning, left her pram outside a shop. When she came out the baby had been stolen. Efforts were made to find it and a baby was soon discovered in a foundling home some miles away that could have been the child, judged by its date of arrival in the home and apparent age. The mother saw this child and thought that she recognized it as her own. The blood groups were:

Mother:	A	MN	Rh-negative (rr)	(cde/cde).
Father:	O	N	R_2r or R_2R_2	(cDE/cde or cDE/cDE).
Foundling:	A	M	R_1r	(CDe/cde).

It will be seen that the foundling could not have been the child of those parents because they could not have a type M child, and secondly because they could not have a child whose blood contained R_1 which is not present in either parent. Thus, the child was excluded on two counts. This case was investigated several years ago when only the main Rh subdivisions were known and it must have been one of the first cases in England in which the Rh subtypes were used. It will be noticed that the group A subtypes are not stated. This is because they would not have been of certain value in babies.

Individuality of the blood

Landsteiner hoped that one day the blood groups would distinguish one person from another just as finger prints do at the present time.

When Landsteiner died, four blood group systems were known. Now there are eight, nine including the recently discovered Kidd group, and the S subdivisions

have been added to the MN groups. If the common antibodies of all the blood groups are used, about 13,000 different phenotype combinations are known, but if the antibodies generally available in some specialized serological laboratories are used then almost 300,000 different phenotype combinations can be recognized in human blood. Recently a rare Rh chromosome C^wD^ue was recognized (Sanger, 1950) in a person whose genotype was C^wD^ue/cde. The frequency of this type is about 1 : 10,000 persons.

If a person is of Rh type D^u it may be possible to recognize the type distinctively since there is a qualitative difference between one D^u type and another, and the degree of distinction in some instances depends on the number of antisera used. It is probable also, if sufficient and suitably absorbed sera were used, that distinctive differences in the D antigen could be recognized. Bertinshaw, Lawler, Holt, Kirman and Race (1950) examined 475 samples of blood for the groups A_1, A_2, B, O, MNS, P, Rh, Lutheran, Kell and Lewis. The 475 samples fell into 196 group combinations and of the 475, 211 (or 44 per cent) occurred only once.

The blood groups differ in their ability to distinguish one person from another, the Rh system being the most useful and the MNS next. The least useful are those such as Lutheran. If a person happens to be of a rare genotype or combination of groups the chances of individual recognition are high. There is no doubt, therefore, that the ability to recognize an individual by blood groups is becoming increasingly practicable. Several pedigrees showing persons typed for many groups are shown in Figs. 295–300. They are split up to illustrate the inheritance of single groups or antigens. This is a formidable array of groups and the many possible phenotype and distinctions will be understood from an inspection of these pedigrees.

Laboratory work and blood transfusion

Clinical considerations

Nothing has been said about the value of blood groups in blood transfusion since this is well known. It is, however, useful for haematologists and pathologists to remember that blood groups are inherited, although in ordinary routine serological work in connexion with blood transfusions the knowledge is rarely required. The following case illustrates one instance in which it proved useful:

A male suffering from acute haemolytic anaemia required a blood transfusion. He was found, on typing, to be group AB but to have strong auto-agglutinins present in his serum acting *in vitro* at 37°C. It is common for persons whose sera contains auto-agglutinins to be falsely diagnosed as AB, especially when those antibodies are present *in vitro* at body temperature. Exhaustive serological work, however, failed to show that the patient was any group but AB. His wife and two daughters were typed with the following results: wife, group O; first daughter, group A; second daughter, group B; and husband, group AB.

He was, therefore, successfully transfused with group AB blood.

One case has also been described in which a mother received her husband's blood and became sensitized to the Kell antigen. Children born subsequent to this transfusion, having inherited the Kell antigen from the father, were severely affected with haemolytic disease. Thus, in practical transfusion work, mothers should never be transfused with their husband's blood lest they become sensitized to some antigen he possesses and which his children may inherit.

Statistical aspects

It is useful also in laboratory work on blood groups to do a statistical test on the results from time to time to determine whether there is need to worry about their accuracy. Of course, this is no substitute for serological accuracy. For example, the frequencies of ABO groups which were done in one month in the Manchester Transfusion Laboratories are given below. The gene ratios of three groups are used to calculate the expected frequency of group AB. This is compared with that observed by the X^2 test.

TABLE XXXIX

STATISTICAL TEST OF LABORATORY BLOOD TYPING

		AB	A	B	O		
		98	1,374	268	1,633		
s	=	$\sqrt{O}$		$\sqrt{1,633}$		=	40·41
t	=	$\sqrt{O + A}$		$\sqrt{3,007}$		=	54·84
u	=	$\sqrt{O + B}$		$\sqrt{1,901}$		=	43·60
v	=	$t + u - s$		$98·44 - 40·41$		=	58·05
w	=	v^2		$(58·05)^2$		=	3,370·0
x	=	$w - (O + A + B) = 3,370 - 3,275$				=	95·0
x	=	expected number of AB bloods				=	95.0
y	=	observed number of AB bloods				=	98·0
z	=	$(x - y)$				=	3·0
X^2	=	$\frac{tuz^2}{wx}$				=	0·071

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CHAPTER 25

THE UROGENITAL SYSTEM

TAGE KEMP

THE KIDNEYS AND THE URINARY TRACT

Malformations

CONGENITAL malformations and anomalies of the kidneys and genito-urinary tract are very common, although frequently recognized only at autopsy. They are often predisposing to such diseases as pyelonephritis, calculi, haematuria or uraemia.

Strains of mice, rats and fowls with hereditary congenital anomalies of the kidney (absence of the one kidney, cystic kidneys, as well as other urogenital defects) have been observed.

In man some malformations have been observed as hereditary defects, frequently accompanied by other anomalies.

Horseshoe kidney

Horseshoe kidney and various other forms of renal fusion have been observed as concordant in uniovular twins (Yoshioka, 1935).

Congenital unilateral renal agenesia

Congenital unilateral renal agenesia or renal hypoplasia is not uncommon—it has a frequency of 1 : 1,000—and has been observed in uncle and nephew. Waardenburg (1952) has described unilateral aplasia in mirror-image form of the kidney and the corresponding ureter in monozygotic male twins.

Megalo-ureter

Congenital bilateral megalo-ureter with hydronephrosis has been recorded in a family of 7 siblings; 5 were known to have congenital lesions of the kidney or ureter, 3 had megalo-ureter (two bilateral), and two congenital sarcoma of the kidney (Wilms' tumour). The paternal grandfather died with a pyelonephrosis, so he may have had a congenital hydronephrosis (Mackay, 1945).

Wilms' tumour

Wilms' tumour is generally sporadic, and apart from the above case there are a few other records of its occurrence in sibs.

Renal dysplasia

Hawkins and Smith (1950) have described renal dysplasia in a family with multiple hereditary abnormalities including iliac horns of the pelvis. The kidney lesion showed itself clinically as chronic glomerular nephritis. In the same family there occurred many congenital abnormalities affecting tissues both of ectodermal and mesodermal origin.

Lesions of the fingernails, elbow joints and patellae were commonest, and were known to be inherited in the family together with the renal dysplasia. Other changes included lesions of the skin, vertebral column and pelvis. A single rather versatile gene, which shows variation in penetrance for particular characteristics is assumed by the authors, but the possibility also exists, however, that several genes, closely associated on the same chromosome, may be responsible. These loci may be so near together that crossing-over hardly ever occurs and they act as a unit in inheritance. On the whole the syndrome is inherited as a dominant character, showing great variation of manifestation and expression.

Polycystic disease of the kidneys

In this not uncommon affection heredity is an important factor. Clinically, two distinct varieties of the disease are described, congenital cystic kidney, and cystic disease of the kidney in adults. The adult type generally develops about the age of 40 years and is often complicated by hypertension, apoplexy and uraemia. There is, however, no gap in the age of onset of the two forms; probably all cases are congenital, though many remain undiscovered until symptoms of renal insufficiency set in. The disease is often associated with cyst formation in other organs such as the liver and pancreas, as well as other malformations (Fergusson, 1949). In about 10 per cent of cases the malformation is unilateral.

Congenital cystic kidney, causing death during or shortly after birth, is believed to be recessive, whilst the adult form is dominant (Figs. 302 and 303). Sporadic cases are common. It has been suggested—without any proof at all—that the phenomenon of " anticipation " occurs in cystic kidney.

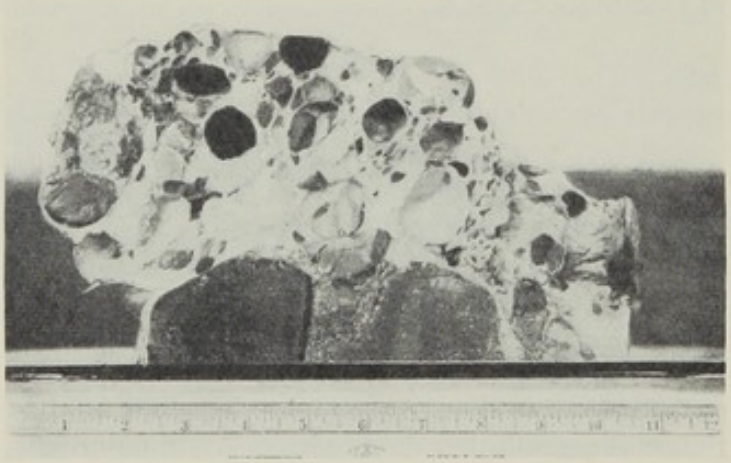

FIG. 302.—Sagittal section of polycystic kidney; autopsy specimen from a member of the family shown in Fig. 303. Note numerous smooth-walled cysts of widely varying size, some filled with organized blood clot. No grossly recognizable functioning kidney tissue is seen. (*By courtesy of Dr. C. Nash Herndon.*)

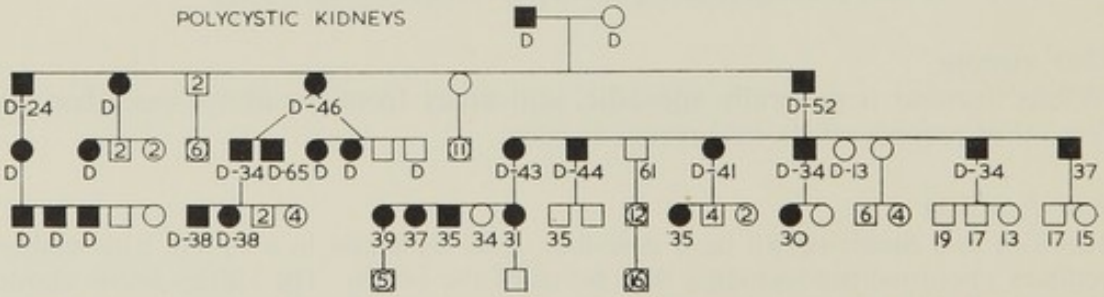

FIG. 303.—Pedigree showing 28 cases of polycystic kidney disease in 4 generations, regular dominant pattern. (*By courtesy of Dr. C. Nash Herndon.*)

Nephrosclerosis, nephritis, and albuminuria

Nephrosclerosis

Nephrosclerosis and essential hypertension—which are discussed on page 438—constitute a genetic entity. The two diseases are phenotypical manifestations of the same gene, the particular clinical form being determined by exogenous factors. Inheritance is dominant. The frequency of the gene is high, probably as much as 30 to 40 per cent in the population (Søbye, 1948).

Juvenile nephrosclerosis.—Children may present a pathological picture similar to that of nephrosclerosis. Juvenile nephrosclerosis is rare, many of the cases published have actually been examples of chronic glomerulonephritis or pyelonephritis—and familial occurrence has been recorded.

Congenital nephritis has been recorded as a familial disease observed in one or more siblings and in some cases also in their mothers. The lesion of the kidneys of the children may, however, be due to vasoactive substances circulating in the mothers. Newborn children whose mothers have had eclampsia during the pregnancy may in fact present a transient hypertension.

Glomerulonephritis

Glomerulonephritis is generally environmental in origin, but markedly familial occurrence with regular or irregular dominant inheritance has been observed occasionally (Fig. 304). Twin investigations show frequent discordance as regards nephritis both in one-egg and two-egg twins.

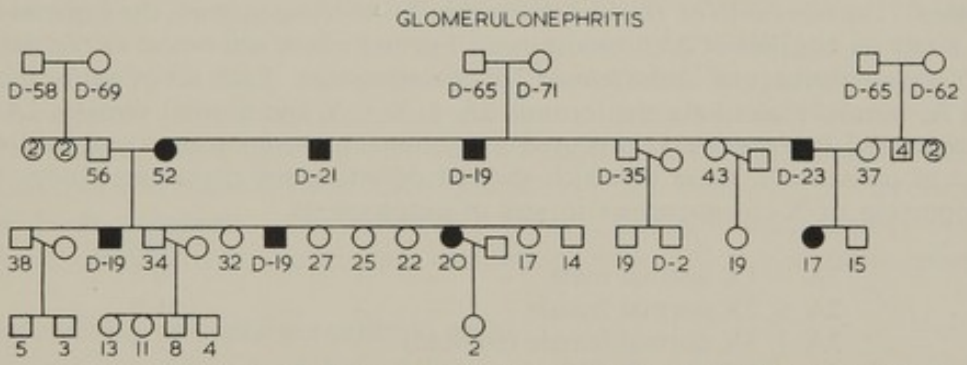

FIG. 304.—Family with 8 cases of glomerulonephritis in 2 generations, 5 individuals dying of the disease as young adults. (*By courtesy of Dr. C. Nash Herndon.*)

Essential haematuria

This condition has been observed as familial, but many of the cases of both nephritis and of haematuria reported as familial were probably instances of nephrosclerosis or hypertensive disease, or of cystic kidney (Kehler and Weber 1940).

Orthostatic albuminuria

Orthostatic albuminuria—a constitutional anomaly—is occasionally familial. Presumably it is the underlying lordosis that is hereditary. It is most commonly seen in young men who are tall and thin, and is frequently discovered accidentally. It has been observed in siblings or in several generations.

Other affections

The metabolic disorders of alkaptonuria, cystinuria and porphyrinuria and their urological aspects, as also stone formation, are discussed elsewhere.

THE GENITAL ORGANS

Sex determination and intersexuality

Sex chromosomes and sexual determination

The sex-determining genotypic factors are located partly in the sex chromosomes, partly in the autosomes and partly in the cytoplasm of the egg cell.

Early in foetal life, sex develops under the influence of chromosomal and autochthonous substances produced in all body cells and called chromosomal hormones. Later, the incretoric hormones, produced in the endocrine glands, begin to exert an increasing influence on the development of the sexual characters.

The embryonic hormones are assumed to influence the development of the gonads themselves and the derivatives of the müllerian and wolffian ducts, whereas the final hormones influence the secondary sex characters and the derivatives of sinus urogenitalis.

The mechanism of intersexuality

From animal experiments it is known that the sex-determining factors are attached to the X-chromosomes and the autosomes, and that sex results from a balance between male and female factors.

In the fruit fly the decisive influence is the proportion of X-chromosomes to sets of autosomes. The body cells of *Drosophila* contain 2 sets of autosomes, the gametes contain 1 set. Each set consists of 3 chromosomes. Further, there are found in the male 1 X- and 1 Y-chromosome, and in the female 2 X-chromosomes. Each set of autosomes being termed A, normal males have the formula 2A + X + Y and normal females 2A + 2X. Experimentally, Bridges (1921) procured the following chromosome combinations in a number of individuals, some of which showed deviating sex characters (Index denotes the proportion of X-chromosomes to sets of autosomes):

	Index
2A + 1X normal male	0·5
2A + 2X normal female	1·0
3A + 3X normal female (triploid)	1·0
2A + 3X superfeminine	1·5
3A + 2X intersex (triploid intersexuality)	0·66
3A + 1X supermasculine	0·33

The type 3A + 2X is called a triploid intersex, a mixture of male and female parts. The supermales have all the male characters exaggerated, and the superfemales all the female. They are both sterile. The haploid individual is unknown among fruit flies, but probably occurs among other species; for example, bees and ants. Where haploids occur they are always males.

By crossbreeding of various races of the Gipsy moth, *Lymantria*, Goldschmidt (1931) could produce any degree of intersexuality. These investigations have shown that there is a gradual transition from the normal female through the different forms of intersexuality to the normal male. The male-producing genes or factors (M) act in one direction and the female producing (F) in the other. A certain ratio between M and F gives normal males, and another normal females. Disturbances of these ratios cause intersexual forms of different degrees.

The theory has been advanced, on the basis of experience with *Lymantria dispar* inter-

sexes as well as on observations made on higher animals and humans, that the intersexual individuals genotypically belong to one sex, but change at a certain point of time during ontogeny, because the factors of the other sex then preponderate. The earlier the change takes place the more complete will it be. In conformity with this fact, the genitals and other sexual characters developing the last should change the fastest and the most completely. An individual that is laid down as a male and changes in the female direction is designated as a *male intersex*. If laid down as a female, it is a *female intersex*.

According to Goldschmidt human hermaphrodites are to be considered as female intersexes as are all intersexes in other mammals. In female intersexes the sex should—on this view—at some time or other turn over from female to male. If the turning point occurs in adult life only a slight degree of intersexuality will result, corresponding almost to the sequels of castration, that is a state of mild virilism. If the turning point occurs in childhood, the intersexuality becomes somewhat more marked. If it occurs *in utero*, it may bring out different forms of intersexuality. The most pronounced intersexual condition, though not the most complete change, is seen when the turning point occurs at a fairly late embryonic stage, before the wolffian ducts have been retransformed, but after the müllerian ducts have reached a certain development. An almost normal seminal duct may then be seen side by side with relatively well-developed müllerian ducts, which may possibly even form a uterus bicornis. The sexual glands become ovo-testes; as a rule no spermogenesis is seen. The sinus urogenitalis has a female appearance. If the turning point occurs still earlier the change in the male direction becomes more complete. The sexual glands become testes; and of the müllerian ducts only a negligible rest remain as in the normal male. In the most pronounced cases the external genitals also approach the male type in appearance. The intersexuality is then recognizable by hypospadia, cryptorchism or similar slight anomalies. The most complete change will result in individuals of a male type, but with a female chromosome combination (2 X-chromosomes). Theoretically such persons should only have daughters; but this form of intersexuality has not been observed. Goldschmidt's theory, though illuminating, does not explain all observations on human hermaphrodites and pseudohermaphrodites.

Hermaphroditism and intersexuality in man

Clinical aspects.—The possibility of hermaphroditism in man arises from the fact that at a certain stage in embryonic life the rudiments of the future sexual organs are in a bisexual undifferentiated stage. All intersexual forms between the two sexes appear also to exist in man. The different forms of hermaphroditism and pseudohermaphroditism in man have also been termed intersexuality. Ontogenetic and phylogenetic experiences regarding the sexual evolution in man agree to a certain extent with this view, but the conditions are complicated by the fact that the specific sex hormones begin to exert their influence at a certain point of life. No person is completely masculine or completely feminine; life begins with potentialities for either sex. Different reactions of the soma to the sex hormones are seen within one individual where the various organs differ in hormonal sensitivity.

True hermaphroditism is rare in man. A distinction has to be made between true hermaphroditism and pseudohermaphroditism where only one type of sexual gland tissue occurs—with testicular tissue we have male, and with ovarian tissue,

female pseudohermaphroditism. With heterosexual external genitals, the pseudohermaphroditism is said to be of the external or copulative form; if it is the internal genitals that differ we have the internal or tubular form.

Human pathology shows many forms of intersexuality, both physical (such as genital deformities, gynaecomastia and androtrichosis), and mental (such as homosexuality, bisexuality, feminism and virilism). These may all be of great importance for the individual and for society. The intersexual conditions may be present at birth, or heterologous sexual characters may develop sooner or later in otherwise normal individuals.

Sevringhaus (1942) studied the testis of a male pseudohermaphrodite cytologically. He found XY-chromosome pairs present, and assumed that intersexes are determined by a gene in the X-chromosome.

Heredity.—Familial occurrence of intersexuality or hermaphroditism in its different forms has often been observed. The literature up to 1908 has been summarized by Neugebauer and by Bulloch (1909). According to these authors male pseudohermaphroditism was observed in 17 families in 2 brothers, in 2 families in 3 brothers and in 1 family in 4 brothers; female pseudohermaphroditism was observed in 3 families in 2 sisters; altogether male pseudohermaphroditism was observed several times in 20 sibships including 44 individuals, and female pseudohermaphroditism was observed in 3 sibships including 6 individuals. These observations confirmed the old experience that male pseudohermaphroditism is about 7 to 8 times as frequent as female.

In 1908, Neugebauer collected 1,253 cases of intersexuality and 112 of these cases were familial; he found the frequency of hermaphroditism to be about 1: 1,000. An old and well-known instance of familial pseudohermaphroditism (peniscrotale hypospadia) was described by Heuermann (1767); this anomaly occurred in 3 generations, in 1 of them in 2 siblings. Another large family with many cases of male pseudohermaphroditism was recorded by Diefenbach (1912) in 5 generations inherited through females, and there are also many smaller pedigrees such as those of Petterson and Bonnier (1937). Hirschfeld (1928) has observed consanguinity among the parents of pseudohermaphrodites in 37 per cent. In many of the cases the anomaly is inherited through normal females, a fact which can probably be reconciled to Goldschmidt's views on the genesis of intersexuality.

It is, however, hardly justifiable to regard all forms of pseudohermaphroditism in man as female intersexuality; some cases of pseudohermaphroditism are probably males genetically, or they may represent an inherited sex-mosaic. The origin of pseudohermaphroditism in man is not yet fully understood, as is obvious from the fact that intersexuality of an endocrine character is seen in cases of tumours in adrenal glands or gonads. None the less, as can be seen from Cawadias' recent study (1943), intersexuality and intersexual conditions have frequently a genetic basis.

Gynandromorphism

Gynandromorphism is characterized by the occurrence of cells with male as well as with female chromosome combinations in the same individual. The intersex is a sex-mosaic in time, the gynandromorph an intersex in space. Gynandromorphism may be unilateral, transversal or mosaic-like. True gynandromorphs with a testis and the Wolffian system

on one side and with an ovary and Müllerian system on the other have been observed, Lindwall and Wahlgren (1936) and Young (1937).

Gynaecomastia is regarded by some as a form of gynandromorphism. In some cases it is familial, Bonhoff (1926). The condition may be unilateral or bilateral and associated with other genital malformations such as hypogenitalism, lack of prostate development and sterility.

Maldevelopmental anomalies

Hypospadia

Hypospadia has been regarded as a slight form of intersexuality, and is found in about 3 of every 1,000 males. It is presumably inherited as an irregularly recessive defect. Some 75 per cent of the cases occur sporadically (Rahbek Sorensen, 1953). Hypospadia shows considerable interfamilial and intrafamilial variation. It is often associated with cryptorchism. Peniscrotal hypospadia and especially the pseudovaginal hypospadia are often mistaken for pseudohermaphroditism. Hypospadia is more frequently concordant in one-egg twins than discordant.

Epispadia (*fissura urethrae superior*, *ectopia vesicae*)

This is very rare. It is observed concordantly in uniovular twins.

Cryptorchidism

This is rather common. According to Young (1937) it occurs in 1 of 30 boys under 14 years of age and in 1 of 250 men over 21 years of age. In dogs and pigs it has been observed as a simple recessive. O'Connor and Corbus (1922) described familial occurrence of undescended testes in 6 brothers, and Birkenfield (1928) has seen the anomaly concordantly in one-egg twins.

Eunuchoidism

Eunuchoidism or hypogenitalism is often familial, Hurxtherl (1943), Kallmann, Schoenfeld and Barrera (1944). The anomaly is often attended by anosmia, colour blindness, mental deficiency, synkinesia and various genital malformations or abnormalities.

Valves in the prostatic urethra

This has been described in a pair of one-egg twins both with undescended testicles.

Absence of the uterus

Absence of the uterus has been observed by Delbet (1940) in a family with 5 cases in 3 generations transmitted through normal sisters of the affected patients.

Atresia vaginae

Atresia vaginae has been recorded in 2 and imperforate hymen in 3 sisters, McIlroy and Ward (1930).

Other affections

The adrenogenital syndrome

This syndrome has been described by Broster and others (1934, 1938) in women,

and showing four types: (1) Adrenal pseudohermaphroditism at puberty; (2) adrenal virilism after puberty; (3) mild virilism with obesity; and (4) post-menopausal virilism. The affection has been observed in one-egg twins, in a mother and her daughter and in several sibs. In many of the cases there is frequent occurrence of hirsutism among the female relatives. Some cases have been reported as instances of "*interrenalism*" or of pseudohermaphroditism.

Pubertas praecox

This syndrome in boys has been noted several times in siblings as has *Macrogenitosomia.*

Sterility

In animal experiments recessive mutations causing sterility have often been observed. Partial infertility has been described in human families by Galton and others. A pedigree showing many sterile or partly sterile males is given by Crew and Miller (1931), whilst Kup (1936) has recorded a pedigree with sterility in both sexes; many childless or impotent individuals were observed, also several cases of *hypogenitalism.*

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CHAPTER 26

ENDOCRINE DISORDERS

ERIK D. BARTELS

THE PANCREAS

Diabetes mellitus

FOR AT LEAST 300 years it has been known that diabetes mellitus often occurs in several members of the same family. The family histories that have accumulated present many difficulties and in some ways are contradictory. Were it proved that a considerable proportion of the cases of diabetes mellitus are hereditary, this affection would easily rank as the most important, numerically and socially, of all hereditary diseases.

Clinical aspects

The essential feature of diabetes is the presence of a diabetic glucose tolerance curve in the blood under given conditions. Generally there is also glucosuria and in untreated patients polyuria, thirst and dehydration; in severe cases there is ketosis. Sometimes a patient presents a diabetic glucose tolerance curve without clinical symptoms—a condition known as latent diabetes. Diabetes mellitus is thus not a disease but a syndrome. It has many different causes. Lesions of the pancreas, either operative or accidental, can be followed by diabetes, whilst pancreatitis, hepatitis, acromegaly, Graves' disease, Cushing's syndrome and other affections are accompanied sometimes by diabetic syndromes. In most cases, however, the aetiology is totally obscure.

Many attempts, mostly unsuccessful, have been made to separate diabetics into different groups according to the clinical picture, the type of onset, sensitivity to insulin and so on. The only grouping generally acknowledged is (1) severe cases with a tendency to ketosis and great sensitivity to insulin, most frequent in young people; and (2) milder cases with slight tendency to ketosis and relative insensitivity to insulin, as seen especially among older patients. Genetically, these two types are not distinct. Diabetic families often show members with both types.

Physiological considerations

Houssay, Young, Lukens and Dohan have shown that certain pituitary extracts nearly related to, if not identical with, the growth hormone cause diabetes if injected into animals. Different species show varying degrees of resistance to this action of the hormone, but if partial pancreatectomy is carried out before the injection even the more resistant species succumb. Dogs are especially sensitive to the extract but show great individual variations. During treatment the pancreatic islands undergo various histological changes ending with atrophy. According to Lukens, the process may be interpreted as an attempt by the gland to keep pace with an overloading of its function ending with exhaustion. The factor producing this overloading probably is prolonged hyperglycaemia.

From the fact that many cases in children begin after a period of accelerated growth, that is to say, a period of hypophyseal hyperfunction, and that the pancreas in diabetics often seems to be smaller than normal, he concluded that the hereditary factor in diabetes mellitus may affect either the hypophysis, producing a tendency to hyperfunction, or the pancreas, producing a lowered reserve of insular tissue. This, however, is an oversimplification, for the defect producing diabetes may occur in some enzyme system in the liver or in all cells. If the vascular complications of diabetes are in fact not complications of, but aspects of the disease, the causative factor cannot be pancreatic or hypophyseal.

Frequency of the affection and individual risk of developing it

Many attempts have been made to assess the frequency of diabetes in different countries. The frequency of diagnosed diabetes is rising owing to better diagnostic facilities, a higher mean age in the population (most cases of diabetes arise after middle age (Fig. 305)), and increased longevity of diabetics; and there

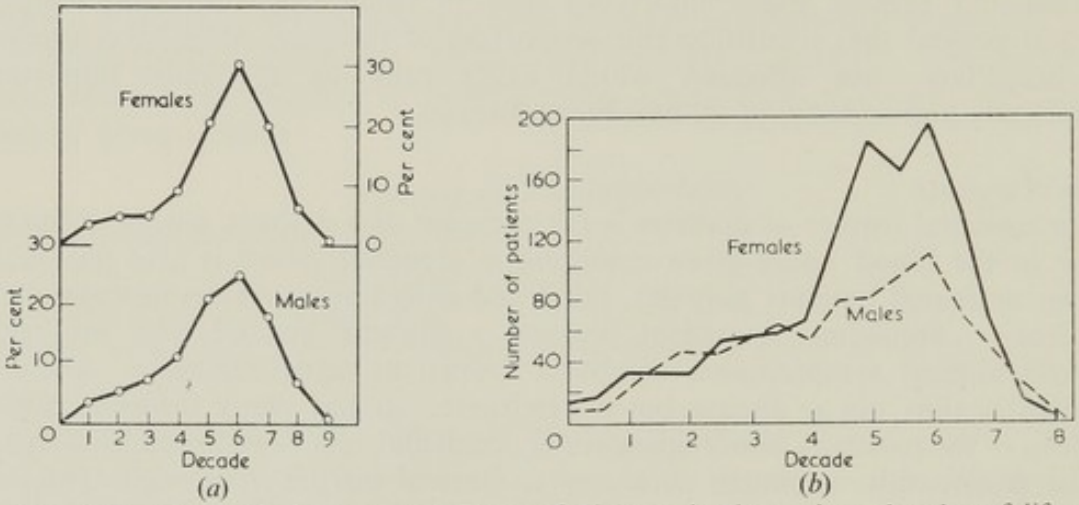

FIG. 305.—Onset of diabetes. (*a*) Onset of diabetes in the various decades of life. (*After Joslin.*) (*b*) Age at onset of 2,132 diabetics attending King's College Hospital 1930–47. (*After Harris.*)

is also the possibility that diabetics now have more children, and thus add to the number of diabetics. According to Joslin (1948) the frequency in the United States of America is from 3 to 7 per thousand. In other countries the rate is the same, or slightly lower—Finland 1·6, Sweden 2·5, Norway 3·8 to 4·3, United Kingdom 3–4 per thousand. From these figures, and evidence supplied by twin studies, the frequency of a hypothetic gene in the population can be estimated.

Some frequencies observed.—Wilkerson and Krall (1947) investigated the New England town of Oxford with a population of 4,983. In 3,516 persons analysis of urine and blood was carried out; 40 persons were known to be diabetics before the investigations, and 30 new cases were found. If the frequency of diabetes among the persons not examined is the same as among those examined, the total number should be 87, that is to say 17 per thousand, ranging from none among children under the age of 15 years to 51 per thousand in the age-group 65–74 years (women 69 per thousand, and men 52 per thousand). Among the eldest 97 per thousand were found, but this group is too small to allow any conclusions to be drawn.

Horstmann (1950) carried out an inquiry in the Danish county of Odense. Out of 174,396 persons 695 diabetics were found, that is to say 4 per thousand. The highest incidence was found among women in the age-group 60–79 years with 20–22 per

thousand. In this investigation only known cases are recorded. If the same social circumstances as in Oxford prevailed in Odense it might be expected that the figures would be doubled; this is not so. In Denmark everybody has to be insured against sickness so that medical attendance is free. Among the 30 new cases found in Oxford 25 showed clinical symptoms, 9 being severely affected, and 7 moderately. In Denmark, these 16 cases at least would probably have been known, but even if doubled the Danish figures do not reach the American.

These statistics only take into account living persons. Nevertheless, they show that if people who have a tendency to contract diabetes do not live longer than others the chance of getting diabetes is at least 1 to 5 per cent for men and 2 to 7 per cent for women.

Among identical twins investigated by Then Berg both were examined personally in 88 cases. It was known in every case that one twin was diabetic. Frank diabetes in the other twin was found in 26 cases, no diabetes in 39, and latent diabetes in 23 cases. If these proportions prevailed in the population as a whole, the number of diabetics would be double the actual figure found, but the studies by Joslin, among others, seem to show that while pathological curves are very common among relatives of diabetics, they do not often occur in the population as a whole.

The chance of developing diabetes is therefore in the order of 4–8 per cent. If all diabetes is assumed to be hereditary, partial penetrance must also be assumed. Consequently, an estimate of potential diabetics at 6 per cent of the American or Danish population would not be too high.

If the assumption of recessive inheritance is correct for all diabetes of obscure aetiology, the number of carriers of the gene in the population would be in the order of 25 per cent. Every fourth person would then be a transmitter of diabetes.

Social factors

Age and sex distribution.—The age incidence of diabetics by sex is shown in Fig. 305*a* and *b*. It will be seen that up to the age of 40 years the frequency is about the same in both sexes with a slight preponderance amongst males. Subsequently there is a female excess. Harris holds that the sex difference is determined by exogenous factors, as women generally tend to grow fatter than men so that the relative obesity of women would have the same significance as the excess of diabetes amongst the well-to-do. A more likely reason is that the hormonal imbalance seen at the menopause may unmask a diabetic disposition.

Racial predilection.—It is generally held that Jews are especially prone to diabetes and that this is a racial characteristic. It is, however, just as likely that the urban life of Jews and consequent more ready access to medical services may well explain such differences that have been observed. Negroes were once regarded as immune from diabetes; this is not the case. The presumed lower susceptibility of the Mongol races to diabetes is readily explained by the lack of medical facilities and consequent opportunities of observing such cases. It is perhaps true that the Latin races show a lesser number of diabetics than the Northern Europeans.

Concentration in towns.—There are more diabetics in towns than in the country. Horstmann has shown that this was not due to a difference in medical facilities and suggested that diabetics, who are often pyknic in type and social in their attitude, are prone to settle in towns.

Frequency of diabetes among relatives of diabetics

The first evidence of heredity in diabetes mellitus were the observations by many clinicians of increased incidence of disease among relatives of diabetics.

Of 3,500 diabetics seen by Umber, 26 per cent presented other cases in the family, whilst the incidence of diabetes amongst the relatives of non-diabetics was 3·8 per cent. Likewise, Cammidge found 28 per cent against 3·4 per cent. The number of hereditary cases found depends on the completeness of familial studies and the length of time since the occurrence of the first diabetic in a family. Thus, von Noorden found 25·4 per cent, Pannhorst 27 per cent, Priesel and Wagner 37 per cent, and Falta 37·7 per cent. Wilkerson and Krall, in their investigation at Oxford, New England, found that 38·6 per cent of diabetics and 18·2 per cent non-diabetics had a positive family history of diabetes; among the 13 diabetics less than 44 years of age, 8 had diabetes in the family. Bartels and Poulsen obtained a positive family in 57 per cent of the 86 juvenile diabetics cited below.

The method of recording familial cases is not very exact and, especially in a disease as common as diabetes, cases in more distant relatives may have arisen from other causes than in the propositus. Joslin, Dublin and Marks therefore compared parents and siblings of diabetics with the same relatives of non-diabetics. They obtained a statistically significant excess in the first group.

Twin studies

Apart from a number of isolated clinical records showing concordance in twins—material unsuitable for genetic analysis—there are 3 extensive studies, those by Pincus and White, Then Berg and by Lemser. They show substantially similar findings and are given as a combined series in Table I.

TABLE I

DIABETIC TWINS

(*After Then Berg; Lemser; and Pincus and White*)

	Total number	Concordant		Discordant	
		Number	Per cent	Number	Per cent
Identical twins – –	98	61	62·2	37	37·8
Fraternal twins – –	176	21	11·9	155	88·9

It will be seen that the incidence of concordance is 5 times as high in identical twins as in the fraternal twins. It would also appear that when identical twins both develop frank diabetes there is a tendency for the disease to develop in the same year—though there may be a difference of as much as 10 years or more in some cases (Lemser). Frequently, too, the severity of the affection is similar in identical twins. It is difficult to estimate penetrance accurately owing to the time lag in the development of frank diabetes in both partners of a pair of identical twins. In frank diabetes only, penetrance was found to be 36·7 per cent in these series, though it is undoubtedly higher.

Mode of inheritance (*Fig. 306*)

Diabetes is regarded by some as genetically heterogeneous, being sometimes determined by recessive genes and at other times by dominant genes. Hanhart, who has compiled a series of the more extensive and complete pedigrees in the

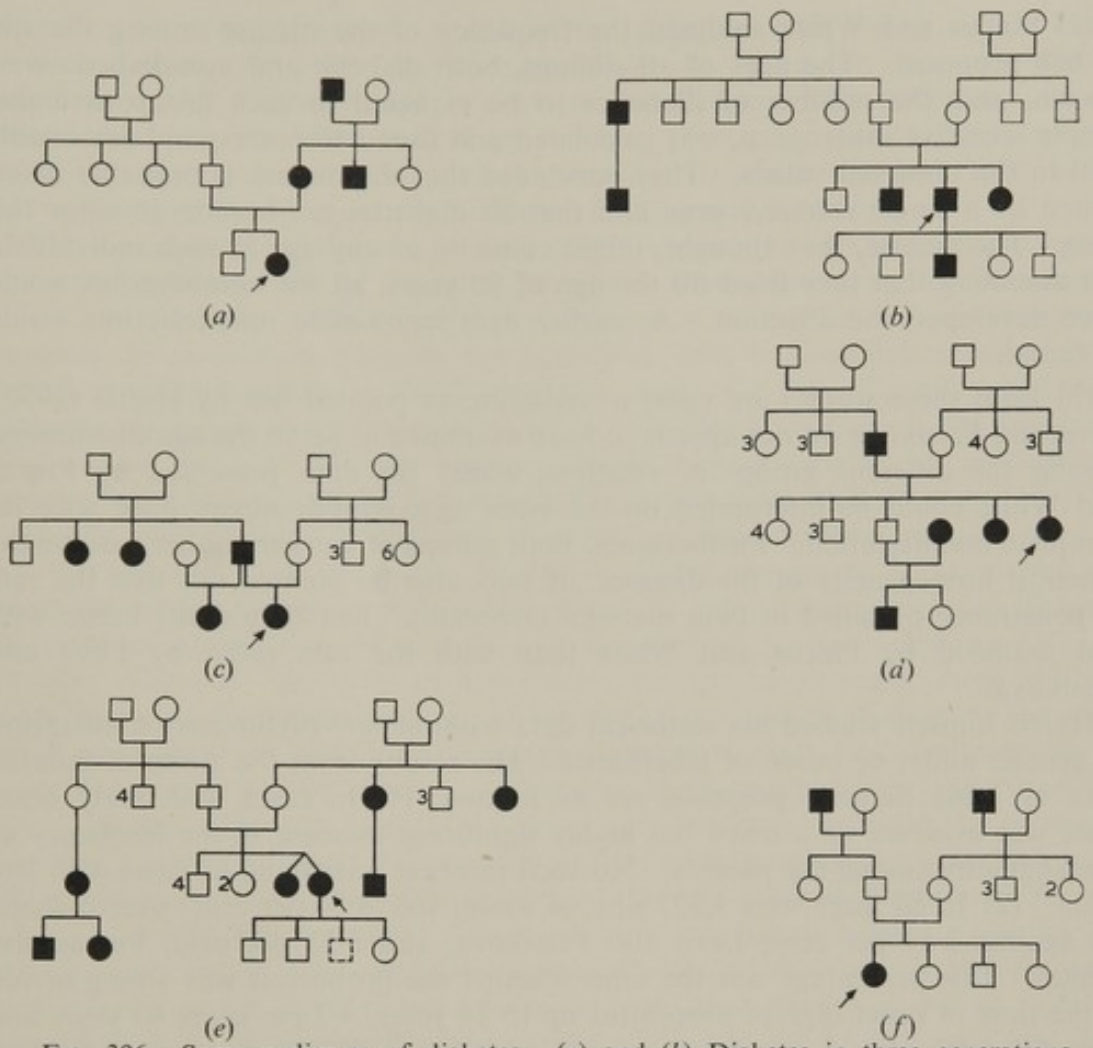

FIG. 306.—Some pedigrees of diabetes. (*a*) and (*b*) Diabetes in three generations. (*c*) and (*d*) Diabetes in half-sisters. (*e*) and (*f*) Diabetes in individuals with a family history of diabetes in both parents.

literature, considers that they can all be interpreted on the assumption that the disorder is genetically homogenous and is inherited in a simple recessive manner. As Falta and Pannhorst, amongst others, have pointed out, pedigrees of recessive diseases for which the gene is very common in the population will often seem dominant if only two or three generations are known. Moreover, families with many affected individuals are more likely to attract attention.

Genetically unselected material, which takes into account adequate distribution according to age in the families is essential for assessment. This is supplied by several studies:

(1) Levit and Pessikowa determined the frequency of the disease among the sibs, parents and other groups of relatives in 258 cases. They found that the frequency in the sibs was very similar to that in the parents, and they concluded that the disease is probably due to a single dominant gene with a low rate of manifestation (approximately 10 per cent). They pointed out that severe, moderate and mild cases might all occur in the same family, and they could see no evidence for subdivision of the cases on genetical grounds.

(2) Pincus and White analysed the frequency of the disease among the sibs of 658 propositi. The ages of all siblings, both diabetic and non-diabetic were known, and the number of diabetics to be expected in each group, assuming simple recessive inheritance, was calculated and found to correspond reasonably well to the observed values. They concluded that the disease is probably determined by a single recessive gene and that all diabetics are homozygous for this gene. The disease, they thought, might come on at any age in such individuals, but assuming that they lived till the age of 90 years, all the homozygotes would have developed the affection. At earlier ages incomplete manifestation would be found.

(3) Both these studies are open to criticism, as pointed out by Harris (1950). Levit and Pessikova do not appear to have examined in detail the age distribution among the different groups of relatives, whilst the data presented by Pincus and White could be interpreted on the basis of a semi-dominant gene with incomplete manifestation. Furthermore, both groups of workers rather assume the genetical homogeneity of the disease. It may also be pointed out that the rate of penetrance obtained in twin material (especially Then Berg's) fits better with that assumed by Pincus and White than with the rate given by Levit and Pessikova.

Harris himself studied his statistical data without any preliminary assumption of genetic unity, or mode of inheritance. His results from the study of familial data of 1,241 diabetic propositi are as follows: (1) In cases with early onset there was evidence of a small but highly significant increase in the frequency of consanguinity among the parents. No such increase was found in cases with late onset. (2) In all there were 3,827 sibs, of whom 166 (4·34 per cent) were diabetic (as against 3·59 per cent, Levit and Pessikova, and 5·53 per cent, Pincus and White). This percentage was the same whether the propositus was young or old at the time of onset (age of propositus up to 14 years, 4·7 per cent; 60 years and over, 4·4 per cent). A significant correlation between the age at onset of diabetes in propositi and in their sibs was found. It was estimated that about 7 per cent of the sibs of propositi aged under 30 years at onset may be expected to develop the disorder by the age of 40 years, while only about 1·3 per cent of the sibs of propositi who developed the disease after 30 years of age will do so by the age of 40 years. (3) Of 2,482 parents 125 (5·03 per cent) were known to be diabetic (as against 8·33 per cent Pincus and White, and 4·34 per cent Levit and Pessikova). There appeared to be little or no parent-child correlation of age of onset of the disease. (4) Less than 1 per cent of the children of propositi were found to be diabetic. It was estimated that about 1·4 per cent of children of a diabetic parent may be expected to develop the disease by the age of 40 years. Because the children studied were still quite young there was no information as to the expectation of these children developing the disease in later life. (5) If one or both parents were diabetic, there was a greater incidence of diabetics among the sibs (a finding also observed by Pincus and White).

The conclusion that must be drawn from Harris' work is that diabetes mellitus is not genetically homogeneous. The early onset and the late onset cases must be determined by different combinations of genes. On the other hand cases of late onset and mild diabetes occur not infrequently among the

parents and other relatives of the severe juvenile and young adult forms of the disease, although there appears to be little or no parent-child correlation with respect to age at onset of the disease. This evidence is hardly compatible with the view that there are two genetically distinct and separate diseases. Nor is it consistent with an explanation which seems to account for the variation in age at onset on the basis of autosomal modifiers.

Harris suggests that the severe early onset cases might represent homozygotes (recessive) while several of the mild, late onset forms, heterozygotes (dominant). It is, however, just as likely that the difference in the time of manifestation between the generations may be due in part at least to common recessive autosomal modifying genes or allelic modifiers, and that the different varieties of diabetes are due to an allelic series of genes. Furthermore, there is the possibility that mutant genes at different loci may bring about anomalies in carbohydrate metabolism which cannot be distinguished clinically from each other.

Bartels and Poulsen studied the frequency of late diabetic complications in 125 persons who had contracted the disease before the age of 35 years and had been followed in Hagedorn's clinic for at least 15 years. Reliable family histories could be obtained from 86 persons, 43 men and 43 women. Among 239 sibs 28 were diabetics. As only 16 had passed the age of 50 years, most of these must be considered juvenile cases. If the risk of contracting diabetes is the same in all ages for these sibs as for average diabetics it must be calculated that at least 25 per cent will be affected. According to Harris, however, this is not the case. In fact, after the lapse of 15 years very few new cases can be expected, provided there is no great difference in age between propositi and sibs. Among 172 parents 15 were diabetics (9 per cent). On the same assumption as for the sibs, it is calculated that about 12 per cent will develop diabetes; 13 among 344 grandparents (4 per cent) and 24 among 645 sibs of the parents (4·4 per cent) were known to be diabetic, but information on these groups is not so reliable. The children of the propositi were on the whole too young (52 were less than 24 years of age; 12 were between 25 and 34 years of age), and during the investigation there was one case of diabetes amongst them.

The material, though limited, consists solely of juvenile cases and covers a relatively long period. The investigation is being continued with cases of late onset. The proportion of diabetic individuals in the different groups of relatives (12 per cent among sibs, 9 per cent among parents, 4 per cent among grandparents and sibs of parents) is compatible with the assumption of recessivity.

Anticipation.—Some authors believe diabetic families to show anticipation. As the fertility of juvenile diabetics is greatly reduced and was especially so before the use of insulin, and since severe juvenile cases practically all come into hospitals, many pedigrees seem to show this. The phenomenon is not known to experimental geneticists. The concept of anticipation is probably based on a faulty collection of pedigrees.

THYROID GLAND

Endemic goitre and endemic cretinism show a familial concentration. This, however, is likely to be caused by the extraneous factors which produce the affection in particular areas and there is little evidence of any genetic predisposition.

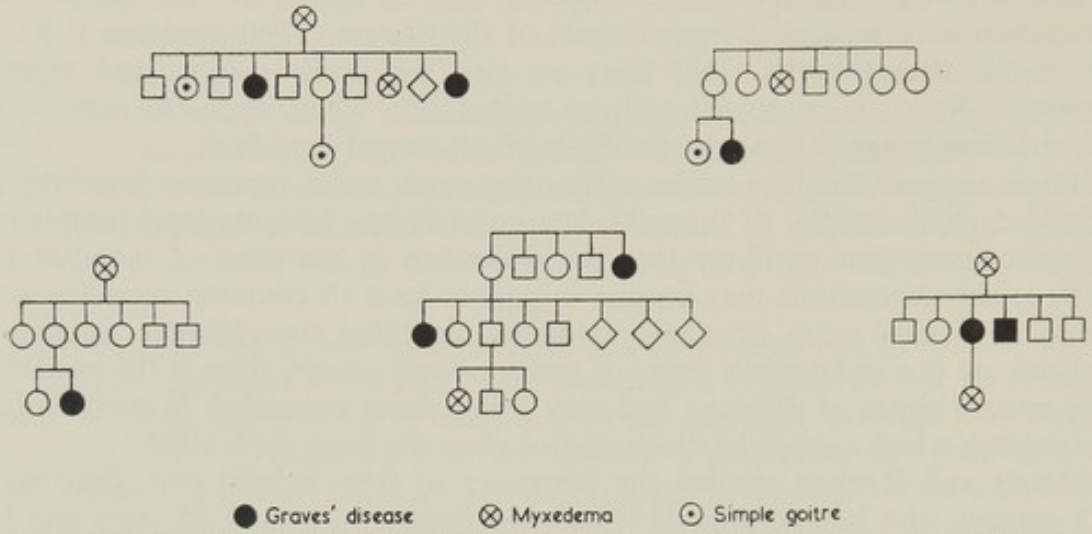

FIG. 307.—Families in which Graves' disease, myxoedema and simple goitre occur.

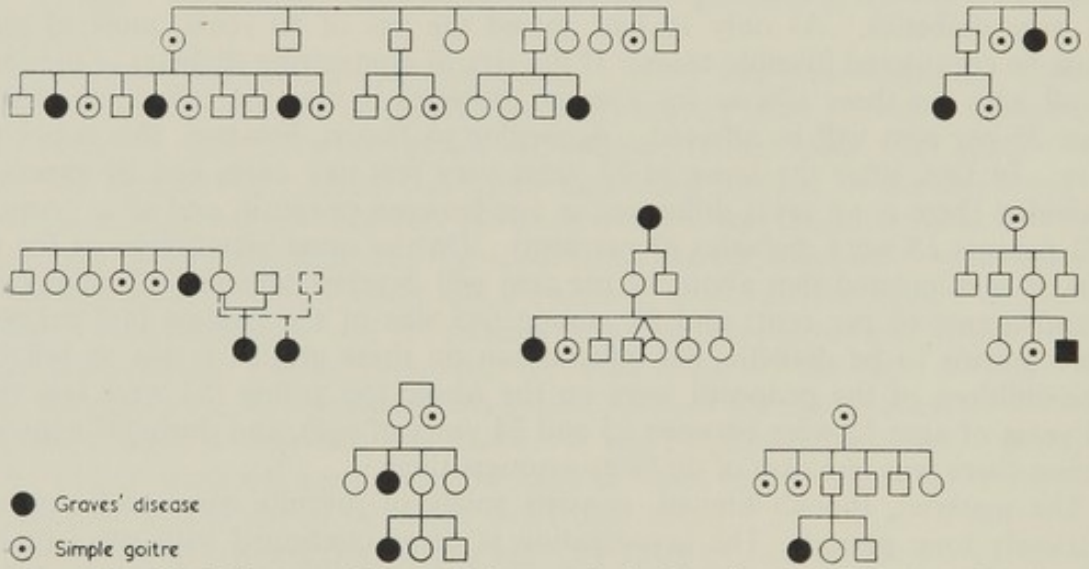

FIG. 308.—Multiple cases of Graves' disease and simple goitre in one family. (*The first of these pedigrees is after Bing.*)

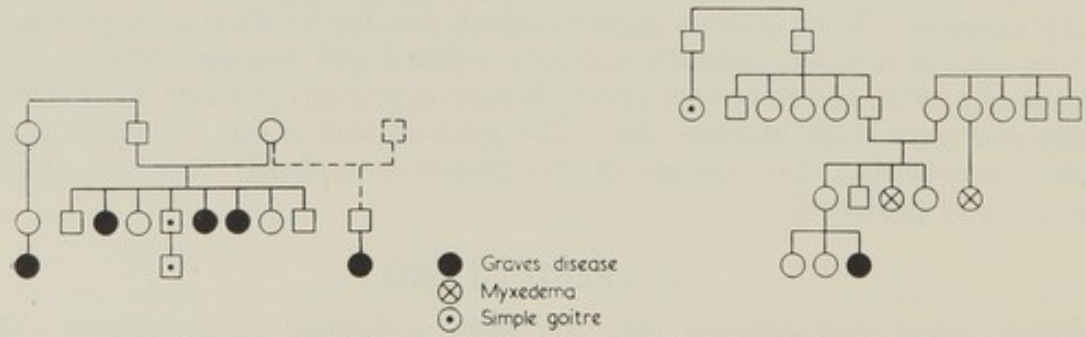

FIG. 309.—Families with a disposition to thyroid diseases on both sides.

In contrast, sporadic thyroid affections, such as simple goitre and the hypothyroid and hyperthyroid states, in spite of their sporadic tendency are probably often genetically determined (Figs. 307, 308 and 309).

Non-toxic goitre

From a study on endemic goitre in Switzerland, Eugster concluded that in a centre where the affection is endemic more than 90 per cent of the population are affected. Uniovular twins showed no greater concordance than dizygotic twins as to the number affected, though the anatomical picture tended to be more similar in uniovular twins—probably because of a similar reaction to the extraneous agent which he held to be responsible. That a constitutional factor underlies proneness to endemic goitre was seen from the fact that the further one went from an endemic centre the greater did the proportion of women to men become (in Danish material, the incidence was 35 women to one man.) It has been suggested that sex-limitation in an hereditary factor is significant.

A number of pedigrees of sporadic goitre occurring in several members of a family are available, and more systematic studies have been carried out by Bing in Denmark, and by Martin and Fisher in England. Bing's cases were collected in a part of the country free from endemic goitre. In material collected at two clinics in Copenhagen, Bing found that a family disposition was noted in some 20 per cent of cases and that such families often showed both simple and toxic goitre. He concluded that sporadic goitre was probably often inherited, and that this inheritance includes a tendency to all forms of thyroid disease. A considerably higher familial disposition was observed in the study of Martin and Fisher. They, too, found both simple and toxic goitre in the families. They also noted that the tendency to other cases of toxic goitre was greater in families with Graves' disease than in families with simple goitre. A fuller understanding of the extraneous factors producing non-toxic goitre is needed before any valid genetic conclusions can be drawn. If the available pedigrees are taken on their face value dominant inheritance is suggested for non-toxic goitre, but until studies on the incidence of non-toxic goitre in non-endemic areas are available it would seem to be rash to draw any conclusions on a hereditary factor.

Myxoedema

A number of observers have recorded the occurrence of myxoedema in siblings; discordance as to the occurrence of the affection has been observed in two or three pairs of twins.

In a series of 145 cases of sporadic cretinism, Lewis, Samuel and Galloway found one sibship with 4 cretins, and 2 more with 2 affected; in 12 further cases either myxoedema, simple or toxic goitre, were found in the family; and in 8 there were " sub-thyroid features " in either the father or the mother. In all they obtained a positive family history in 107 of their cases. In a series of 53 cases of myxoedema studied by Møller, 8 showed a familial disposition to myxoedema and 1 to other forms of thyroid disease. Likewise Jacobsen found a familial disposition to all forms of thyroid disease in 5 out of 9 cases of myxoedema. Fully controlled studies are needed.

Graves' disease

Since Romberg in 1851 recorded Graves' disease in twins many case reports on the familial occurrence of this affection have been published. These, however, are of limited value as the affection is common. Several fuller studies are available.

Levit examined 47 propositi with " Graves' disease or related affections ". In 17, a family disposition was found. He concluded that the classical form of Graves' disease and simple goitre are inherited in a dominant manner, with incomplete penetrance and with sex limitation to women, in whom the gene manifestation is 50 per cent. " Toxic goitre ", too, was probably inherited dominantly.

Lehmann studied fully 25 families and found hyperthyroid individuals in 15. In the remaining 10 families he found several individuals showing v. Bergmann's " thyroid stigmata ". The distribution of affected individuals in the families is seen in Table II. It should be pointed out, however, that Lehmann's definition of the hyperthyroid individual is rather liberal.

TABLE II

LEHMANN'S OBSERVATIONS ON 15 FAMILIES WITH GRAVES' DISEASE

	Number affected	Total number examined in the group
Parents	5	30
Siblings	16	69
Parents' siblings	2	65
Cousins	4	62
Siblings' children	3	76
Children	6	48
Grandchildren	2	22

Martin and Fisher studied the families of 90 propositi with Graves' disease. Their results are given in Table III. In the families a total of 20 cases of thyrotoxicosis and 16 of simple goitre were found (as against 13 and 39 respectively in 111 cases of non-toxic goitre previously discussed). They concluded that Graves' disease is probably inherited recessively. As the proportion of toxic cases in Graves' disease families is much greater than in goitre families, they suggest that the tendency is not for all thyroid diseases in general but for Graves' disease specifically.

TABLE III

MARTIN AND FISHER'S OBSERVATIONS ON 90 FAMILIES WITH GRAVES' DISEASE

	Graves' disease	Toxic goitre	Simple goitre	Goitre (? toxic)	Total
Mothers		1	5		6
Fathers					0
Sisters	8	2	3	3	16
Brothers	8				8
Sons					0
Daughters				1	1
Aunts	1			4	5

These studies are open to the objection that they did not evaluate the frequency of thyroid diseases in the general population—nor the age distribution of the relatives—a matter of importance in thyroid diseases—especially Graves' disease, with their onset in adult life.

TABLE IV

BARTELS' EXAMINATION OF 207 PROPOSITI WITH GRAVES' DISEASE

The groups of daughters and sons according to their young age are of little value in calculating the risk. Two different reduced figures—one for Graves' disease, the other for simple goitres—are given because the risk of simple goitre begins rather earlier in life than that of Graves' disease.

	Graves' disease	Simple goitre	Myxoedema	Number examined			Risk of developing		
				Total	Reduced for Graves' disease	Simple goitre	Graves' disease	Simple goitre	All goitres
Mothers –	6	10	1	201	188	191	3·5%	5·2%	8·7%
Sisters –	17	23		363	213	248	8·2%	9·7%	17·9%
Aunts –	14	18	1	667	554	581	2·7%	3·3%	5·9%
Daughters	2	8		137	22	47	9·0%	17·1%	26·1%
Fathers –				198					
Brothers –	3	2		377	227				
Uncles –	1			659	547				
Sons –		1		169	51				

Bartels followed up 207 propositi from two clinics in Copenhagen (Figs. 307, 308, 309 and Table IV). A distinction between Graves' disease and toxic goitre had not always been made, but it was possible to overcome this difficulty by special examinations. A family disposition was found in 47 per cent of the series as a whole, but was as high as 60 per cent in the families where the propositus showed Graves' disease as against 33 per cent where the propositus showed toxic goitre. Making the necessary allowance for the inequality in sex and age distribution, and estimating the risk of Graves' disease or toxic goitre by examining a control population, it was possible to assess the frequency of the gene for thyroid disease at 12·6 per cent (Bartels, 1941). Bartels concluded that Graves' disease is inherited in a recessive manner with partial penetrance and sex-limitation to women, and that the gene expresses itself either as Graves' disease, toxic goitre, or simple goitre, or perhaps myxoedema. The penetrance in women was estimated at between 50 and 100 per cent. These conclusions agree fairly well with the data obtained in studies on twins (Table V).

TABLE V

TWINS WITH GRAVES' DISEASE

	Total number	Concordant	Discordant
Identical twins – –	13	10	3
Fraternal twins – –	33	4	29
? Homologous – –		1	

A non-genetic form of Graves' disease

When he published his study on Graves' disease in 1941 the present author was inclined to believe that Graves' disease was always inherited, whilst sporadic simple and toxic goitre were partially conditioned by the same gene and partially by extraneous causes, but in the years 1941–45 there was something like an epidemic of thyrotoxicosis in Denmark, and many of these cases were undoubtedly toxic goitres indistinguishable from the classical form of Graves' disease, and lacked all evidence of any genetic background.

THE PARATHYROID GLANDS

Hypoparathyroidism (Parathyrogenous tetany, parathyrogenous epilepsy)

Parathyrogenous tetany generally arises after extirpation of goitres, but spontaneous cases—the so-called idiopathic hypoparathyroidism—also occur.

The frequency of spontaneous cases is unknown, and some hold that it varies with geographic and climatic factors. Lachmann found only 22 cases among patients admitted to Danish hospitals during a period of 15 years.

No systematic study on the inheritance of idiopathic hypoparathyroidism is available. In Lachmann's series three propositi were sibs (2 females, 1 male), and they had a sister who had died probably from the same affection; one brother was healthy, and the family history was clear. The remaining 19 cases were all sporadic. In one family goitre and diabetes mellitus were seen. Hoesch observed parathyrogenous epilepsy once over two and once over three generations, but the data are scanty. Sutphin, Allbright and McCune recorded a family with three out of 9 children affected. The parents were first cousins, and the family also showed familial Mediterranean target-oval cell anaemia. Three of 8 siblings with cataract presumably because of hypoparathyroidism are recorded by Vander Heydt, while Gifford also observed 4 siblings with cataract.

Whether spontaneous hypoparathyroidism is genetically determined, and if so, whether the affection is a single genetic entity, is still to be established.

Parathyroid adenoma

The occurrence of parathyroid adenoma in father and daughter, as also in two sisters, has been reported. These seem to be the only familial cases of hyperparathyroidism so far in the literature.

THE ADRENALS

Little is known of heredity in adrenal disease—perhaps for the reason that affections of these organs are relatively uncommon and diagnosis often difficult.

Phaeochromocytoma

Some 40 cases of phaeochromocytoma have been recorded as part of the syndrome of neurofibromatosis (von Recklinghausen's disease). Phaeochromocytoma must therefore be considered as inherited although it is not the tumour as such but the general disturbance that is inherited.

Calkins and Howard recorded a family in which a young woman and her maternal aunt both showed multiple phaeochromocytomas; her mother had died probably from the same affection. There was no evidence of neurofibromatoses.

Addison's disease

More than half the cases of Addison's disease are clearly due to exogeneous causes destroying the adrenals. The residual cases are caused by atrophy of the adrenal cortex, the origin of which is obscure. A few familial cases are known (Fahr and Reiche). A racial factor was suggested by Maranon, who states that the disease is rather frequent in Spain as well as in other countries with darkish-skinned inhabitants. Negroes do not appear to be specially prone to the disease, and such cases as occur are generally tuberculous in origin.

Other affections

Intersexuality

Werthemann (1941) recorded three sibs out of four and a distant relative who all died at the age of 4–12 weeks. At autopsy intersexuality and marked hyperplasia of the adrenal cortex was found. Similar findings have been recorded by others. This is more fully discussed elsewhere (page 524).

Cushing's syndrome

Heredity does not seem to play any part in Cushing's syndrome.

THE PITUITARY GLAND

Acromegaly

A few familial cases of acromegaly have been recorded. Uniovular twins with occurrence of acromegaly in only one partner has been recorded by Lewis and by Störrig and Lemser (1940). The few familial cases are probably chance occurrences.

Dystrophia adiposo-genitalis

Obesity and dystrophy of the sexual organs are seen in some cases of destructive lesions in the region of the pituitary gland and the hypothalamus—generally by tumours or inflammation.

Whether any other form exists is uncertain. Most so-called primary cases described in the literature are merely obesity in boys before puberty, and if untreated lead to little more than a slightly retarded puberty. An analogous phenomenon is sometimes seen in girls. Some authors hold that there is a familial disposition to this syndrome. Probably it has nothing to do with the pituitary.

The Laurence-Moon-Biedl syndrome is discussed elsewhere (page 248). It is uncertain whether the affection is of nervous or endocrine origin.

Pituitary dwarfism

Genuine pituitary dwarfism is rare, and nothing is known of any genetic aspect.

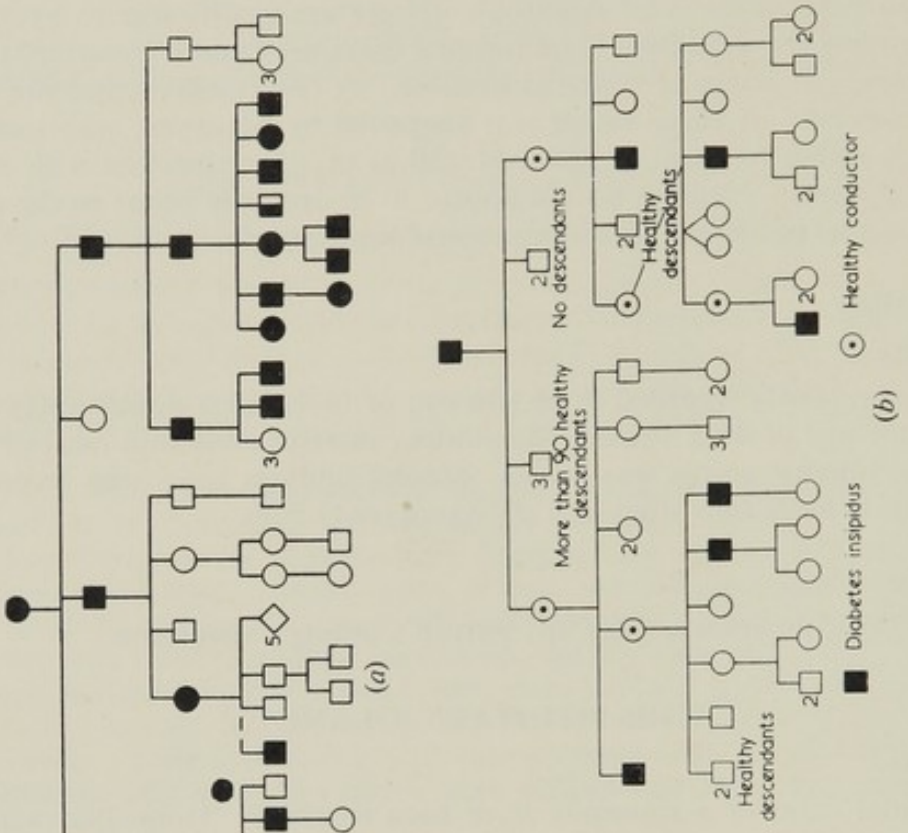

FIG. 310.—Diabetes insipidus. (*a*) Dominant inheritance. (*After Lauritzen (1893) and Ellermann (1939).*) (*b*) Recessive sex-linked inheritance. (*After Forssman (1945).*)

Diabetes insipidus

This is a rare affection though its exact frequency is unknown. In some hospital statistics it figures at 14–16 per 100,000 patients admitted.

Clinical features.—Most cases are caused by exogenous factors, fairly easily established in any particular case. That a hereditary form exists has, however, been known since 1841, when Lacombe published a family with eight affected members in two generations. The hereditary form is probably congenital and generally manifests itself in the first few weeks of life, though frequently it may be overlooked for some years. Occasionally it may set in later in life, and in women the affection may become manifest during pregnancy. Acquired cases generally set in in adult life. The inherited form does not affect health and many of the reported individuals have lived to old age. The prognosis in the acquired type depends on the underlying condition. Only a few hereditary cases have come to autopsy. They showed a diminution of the number of cells in the supra-optic nuclei, or a diminution of the neural elements in the posterior lobe of the pituitary and in the supra-optic-pituitary tract or both. In the different families studied the affection showed considerable variation in severity and in reaction to posterior pituitary extracts.

Heredity.—The extensive pedigree begun by Weil in 1884 and brought up to date by Camerer in 1935 showed autosomal inheritance. In this, as in most of the extensive pedigrees (Fig. 310*a*), there was a male excess. The large Swedish family published by Forsman in 1945 (Fig. 310*b*) showed recessive sex-linkage; women were seldom affected and always much more mildly. That there is, however, a dominant autosomal type is undoubted, and is well shown by the Weil-Camerer pedigree in which there were 37 affected members over six generations; and in three other pedigrees recording affected over five generations. In Forsman's family, haemophilia and colour-blindness did not occur so that linkage or crossing-over could not be studied. The exact status of isolated cases is not always clear.

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CHAPTER 27

INFECTIOUS DISEASES

ERNST HANHART

THE STILL unsolved problem as to whether conjugal metasyphilis is due to neurotropism of certain strains of *Spirochaeta pallida* or to coincidences of particular human constitutions, illustrates the difficulty seen in almost every infectious disease, for we have to establish the inherited qualities of the host as well as of the guest. Both host and guest consist of living substance depending on each other and capable of evolution, and nowhere in genetics are relations more complex and less stable than in the processes of adaptation between macro-organisms and micro-organisms. The embryopathies—specifically localized lesions quite unlike the symptoms of infectious disease in the pregnant mother—are illustrative of the significance of one of these variables, the time factor. The other variables are no less far-reaching and complex.

INFECTION, IMMUNITY AND NATURAL RESISTANCE

The nature of infectious disease

Anthropocentric views on the nature of infection have dominated medical thought. Bacteriologists have come to recognize infection as a biological phenomenon—the interaction between micro-organisms and macro-organisms—and have stressed that very few indeed of the total number of species of micro-organisms are significant to man from the point of view of infectious disease. Each macro-organism is full of harmless parasites and saprophytes and pathogenicity is not equivalent with parasitism or saprophytism; in fact there is a continuous range extending between these two, for some organisms may be parasitic under certain conditions and pathogenic under others. Clinically, bacteriology provides many such examples, and a striking instance in which the time factor predominates is seen in the case of the spirochaete *Borrelia* which is pathogenic to the embryo of the fowl, but only over a few days. Other aspects of the continuous range of action are seen from the fact that a pathogenic strain is not always equally virulent, nor is a susceptible organism always equally sensitive. It has been suggested by Burnet (1946) that virulence may be the result of mutation-producing enzymes, especially hyaluronidase, capable of dissolving the intracellular substance.

Whilst infection can be regarded as the settlement, growth and multiplication of micro-organisms in macro-organisms (Doerr), an infectious disease is a more difficult concept to establish. We speak of disease when the reactions of the host are more important than those of the microbes.

Immunity

Immunity is a specific alteration of an organism, generally lasting throughout life. It has been suggested that it is a result of a somatic mutation. The different

organs react differently to one and the same infectious agent. Its acid secretions give the skin a protective mechanism against organisms sensitive to acids, but the suggestion that there is a close relationship between the skin and the formation of antibodies does not seem well founded: the amount of antibodies in the serum is not an absolute measure of the degree of immunity, and humoral immunity is not the same as the immunity of the organism as a whole.

Natural resistance

Acquired immunity is a personal quality and some factors, such as the reaction of the sympathetic nervous system, the alarm reaction of Selye, phagocytosis, leucocytosis and various thermal labile and thermal stabile factors, have been recognized as possible agencies. Natural resistance is, in contrast, never the consequence of a microbiotic reaction, but like the converse state of susceptibility is a hereditary quality of a species. Many examples are known from clinical and comparative bacteriology. Cold-blooded animals are less prone to infectious disease than the warm-blooded variety. Frogs and birds are not susceptible to infection by *B. anthracis*, but this lack of susceptibility is due entirely to such a relatively simple factor as the temperature of the animals, for frogs can be made susceptible by raising their temperature, and birds also by having their temperature reduced. Generally, matters are more complex. Differences in natural resistance and susceptibility may occur within closely related species. White mice are said to be more sensitive to streptococcal and pneumococcal infections than mice of other colours. Even in the same species selection can determine susceptibility: mortality from infection of *Salmonella aertrycke* has been reduced from 82·3 per cent in the first generation to 24·7 per cent in the sixth generation by selective inbreeding (Schott, 1932). The Asiatic mouse is susceptible to *B. piliformis*, and the common mouse resistant to it. In crossbreeds, resistance to this liver disease segregated as a single dominant factor (Gowen and Schott, 1933). A striking application of such observations is seen in the Santa Gertrudis race of Texas cattle. This has been deliberately evolved to reduce susceptibility to foot and mouth disease, anthrax and Texas fever by breeding ordinary cattle, which are very prone to it with Zebu cattle, which show considerable resistance to these infections.

Racial predisposition in man

True racial predisposition to infectious disease hardly exists in man for there are no true races. None the less, there are various degrees of susceptibility owing to selection. Negroes are supposed to be immune to yellow fever, and Japanese to scarlet fever—the latter is rather unlikely since scarlet fever is common in Chinese. Smallpox, once exceedingly fatal to American Indians is now relatively mild in Mexico. The protection that Eskimos enjoy against infectious disease disappears in temperate climates. In contrast, the relative immunity of Chinese to *B. tetanus* seems to be due to a long period of selection. In the Maya Indians of Yucatan syphilis runs a very mild course, generally lacking neurological complications. It is more severe in Mestizos (hybrids with white), but severe epidemics have been observed in other Indian tribes. In the Fiji Islands no less than 40,000 of the 150,000 inhabitants died from measles when this infection was first introduced there. In chronic infectious disease the severity diminishes with its frequency;

this is seen in tuberculosis—the high sensitivity of Kalmucks, Indians and Negroes is largely the result of the previous isolation from tuberculosis.

Individual factors

An adequate reticulo-endothelial system seems to give considerable protection against bacterial intruders. The achondrodystrophic dwarf with his obviously strong mesodermal tissues is particularly resistant to infectious diseases, whilst mongoloid individuals show the opposite, though occasionally Mongolian idiots show an exceptionally good resistance to infection as I have noted in an examination of about 1,000 such patients. Attempts to correlate a particular resistance or susceptibility to infectious disease with such physical body types as classified by Kretschmer and by Sheldon are hardly valid, for these body types are only variations of the normal. Some definite feature, such as a state of hormonal deficiency, seems necessary, and it is noteworthy that there is no increase of susceptibility to infectious disease in infantile or juvenile diabetics who have been adequately treated.

The so-called exudative diathesis of Czerny has been held to predispose to infectious disease owing to an increased permeability of the mucous membranes, and has been recorded as a dominant condition. The concept is, however, rather vague and the aspects it stresses are seen in the so-called allergic diathesis with which, however, it cannot be identified. The diathesis to the allergies is determined by a dominant gene which facilitates both sensitization and the formation of specific antibodies, mostly, but not exclusively, against substances alien to the tissues of a macro-organism. As such it undoubtedly plays an important part in the development and course of infectious disease. In the author's experience strongly allergic individuals show a marked tendency to contract infections, and also a considerable facility to dispose of them. Severe reactions may, however, occur in allergic individuals. The author knows of an allergic woman who died at 34 years of age from infective endocarditis, and lost her only son from necrotizing streptococcal angina setting in on a severe allergic eczema.

It is possible that a peculiarity of the nervous system, as distinct from the humoral capacity to form antibodies, plays a significant part—as is suggested by the fact that individuals who have had epidemic encephalitis show peculiar reactions to infections.

The background to infection

Experience with the many thousands of war victims of recent years suffering from exhaustion, depletion and alimentary disturbances has shown that the incidence of the acute anginas, otitis media and endocarditis, was not higher in them than in the normal population. It would seem that the fundamental background to susceptibility to infectious disease consists of one's inborn constitution and the changes that every infectious disease produces in it. Some infections, like many of the virus infections, produce a lifelong immunity, others such as typhoid fever produce an immunity lasting for a few years, whilst still others produce a definite predisposition to re-infection. During the influenza epidemic of 1918–20 it was common experience that in isolated populations the infection ran a more severe course, whilst individuals liable to minor infections generally did better than those not so disposed. It is likely that the same holds good for

poliomyelitis, and there is considerable evidence that a combination of infections sometimes has a favourable result. Thus, a favourable influence from a superadded infection—such as scarlet fever, erysipelas, malaria and even gonorrhoea—has been observed in sympathetic ophthalmia, trachoma, and ocular tuberculosis. The malarial treatment in neurosyphilis is a further illustration.

SOME INDIVIDUAL INFECTIONS

Some virus diseases

The six virus diseases discussed here all show the characteristic trait of complete immunity against further attack. Only exceptionally is such immunity not achieved.

Smallpox

Susceptibility to smallpox is almost universal. A very small number of people appear to be insusceptible throughout life, whilst temporary immunity is developed by patients with measles, scarlet fever or typhoid fever. According to Paschen, Negroes occasionally develop a second and even a third attack of smallpox. When the infection was first introduced in Iceland in 1707 some 18,000 of the 50,000 inhabitants died.

Resistance to vaccination against smallpox has been observed as a familial trait.

Chickenpox

Susceptibility is even higher than in smallpox, but twin studies have shown that there is a hereditary resistance to infection.

Measles

Susceptibility to measles is almost universal. Abortive cases generally occur in the first 6 months of life and temporary resistance may develop later. Immunity is lifelong. Rarely there is resistance to the infection, and this would appear to be genetically determined, for late onset—after the sixth year of life—runs in families, and dizygotic twins are more often discordant than uniovular twins in their proneness to the infection. A familial tendency to a second attack of measles has been observed.

Rubella

Susceptibility is less common with rubella than with measles. Onset is generally between the second and tenth year of life, but is also not infrequent in adult life. Immunity is lasting. Nothing is known of any hereditary influences in predisposition or resistance to the infection.

This infection has a special genetic interest owing to the embryopathies it produces resulting in phenocopies of genetic disease.

Mumps

Susceptibility is considerably less than for the other infections considered Studies on twins suggest genetic factors, both for average course of the infection and for complications observed, especially for the relatively rare cases of meningitis without involvement of the salivary glands (Paddock).

Poliomyelitis

The susceptibility of this affection is probably high, but only 1 : 2,000 of the

population contract it, and of these only 1 : 100 show paralytic symptoms. Furthermore, against 100 typical cases with palsies, there are some 800–900 abortive, but clinically detectable, cases. In town populations it is children who are apt to be infected, and middle-aged adults in rural populations—probably because of differences in contact. The affection is more lethal to adults than to children, the respective mortality being about 30 per cent and 9 per cent. There is a male excess as in other neurotropic infections. In Denmark, people of fair complexion appear to be less disposed than people with more pigment. Endocrine disturbances appear to be predisposing factors; and the affection is said to be more common in those with high and narrow palates. Different constitutional types have been described as being especially prone to poliomyelitis. It has also been suggested that there is an excess of people with blood group O, and a deficiency with blood group A in those who contract the affection. Some individuals develop immunity particularly rapidly. Very rarely a second attack may occur. In contrast to other virus diseases, the severity and frequency of epidemics of the affection seem to be increasing. Poliomyelitis may produce embryopathies similar to those seen with rubella (Tondurg).

Bacterial and other infections

Diphtheria

At the present time only 10–20 per cent of the population contract diphtheria, but many cases are sub-clinical. The virulence of the organism appears to vary. The faculty to develop antibodies against the micro-organism is in part determined genetically, as is suggested by studies with the Schick test. In one series the incidence of diphtheria in children of parents who had not suffered from diphtheria was 8·5 per cent as against 15·4 per cent and 19·6 per cent respectively in children of parents, one or both of whom had had diphtheria. In only three cases did one of the parents have the infection at the same time as the child. There was no difference in incidence in relation to the different blood groups. Individuals with fair complexion appeared to be rather more predisposed.

Scarlet fever

White races show a susceptibility similar to that for diphtheria. An index for the degree of immunity is given by the Dick test, whilst the index of contagion according to de Rudder is 0·35–0·4. In Thomshaven, in the Faroe Islands, where there had not been an outbreak of scarlet fever for 57 years, 38 per cent of the population contracted scarlet fever during an epidemic in 1873–5. In the second outbreak in 1875 no less than 99 per cent of the people previously uninfected contracted scarlet fever. The possibility of a genetic factor is indicated by the fact that if parents had not had scarlet fever 11·3 per cent of the children contracted it, as against 16·1 per cent and 32·5 per cent respectively of children with one or both parents previously affected. Studies on twins are also suggestive. It is likely that such complications as nephritis occurring in the third week are genetically determined. Susceptibility and resistance to scarlet fever do not seem to be linked to any blood group.

Erysipelas

Here recurrence is common. A pedigree is on record showing cases over three generations.

Pneumonia

With pneumonia, too, there is a tendency to recurrence, and whilst environmental factors are important, hereditary influences appear likely. Occasionally pneumonia is concentrated in sibships and it has been recorded over three generations. Individuals with many repeated attacks are not uncommon.

Typhoid fever

Some 80 per cent of cases occur between the ages of 15–35 years, fortunately so, for the affection is particularly dangerous in the very young and very old. A fatal outcome has been recorded as occurring more commonly in strong individuals. Obesity appears to be an unfavourable factor. Complications, such as epistaxis, encephalitis, and psychosis appear to be determined by the genetic background. Like pneumonia, typhoid fever is an outstanding example of the interaction between host and guest as the determining factor in the outcome of the infection

Rheumatic fever

This is discussed on page 437.

Tuberculosis

Once regarded as an hereditary affection, the discovery of its causative agent led to the view that differences in the clinical appearances of the affection in different individuals were entirely conditioned by the quantity and quality of the bacillus. That different strains of the bacillus do show considerable differences in virulence is known from observations on the retention of virulence by some particular strains through very many direct passages from one guinea-pig to another. None the less, there are constitutional factors which influence the reaction of the individual to the infecting agent. It is generally held that almost all adults show evidence of infection earlier in life, and it has also been held that delayed infection, that is to say, a first infection in adult life, leads more quickly to clinical complications. Re-infection is apparently not uncommon.

Evidence for constitutional factors other than age is available from the study of different families under similar conditions. In some families the affection runs a benign course, and in others a severe course. A constitutional factor is also suggested by the widespread experience that red-haired individuals—as distinct from individuals with Titian hair—are predisposed to a severe course of tuberculosis; this probably also applies to individuals inclined to freckling. There does not appear to be any greater tendency to tuberculosis on the part of patients with otosclerosis, or on the part of individuals of the leptosome body-build—a normal variant which is unrelated to the Hippocrates habitus phthisicus, or to any other trait of asthenia. There is likewise no correlation with schizophrenia or schizoid type. It has been suggested that the asthenic constitution is the result and not the cause of a tuberculous infection early in childhood.

From their studies on twins, Diehl and von Verschuer have concluded that a hereditary disposition to tuberculosis depends on 2 particular genes; when these are lacking there is good natural resistance. Marked concordance is sometimes observed, thus a pair of uniovular twins both developed tuberculosis of the calcaneous at an interval of 4 years. A monozygotic pair developed left-sided renal tuberculosis with an interval of 9 years; one had epididymal tuberculosis

13 years before his kidney lesion and the other some time after developing the kidney lesion. The localization of tuberculosis occasionally presents unusual features. Some families show a concentration of urogenital tuberculosis, whilst others show a concentration of such infrequent forms of tuberculosis as those of the joints or the skin. Erythema nodosum has likewise been observed concentrated in certain families.

As distinct from these suggestions that there is a specific organ susceptibility to tuberculosis, there is the view that tuberculous infection is an aspect of inborn weakness to certain diseases—a view supported by observations including the author's own that unselected tuberculous patients show a considerable number of constitutional anomalies. Whether there is a specific or a non-specific genetic background is a complex problem which cannot as yet be answered. Breeding experiments with guinea-pigs have shown hereditary resistance to tuberculosis. That these differences are in fact transmitted is suggested by the work of Diehl (1941) who by inbreeding 2 different strains of rabbits with a different susceptibility to the affection could isolate over 4 generations 2 distinct clinical types of reactions.

Leprosy

This once common disease was at one time regarded as the result of infected cereals. Steiniger (1941) found conjugal cases only exceptionally, whilst in pedigrees over 5 generations blood relations were frequently affected. There are several pedigrees which suggest dominant inheritance. Reports from areas where leprosy is still fairly prevalent give conflicting evidence as to the accumulation of this affection in certain families and in certain regions.

It would appear that those susceptible to leprosy are also likely to be susceptible to tuberculosis.

Toxoplasmosis

According to Paul (1951) a familial disposition to exogenous affections of the central nervous system is an underlying cause for the development of the encephalomyelitis of toxoplasmosis.

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CHAPTER 28

ALLERGY

MICHAEL SCHWARTZ

BY ALLERGY is meant an altered response to specific antibodies. The term was coined in 1906 by v. Pirquet, but the phenomenon itself was first described by Richet in 1902 under the name of anaphylaxis. The concept of allergy includes: anaphylaxis, immunity, allergic diseases and latent allergy.

The term anaphylaxis is restricted to an artificial condition produced in animals and is thus outside the scope of the present chapter, whilst immunity in the infectious diseases is discussed elsewhere (page 544).

GENERAL CONSIDERATIONS

Allergic diseases

The term allergic diseases dates back to the beginning of the century, when Wolff-Eisener (1906) suggested that hay fever was an allergic disease, and in (1907) that urticaria might be so too, whilst Meltzer (1910) regarded asthma as an anaphylactic disease. Since then eczema, migraine, angioneurotic oedema, epilepsy, polyarthritis (rheumatoid arthritis, rheumatic fever, gout), certain gastro-intestinal disorders and many other affections have been described as allergic—not always on good grounds.

Since allergic antibodies are presumed to be ubiquitous, allergic reactions should occur anywhere in the body. Allergic reactions have, in fact, been reported in practically every system of organs such as the eye (conjunctivitis, choroiditis, cataract), the ear (otitis media, Menière's disease), the heart (myocarditis), peripheral vessels (periarteritis nodosa, thrombo-angiitis obliterans), the central nervous system (multiple sclerosis) and in other systems and tissues.

In actual fact, only one disease—hay fever—is due to allergy in all cases. In all the other diseases ascribed to allergy such as asthma, eczema, urticaria and others, an allergic genesis is probable in many, but not in all cases. Thus, urticaria which is characterized by a special type of reaction on the part of the skin is not always a specific of antigen-antibody reaction; it may be produced by morphine, codeine and other agents. It is therefore not possible to speak of " the allergic diseases " as a specific entity, nor of heredity of allergic diseases as a whole. This point of view, however, is not generally accepted, and most workers still interpret allergic diseases as a whole (a whole, of course, with varied contents) in which diseases such as hay fever, urticaria and migraine are considered " allergic equivalents ".

Heredity in allergic diseases

Although the allergic diseases are ill-defined as a group, several of the affections are no doubt inherited. The familial occurrence of asthma was recognized by

Sir John Floyer as early as 1698, and Salter in 1860 found 40 per cent of his cases to be familial. Likewise, the familial occurrence of hay fever is well recognized. Angioneurotic oedema (Quincke) is known in a typical inherited form, and migraine—the allergic genesis of which is subject to discussion—has been acknowledged as an hereditary disorder for at least 100 years.

After the concept of allergic diseases was set up, many investigators (Cooke and Vander Veer (1916), Atkinson (1920), Spain and Cooke (1924), Balyeat (1928), Bray (1930), Hanhart (1936, 1943), Edgren (1943) and others) tried to demonstrate the inheritance of allergic diseases by means of a variety of propositus materials. In such studies the incidence of allergic disposition was found in some 50–70 per cent of allergic subjects as compared with an incidence of 5–10 per cent in normal subjects. These values are taken to mean that allergic diseases are inherited. On rather indefinite evidence, some have maintained that the heavier the allergic inheritance, the earlier the age at the onset of allergic disease.

There is no agreement as to what is inherited. Most observers hold that it is only the tendency to be sensitized that is inherited, and that it is chance or possibly a special " localization factor "—as shown by Clarke and his associates in the case of asthma and hay fever—that determines the type of allergic disease in any particular individual. This view comes up against the difficulty that the capacity of being sensitized is by no means confined to persons with allergic disease. Everybody can be sensitized with eczematogenic substances (such as primin from the plant *Primula obconia*) as well as to substances giving immediate wheal skin reactions (such as extract of ascaris and species of different sera (serum sickness)).

It is generally agreed that the inheritance is dominant, but the available figures do not conform entirely to simple dominance. On Spain and Cooke's material, Wiener and his associates (1936) suggested that the gene for allergy is recessive (h), and that the genotype Hh occurs in two phenotypes—some of the carriers developing allergic disease (always after puberty) and others never showing manifest allergy. It is doubtful, however, whether the development of allergic disease before or after puberty depends on the degree of allergic predisposition. It has been pointed out by Ratner (1941) that this phenomenon is apparent only in mixed propositus materials including many cases of hay fever.

Twin studies

The heredity of asthma, hay fever, migraine and urticaria has been studied systematically by Spaich and Ostertag (1936) who found a considerably higher concordance among monozygotic twins than among dizygotic twins of the same sex. This applies to the individual diseases as well as to the 4 conditions as a whole.

The literature contains reports of at least 27 further cases of asthma occurring in monozygotic twins; of these, 22 exhibited concordance with regard to asthma and 2 more concordance with regard to allergic disease as a whole.

The need for caution

These studies strongly indicate the significance of hereditary factors in the development of these affections. None the less, not all workers accept these

views. Ratner (1937) did not observe a more marked allergic disposition among 250 asthmatic children than among 315 normal children. Several authors have reported so high an incidence of allergic diseases among the normal population (Vaughan (1934) 58 per cent; Rowe (1934) 35 per cent; Service (1934) 22·7 per cent) that every person must be presumed to be affected with major or minor allergic disposition.

Dahlberg (1939) concluded rather pessimistically: " The investigations reported hitherto into the heredity of allergy have . . . afforded only meagre results. They give one the vague impression that an hereditary predisposition must play a certain rôle, but do not convey any clear idea as to the extent of this rôle. Neither is the mechanism of this heredity clear."

THE ATOPIC DISEASES

Coca (1923) advanced the view that some of the allergic diseases occupied an exceptional position in several respects, having in particular a common hereditary basis. These diseases were asthma and hay fever. Later, he added vasomotor rhinitis and Besnier's prurigo (atopic dermatitis) and suggested the name atopic diseases (atopia = a strange disease) for the group. Coca's views, though severely criticized, have proved extremely viable, and the study recorded here seems to support it.

TABLE I

DISEASES FOUND AMONG THE RELATIVES OF 191 ASTHMATICS AND 200 NORMAL SUBJECTS. THE STUDY COMPRISES ONLY THOSE RELATIVES WITH WHOM THE AUTHOR HAS BEEN IN PERSONAL CONTACT

	Asthmatics (No. affected)				Normal Subjects (No. affected)			
	(191 propositi). A total of 1,634 relatives (777 males and 857 females) were examined				(200 propositi). A total of 1,790 relatives (855 males and 935 females) were examined			
Affection	Males	Per-centage	Females	Per-centage	Males	Per-centage	Females	Per-centage
Asthma	48	6·19	60	7·0	9	1·05	9	0·96
Vasomotor rhinitis	35	4·51	67	7·82	10	1·22	15	1·60
Besnier's prurigo (atopic dermatitis)	5	0·6	6	0·4	—	—	1	—
Hay fever	8	1·0	6	0·7	2	0·2	4	0·4
Urticaria	40	5·15	94	10·9	53	6·20	76	8·15
Eczema	40	5·15	50	5·8	33	3·86	49	5·25
Migraine	20	2·5	65	7·6	13	1·52	61	6·54
Angioneurotic oedema	9	1·2	28	3·3	9	1·0	17	1·8
Psoriasis	13	1·7	12	1·4	13	1·52	14	1·5
Gastro-intestinal allergy	1	—	2	—	1	—	2	—
Ichthyosis	1	—	1	—	—	—	3	—
Epilepsy	—	—	—	—	—	—	4	—

Among a propositus material of 191 asthmatics (87 females and 104 males) at all ages, I collected information about a number of more or less allergic diseases in the family through 4 generations, grandparents, parents and their siblings, the propositi's own

siblings and the propositi's children. The study covered all the living members of the families and included the following diseases: asthma, vasomotor rhinitis, hay fever, Besnier's prurigo (atopic dermatitis), eczema, urticaria, migraine, angioneurotic oedema, psoriasis, gastro-intestinal allergic disorders, ichthyosis and epilepsy.

As a control series, 200 healthy persons of exactly the same age and sex distribution as the asthmatics and their families were studied. A summary of the findings is given in Table I.

A further statistical analysis of the results given in Table I shows that the relatives of the asthmatics showed a significantly increased incidence of asthma, vasomotor rhinitis, and Besnier's prurigo in addition to urticaria and angioneurotic oedema among the females. With regard to hay fever, the incidence among the relatives of the asthmatics was not significantly higher than among those of the normal subjects, but there was a marked tendency in this direction. There was no definite difference in the incidence of any of the remaining diseases in the 2 groups.

Since the 2 groups of relatives have been examined in the same way by the same examiner, and since they are comparable in every respect, it must be concluded that at least asthma, vasomotor rhinitis, and Besnier's prurigo are hereditary and genetically related. To this group hay fever may be added. This is indicated by all the studies reported in the literature, but as hay fever is relatively uncommon in Denmark, the present material does not show this with statistical certainty.

The increased incidence of urticaria and angioneurotic oedema among the females only is puzzling. Since it occurred only within a few groups of relatives and not a trace of it among the males, it may have been due to chance, or possibly to exogeneous factors.

Mode of inheritance

The pedigrees obtained in this study show that asthma, vasomotor rhinitis, Besnier's prurigo and hay fever may be traced through the generations, while the other diseases occur sporadically (several of them are quite common) and without any constant relation to the four atopic diseases. Moreover, the pedigrees show that the inheritance is dominant, but with incomplete penetrance (Fig. 311).

Unilateral allergic (atopic) predisposition was found in 89 out of 191 asthmatics, bilateral in 6, and no predisposition in the remaining 96. In this series there was no difference between the age of onset of asthma in the groups with and without allergic (atopic) disposition, and atopic disease was inherited with equal frequency from the paternal as well as maternal side. The latter finding is of interest, since it has been maintained that extra-chromosomal heredity may take place through the mother due to placental transmission of specific antibodies *in utero*, so that allergic disease was supposed to be inherited more often from the maternal than paternal side. This phenomenon is well known from guinea-pig experiments, but has never been shown beyond doubt in human materials, and there is nothing in the present study to support it.

The penetrance of the gene governing asthma, vasomotor rhinitis, Besnier's prurigo, and hay fever may be calculated from this series as about 40 per cent. Among these, about 65 per cent of the cases manifest themselves as asthma, the remainder as vasomotor rhinitis, Besnier's prurigo, or hay fever. Moreover, these diseases may often coexist in the same person.

The propositus material of this series consisted of asthmatics, and it is seen that a certain " localization factor " was demonstrable for asthma. This accords with the findings of Clarke and his associates in asthma as well as hay fever.

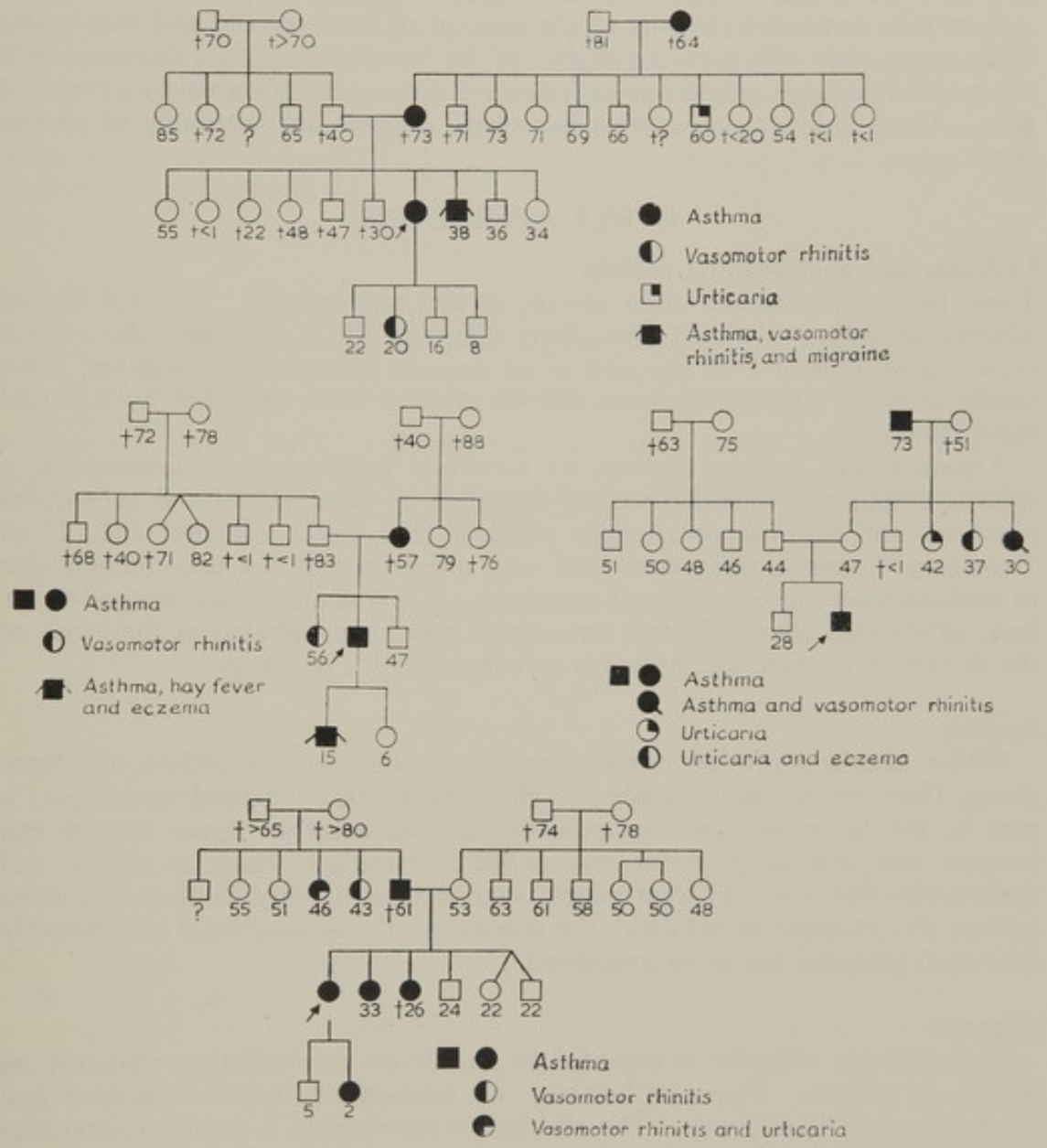

FIG. 311.—Some pedigrees in the atopic diseases. (The numbers under the symbols indicate age in years; † before such numbers indicates deceased.)

Knowing that the inheritance is dominant with penetrance at 40 per cent, it is possible to calculate the probable incidence of the diseases at various combinations of genes. Thus, of the offspring of a marriage between a normal person and an asthmatic, 50 per cent will be carriers of the gene; 40 per cent of the latter, for example, 20 per cent of the children, manifest the disease, which will be asthma in 13 per cent and vasomotor rhinitis, Besnier's prurigo or hay fever

in the remaining 7 per cent. Since we are probably dealing with polymeria, the risk of manifesting the disease is distinctly higher for the members of a sibship where one has already manifested the disease. In such instances, the frequency of manifestation may be calculated as ranging from 60 to 95 per cent.

It may be concluded that the atopia concept of Coca is valid and that is also easily compatible with previous studies of the heredity in allergic diseases—with the modification that only the so-called atopic diseases are governed by a common gene. These findings suggest that the atopic diseases are invariably of allergic origin.

OTHER AFFECTIONS

Urticaria and angioneurotic oedema

These two conditions are often present in the same person. It is not known whether urticaria is subject to hereditary influence. It is a common disturbance occurring in at least 8–10 per cent of all persons at some time or other. One family showing inherited urticaria due to cold has been described by Kile and Rusk (1940).

Angioneurotic oedema appears to manifests itself in two varieties: (1) a specific dominantly inherited variety described by Osler (1888) and subsequent observers and showing occasionally cases of fatal glottis oedema; and (2) an "ordinary" variety, often combined with urticaria, and not uncommonly due to demonstrable antigen-antibody reactions. It is a characteristic feature of the first variety that allergic factors have never been demonstrated as the cause of the disease; it is, therefore, probably entirely unrelated to allergy.

Eczema

Whilst Besnier's prurigo (atopic dermatitis) falls into the asthma-hay fever group, there are no special studies to elucidate whether inherited factors play a part in the far more common, so-called contact eczema. Since anyone can become sensitized to powerful eczematogenic sensitizers (such as primin and dinitrochlorobenzene), different people vary in their liability to develop contact eczema (for example, in industry), the possibility of a constitutional (and possibly inherited) tendency has to be considered.

Migraine

This common affection is regarded as an allergic manifestation especially by American authors. There is, however, no relationship between migraine and the asthma-hay fever group. The affection is inherited as a dominant character (*see* page 319).

Hereditary specific sensitization

Apart from hay fever—all the victims of which are allergic to pollen—few cases of allergy to given substances have been reported as inherited from generation to generation. The best known of these reports are those of Laroche and his associates (1919) of allergy to eggs, and the family reported by Fantham (1925) in which allergy to rabbits (rabbit's hair and meat) was demonstrable through 5 generations.

Latent allergy

Latent allergy is taken to mean specific sensitization manifesting itself in positive skin reactions (and sometimes circulating antibodies in the blood), but without clinical signs of allergic disease. This condition is common (Salén and Juhlin-Dannfelt, 1935) but does not seem to be definitely related to allergic diseases as such, and is probably not of an hereditary nature. Thus, among the Eskimo population of Greenland in whom allergic diseases are practically unknown, Ehrström (1950) found no less than 50 per cent to give positive skin reactions to substances with which they were in daily contact, for example, birds' feathers, fish, and dogs' hair.

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CHAPTER 29

CANCER

P. A. GORER

STATISTICAL AND DIAGNOSTIC PITFALLS

BROADLY speaking there appear to be three points of view on the nature of cancer. One school holds that malignancy is a tissue reaction that may show as many differences in aetiology as do granulomatous reactions. The other two schools feel that there must be some unifying principle in aetiology, some maintaining that common principle lies in a virus infection to which the tissues may be conditioned in a number of different ways, whilst others consider that the common factor lies within the cell—the viruses being particles produced by the diseased cells in the first instance, and subsequently becoming capable of affecting others. One thing is clear; cancer cannot be considered a unit disease to the same degree as we regard syphilis as a unit disease. Syphilis is protean in its manifestations, but epidemiologically there is little difference between a patient with a gumma of the liver or a gumma in bone. Consider on the other hand cancer of the uterus as one of many other possible examples. Carcinoma of the cervix is found most frequently in multiparous women of the lower income groups, whilst cancer of the corpus uteri is commonest in nulliparous women, shows no association with poverty and occurs at a later age than the former type of growth.

Most malignant tumours occur rather late in life. This in itself complicates genetic studies, which are made still more difficult by the fact that all types of malignant growth show a very considerable variation in the time of onset. Even under experimental conditions where genetic and non-genetic factors are controlled as far as possible, these difficulties are substantial. In clinical investigations they are formidable. Thus we might have three sisters of whom one develops mammary cancer at the age of 45 years, the second dies of a cerebral haemorrhage at the age of 60 years and the third develops mammary cancer at the age of 70 years. Without present knowledge we cannot say whether the different clinical histories presented by these three is due to heredity or environment. This means that we cannot expect good approximations to mendelian ratios and, with a few rare exceptions, we do not find them. With problems such as this, we have two general methods available; the study of twins, and a statistical comparison of families.

The ideal background for a genetic investigation would be to have a large number of families in which all deceased members had undergone post-mortem examinations, and in which there were complete histological data on all operations. Since this cannot be attained we are obliged to rely on death certificates and upon published figures. A brief study of cancer statistics is therefore relevant.

Let us suppose that we are examining a population of 1,000,000 people for some particular characteristic and that, in fact, 100,000 show it. In the absence of any technical

errors the degree of approximation to the true value of 10 per cent would depend in part upon the size of sample tested, becoming closer as this increased. In a series of samples of 100 each, the average should approach the true value closely, but it should not do so in every individual case. The way in which the observed values are grouped round the true value is found by a measure known as the standard error. However, this term does not imply that the fluctuations are due to mistakes; on the contrary one ought to get such fluctuations. If one were publishing a series of 20 such samples, all of which showed values between 9 and 11, the results would be suspect. The word "error" in this case is therefore somewhat misleading to those untrained in statistical methods, random fluctuations might be better. With ideal cases such as this, fluctuations are equally likely to happen in either direction, a sample of 7 having the same expected frequency as one of 13. When comparing 2 populations we make use of the standard errors of each of them. The smaller the standard error, the greater the delicacy of our test.

Errors in the diagnosis of malignant disease are not uncommon, being least with cancers at accessible sites such as the breast or skin. The actual extent of such errors and the degree to which they apply to different sites is not known. The only way in which these could be assessed is by the publication of a large series of cases in which the post-mortem findings are compared with the clinical diagnoses.

TABLE I

AN ESTIMATE OF THE DEGREE OF ACCURACY IN THE DIAGNOSIS OF MALIGNANT DISEASE
(Figures from Willis (1948) except for last entry)

Site	Number diagnosed at autopsy	Number diagnosed clinically	Number correct clinically	False negatives		False positives	
				A	B	C	D
Stomach –	155	149	109 (70%)	18 + 28 = 46		21 + 19 = 40	
Large intestine	145	136	117 (81%)	14 + 14 = 28		11 + 8 = 19	
Lung – –	71	52	43 (61%)	13 + 15 = 28		4 + 5 = 9	
Breast – –	55	51	50 (91%)	3 + 2 = 5		1 + 0 = 1	
Uterus – –	25	25	19 (70%)	2 + 4 = 6		4 + 2 = 6	
Pancreas –	33	36	11 (33%)	8 + 14 = 22		21 + 4 = 25	
Oesophagus (Willis) –	20	19	13 (65%)	3 + 4 = 7		4 + 2 = 6	
Oesophagus (Guy's) –	50	44	44 (88%)	1 + 5 = 6		0 + 0 = 0	

A series of autopsy figures obtained by Willis (1948) at the Alfred Hospital, Melbourne, in the years from 1936 to 1944 is suggestive. The analysis is confined to 1,000 cases that were either thought to be due to malignant disease or found to be so at autopsy. Table I shows a selection taken from this series together with one series from Guy's Hospital. There were 943 cases of proven malignant disease. Had the death certificates been given on the strength of clinical findings alone, the number recorded would have been 872. Of these 55 were not really due to this cause and are therefore false positives, on the other hand 126 cases were missed, which gives a significant excess of false negatives. This is an example of a systematic error as opposed to the random "errors" we considered previously. It may be that this type of error is frequent.

In the whole series the clinicians were correct as to the site of the neoplasm in

69 per cent of cases. For the rest it will be seen that the false positives and false negatives are subdivided further. Thus, in cancer of the stomach, 18 were not diagnosed as due to malignant disease at all (column A), 28 were diagnosed as malignant but either the site was not fully specified (for example, " abdominal tumour " diagnosed) or else attributed to a different organ such as the pancreas (column B). For false positives (column C) we have genuine malignant disease that was not situated in the stomach (21 cases) whilst we have 19 cases (column D) that were called carcinoma of the stomach but were not in fact due to malignant disease.

The one surprise in Willis' figures were those for tumours of the oesophagus, since I could recall very few clinical errors in my own experience. For this reason it was decided to include a series of 50 cases taken from our post-mortem records starting in the year of 1936. It would be interesting to know the considerable differences in the two series.

The best example of a systematic error is to be seen with cancer of the lung, where there was a very definite deficiency as judged by the clinical findings alone. There can be no doubt that this tendency was wide-spread although it may now have been reversed. The bias is less obvious for other sites. For carcinomas of the stomach, large intestine and pancreas the actual numbers diagnosed were approximately correct. However, if one is attempting to draw conclusions as to the aetiology of any of these, the real significance of the figures is obviously much less than that deduced with ordinary statistical methods which only take into account the inevitable random fluctuations. In other words, the real standard error is very much greater than that calculated. The importance of these facts to geneticists is clear. If carcinoma of the pancreas appears on a pedigree, there is about 1 chance in 3 that it is correct. The statisticians could doubtless help us to make some allowance for diagnostic errors, but only if they are given figures with which to do so.

SOME NON-GENETIC FACTORS

Many industrial processes are now known in which the incidence of certain types of tumour is high. It is possible that genetic variables play their part in the development of tumours in those at risk. Provided one could obtain sufficient numbers in any one type of industry this might well repay study since nearly all such growths are easy to diagnose.

However, the main point in our consideration of non-genetic variables lies in the interpretation of results already obtained. A geneticist would very likely exclude a family in which the members had been exposed to some obvious risk such as tar, but might easily disregard more subtle causes. Thus, according to the Registrar General (1936), innkeepers and barmen show a raised mortality from cancer, and this is a type of occupation that tends to run in families.

Much attention has rightly been paid to the Registrar General's analysis of the social incidence of cancer. The figures are based on the mortality figures for 1930–32 and the population divided into 5 groups on the basis of income, group 1 being the most prosperous. Whilst this grouping is not ideal, certain broad tendencies are shown. The absence of a satisfactory statistical yard-stick naturally calls for some reserve, and the suggestion has been made that the great difference

in the incidence of cancer of the stomach between groups 1 and 5 (*see* Table II) is merely a reflection of the greater number of autopsies performed on the latter group. Arguments of this type are relevant for our present purpose and a selection of the Registrar General's figures shown in Table II may be used to test this particular contention.

TABLE II

THE SOCIAL DISTRIBUTION OF CANCER, RELATIVE INCIDENCE IN THE DIFFERENT SOCIAL CLASSES
(From the Registrar General (1936))

Site	Males						Females					
	Percentage all sites	Social Class					Percentage all sites	Social Class				
		1	2	3	4	5		1	2	3	4	5
Lip – – –	0·6		56	68	149	183						
Tongue – –	4·0	78	60	98	110	143						
Oesophagus –	6·6	74	87	98	94	130	2·0	(95)	84	101	95	116
Stomach – –	25·0	55	83	98	112	122	13·5	49	77	105	106	121
Upper alimentary canal* – –	42·0	63	80	97	109	129	17·0	56	78	105	106	119
Uterus – –							20·0	65	78	99	106	130
Breast – –							24·0	136	116	103	84	82
Intestine – –	22·0	98	103	102	100	95	16·0	102	101	103	90	103
Lung – – –	7·0	107	96	101	91	112	2·0	100	100	110	82	91
Liver – – –	4·2	100	115	94	104	95	3·4	76	95	97	110	115

* The term upper alimentary canal includes all sites from lip to pylorus.

To start with we may consider 2 sites at which the diagnosis is known to be uncertain but in which the bias is in opposite directions. Twenty years ago a large number of bronchial carcinomas were missed, and if the figures for cancer of the stomach are due to differences in the frequencies of autopsies, the same tendency should occur here; in fact there is no significant social gradient for either sex.

Cancer of the liver has a bias of the opposite kind; its frequency is over-estimated. There were 3,771 alleged cases in men and 2,485 in women making 4·2 and 3·4 per cent of all cancer deaths respectively. Actually, in European series confirmed at autopsy, the figure is nearer 1 per cent of all cancer deaths and there is a much larger excess of males than that recorded here. In fact a clinical diagnosis of cancer of the liver frequently means that the patient is thought to have malignant disease and has a large liver. One would therefore expect autopsies to show a very much lower incidence amongst the poor than amongst the well-to-do. In males there is no social gradient as one would expect if this erroneous diagnosis is random in nature. Unfortunately, there is a very definite social gradient in females which indicates a systematic error of some kind even if it is directly opposed to the " autopsy " hypothesis.

As for cancer of the stomach, the original figures gave 9 sites between the lip and pylorus, the whole being considered as " Upper Alimentary Canal ". Here we have only considered 4 separately. In the case of females, only the oesophagus and stomach are worth separate treatment since, in the other subdivisions, the number of cases is much too small (only 20 cases of cancer of the lip and 164 for the tongue). Diagnostic errors in cancer of the lip and tongue are very unlikely to be responsible for the social gradient shown, nor in the case of cancer of the oesophagus. In the latter the gradient in females is not very convincing. This may be due in part to the inclusion of post-cricoid tumours

which are agreed to differ in aetiology from other oesophageal growths. Furthermore, there are only 882 cases divided between the 5 classes as against 5,185 in males. For the stomach we find that the gradient is consistent between the 2 sexes, and between this site and the group as a whole. It is difficult to believe that we are dealing with a systematic error here. For additional support we may look at the figures for cancer of the intestine (including rectum) where the diagnostic errors are probably similar in kind if less in degree than for the stomach, and here we see no such gradient in either sex. When we come to consider the true slope of the gradient we are on still less sure ground.

The 2 most important sites of cancer in women are the breast and uterus. In cancer of the breast diagnostic errors are low, and it will be seen that here the social gradient is the reverse of that for the upper alimentary canal and, indeed, for the uterus. The figures for cancer of the uterus are open to the criticism that tumours of the cervix and of the corpus are considered together, although they differ radically in aetiology (Kennaway, 1948; Brøbeck, 1949). Growths of the body of the uterus form about 25 per cent of all uterine growths in Great Britain and should tend to tilt the gradient towards the more prosperous groups. Brøbeck's figures confirm the reality of the gradient for cervical cancer but we can have very little confidence in its magnitude as shown in the table.

The considerations all suggest that there are a number of factors besides genes that tend to concentrate malignant tumours in certain families. Families not infrequently follow the same occupation and generally belong to the same social class, they also share dietary and hygienic habits, medical practitioners and many other things. Lastly, one must bear in mind that they often share infective agents and there is the possibility that virus infection may be of importance in some human neoplasms.

The statistical difficulties and uncertainties that beset geneticists also affect all who deal with the clinical study of cancer. Stocks (1936) has published a number of maps showing the distribution of cancer of different sites in England and Wales. One of the most striking of his findings is the high concentration of cancer of the stomach along the Western seaboard. At present we cannot account for this, but it is conceivable that it might be due to a higher frequency of one or more genes in this area than elsewhere. A similar puzzle is set by the incidence of cancer of different organs in Malayans (Bonn, 1935). The commonest tumour in males is carcinoma of the liver, whilst that of the stomach is extremely rare. For Chinese living in Malaya tumours of both sites are common, whilst in the Dutch as in other Europeans, cancer of the liver is very rare. All these peoples live very different lives and here again we are set an insoluble problem. Figures of this kind suggest that in attempting to detect the non-genetic factors in the aetiology of any neoplasm, it is advisable to confine the investigation to a single area, rather than to compare 2 geographically or sexually separated peoples.

GENETIC STUDIES

Studies on families

The earliest contributions to the genetics of cancer consisted of the publication of individual pedigrees showing a high incidence of tumours. Such data can be very misleading. Though the probability of finding 5 brothers with cancer of the stomach is very small, this would, however, occur in any sufficiently large series. If found by chance, this event will attract attention, just as do other rare events. In spite of this some of the pedigrees are so striking that they cannot be disregarded.

The earliest attempt to attack the problem on a statistical scale was made by Bashford (1908) who sent a questionnaire concerning their relatives to cancer patients. For obvious reasons no significance can be attached to uncritical data so obtained.

Little (1923) made a study of the relatives of cancer patients and found them to show a definite excess as compared with the population as a whole, but there may well have been a difference in diagnostic skill as applied to the 2 groups, in giving a higher incidence in the group studied by Little.

A thorough investigation of the problem was made in Norway under the direction of Waaler (1931). Information concerning the relatives of cancer patients was obtained in the first instance from doctors, hospitals and other institutions, and, in most cases, followed up by 100 specially trained medical students. As control material he used the spouses of patients and the general statistics for the country covering the years in question. He divided his material into 3 series; an F series in which all sibs were dead, a U series where some sibs were still alive and a G series which was not followed up. The cancer incidence was measured by a figure he called the " B value " which was the deaths from cancer divided by deaths from all causes over the age of 60 years.

When the F series was considered it was found that the B value was slightly higher for male relatives of patients than for the husbands of cancer patients and than that for the general population—both of which groups showed the same value. For females the situation was different. The wives of patients showed a considerably higher incidence of cancer than the general population in the earlier age groups, whilst women of the F series showed the highest cancer incidence of all.

He also considered the significance of cancer in the parents of members of the 3 series. There were very few cases in which both parents were known to have died of cancer, so he pooled these with those in which one was known to have died of cancer whilst the cause of death in the other parent was unknown. Four more groups were used, one cancer and the other not cancer, both unknown, one unknown and the other not cancer, and both not cancer (only deaths of parents over 60 years of age were considered for non-cancer patients). In general, the incidence of cancer seemed higher amongst sibs, one or both of whose parents were known to have died of cancer.

His consideration of the significance of the organ affected is particularly important. He found an increased B-value in the sibs of patients with oesophageal and abdominal cancers, cancer of the prostate and cancer of the mamma, uterus and ovary. There was no excess in the case of cancer of the lip; however, the number of cases was small, as indeed it was with the prostate or ovary.

One of the objections that might be raised against this study is the great heterogeneity of skill that must have occurred with such a large number of investigators. In the case of parents there was a very large number of cases in which the cause of death was unknown. Nor, of course, do we know the reliability of the data on death certificates, nor in which direction they may have been biassed. The excess of cancer amongst the wives of patients is not surprising if the bulk of cases are those that show the effects of social environment. However, it is difficult to see why this should be shown by wives and not by husbands.

Wassink (1935) made an extensive investigation in Holland. Most of his data consisted of material supplied by the patients themselves. The findings are of interest when applied to specific sites rather than in showing any familial concentration of cancer in general.

More recently Hanhart (1943) studied the offspring of parents both of whom were certified to have died of cancer. He found no excess amongst the offspring. In contrast there are the observations of Schinz, Cocchi and Neuhaus (1948) on patients with carcinoma, sarcoma, leukaemia and Hodgkin's disease. They used a small number of tuberculous and hypertensive patients as controls. The patients and their relatives were not interviewed, reliance being placed upon death certificates and hospital records for further data. The number of controls was very small (12 propositi as against 144 for those with malignant disease). Some evidence of an excess of carcinoma was found amongst the close relatives of propositi with carcinoma. The relatives of patients with sarcomas apparently showed a lower incidence than the general population.

All these methods are open to the possibility of serious errors. No attempts to solve the cancer problem in general have yet met with success, either in the experimental or statistical spheres.

In recent years Danish workers, each dealing with some special branch of malignant disease, have contributed a series of monographs, and all distinguished by a high standard of clinical and pathological skill. On statistical aspects they labour under the difficulties already discussed here.

Studies on twins

The study of twins has long been a favourite method of assessing the relative importance of heredity and environment in those cases where simple mendelian expectations are unfulfilled. Most of the earlier literature on cancer in twins is badly biassed. Prior to 1940 there had been a few very small unselected series of cancer in twins and a large number of specially selected cases. If one were to take this earlier data at its face value, the overwhelming influence of heredity in the development of neoplasia would seem to be established. Typical of this earlier work is that of Macklin (1940) who draws her conclusions indifferently from selected cases and the small unselected series that were then available. This in itself is misleading, but it becomes even more so if one also includes all swellings such as exostoses, cervical polypi and popliteal cysts under the general heading of tumours. To the statistical error of employing a very heterogeneous and largely biassed body of data is added the error of attempting to deal with the tumour problem as a whole.

It is by no means easy to obtain an unbiassed series of any size, and the number of twins with a specific type of growth such as carcinoma of the stomach remains very small. Theoretically there are two possible methods of obtaining unbiassed data. One could survey a large population for twin pairs and study all causes of mortality and morbidity amongst them. This would perhaps be the ideal technique but would be excessively laborious. The second is that actually carried out by von Verschuer and Kober (1940) in Germany and by Busk, Clemmesen and Nielsen (1948) in Denmark. Registration of cancer patients was made covering a large area and these were then investigated to see whether they were members of

a twin pair, those which were found to be so were further examined to decide whether they were monozygotic or dizygotic. Some such pairs are of little use to the investigator owing to early death of one member, and for various other reasons. Thus, beginning with nearly 17,000 cancer patients, von Verschuer and Kober were left with 79 useful twin pairs, whilst the Danish workers obtained 183 such pairs from an initial 30,000 patients. Shorter relatively unbiassed series have been published by Waaler (1931), Kranz (1932), Versluys (1934), Habs (1939) and Weitz (1939).

Unfortunately, the reports on the two larger series are in the nature of preliminary communications; however, through the kindness of Dr. Clemmesen I have been able to obtain further data on the Danish material.

There are two equally important questions that may be asked concerning the twin material. First, is malignant disease concentrated in certain families ? If it is one should find an excess of concordant pairs with both monozygotic and dizygotic twins. Secondly, is such concentration mainly genetic ? If so, the excess should be greater for the monozygotic pairs.

TABLE III

CANCER IN TWINS (Large unselected series only)

Type of twin	(*a*) From Busk, Clemmesen and Nielsen (1948)				(*b*) From von Verschuer and Kober (1940)		
	Concordant observed	Concordant expected	Discordant	Total	Concordant	Discordant	Total
Monozygotic –	7	5	43	50	2	21	23
Dizygotic –	7	9·2	126	133	7	49	56

The frequency of cancer in twins as evidence of concentration in some families

This has been studied by Busk, Clemmesen and Nielsen; their method was as follows:

We start with 50 monozygotic twins who have 50 partners of known age of whom one is known to be cancerous. From the statistics of Denmark it may be calculated that 5 of these would be expected to be cancerous by chance alone; similarly amongst 133 dizygotic partners, 9·2 cancer cases are expected. It will be seen from Table III that there is no obvious excess with either group. Similarly there is no very obvious excessive concordance for monozygotic twins as compared with dizygotic twins. On the face of it one might say that there was no evidence of a familial concentration of tumours, and hence none for the importance of genetic constitution. Such a judgement would be premature for reasons that may be made clear by reference to our knowledge of the occurrence of tumours in strains of mice, as the author has done previously (Gorer, 1938). For simplicity we will confine our attention to mammary cancer which has been most thoroughly studied, but the principle involved can be applied generally.

It is known that pure strains of mice differ widely in their cancer incidence, but they do not fall sharply into susceptible and resistant groups. One may find any incidence

from under 1 per cent to 90 per cent. If the same is true of mankind we may compare twin pairs to pairs of mice selected at random from various strains. Obviously the greater the number of highly susceptible strains, the more often would the pairs be concordant; but two other factors are less obvious: (1) the importance of the age of the " notified " twin; and (2) the period of time during which the partner is observed.

TABLE IV

THE DATA OF BITTNER (1935) SHOWING THE CANCER INCIDENCE IN A HIGHLY SUSCEPTIBLE STRAIN OF MICE

Age (months) –	4·5–5·5	6·5–7·5	8·5–9·5	10·5–11·5	12·5–13·5	14·5–15·5	16·5 and over
No. dying:							
Cancer free –	35	32	26	23	17	15	4
With cancer –	3	20	49	62	64	37	34

In Table 4 are some data by Bittner (1935) of breeding females of the A strain of mice. No cancers occurred before the age of 4·5 months, thereafter of 421 mice, 269 or 64 per cent died cancerous, (an incidence of the disease more than 4 times that found in a human population) the material being arranged in bi-monthly groups. In drawing the pairs, we are given that the first member is cancerous but cannot specify in which age group. The chance of picking a cancerous mouse in the period 12–13 months (the peak period) is 64 : 269. The only specification for the second member is that it must have survived to 4·5 months. To be classified as concordant it must have developed cancer between 4·5 months and 13·5 months. The frequency with which such a mouse will be obtained is 198 : 421. Thus, even when the propositus has developed cancer during the peak period, only 64 : 269 × 198 : 421 or 11 per cent of pairs will be concordant at the time of notification. Had the notified case been found between 8 and 9 months, the probability of concordance would be just over 3 per cent. It will be seen that even if the frequency of susceptible types is high, we are still likely to obtain a large proportion of discordant pairs. Amongst the discordant pairs, there will be some in which the partner has died free of cancer, and others in which it is alive and well. In this strain of mice, most of the latter would develop cancer later and the percentage of concordance would rise accordingly, but we should only obtain a really adequate idea of the susceptibility of the strain after observing the living partners over a period of several months. How far it is justifiable to equate the time scale of mice and men is debatable, but for the sake of argument we may approximate 2 months to 5 years.

The survey of van Verschuer and Kober covered the years 1933 to 1938 but we have no further data concerning the length of time during which the non-cancerous partner has been observed, nor how many are dead.

As for the Danish series, it will be seen from Table III that of the monozygotic twins, 43 had a non-cancerous partner. Of these, 12 were dead at the time of publication. Of the 32 pairs with a living partner, none had been under observation prior to 1942. Amongst the 126 dizygotic pairs with an unaffected partner 22 had died, and 104 were still living; of these only 9 had been under observation prior to 1942. Thus, very few pairs had been under observation more than 5 years.

Some might consider that pairs with a deceased partner should be excluded; if this were done, one would have to exclude almost all the concordant cases. It must be realized

that when one finds such a case in a systematic survey, either the tumours have developed simultaneously or the partner has developed a tumour *prior* to that of the notified twin. Clearly, one must draw a line somewhere if one partner is dead—such as death in infancy —but the precise age at which it should be drawn is difficult to decide. Busk, Clemmesen and Nielsen excluded all cases in which one partner died before the age of 5 years. This limit might apply to neuroblastomas and suchlike tumours, but would have little pertinence to mammary cancer. Clearly, one must modify one's method, according to the neoplasm in question.

One must agree with the Danish observers that we shall have to wait many years before valid generalizations can be made. Probably positive evidence will come first. It may be within a decade that one will be able to say that the degree of concordance is greater than would be expected for patients observed during that period. Already we can say that the genotype does not irrevocably determine the time at which a tumour will appear. If it did, monozygotic twins would always develop tumours almost simultaneously, and there would be considerably greater agreement in this respect as compared with dizygotic twins. In the Danish series, the average interval is slightly shorter in the latter group, but not significantly so. Amongst the monozygotic pairs there is one pair in which both developed mammary cancer at an interval of 16 years which accounts for most of the difference. In this connexion we may note a similarity between mice and men, since in mice there is undoubtedly considerable non-genetic variation in the time of onset of both spontaneous and artificially induced tumours. However, the existence of these non-genetic variables does not justify ignoring genetic variables in experimental work, nor in stating that twin studies indicate their absence in man.

Differences in affected monozygotic and dizygotic twins

Table V summarizes the data from all the unselected series.

TABLE V

THE DEGREE OF CONCORDANCE FOR TYPE OF GROWTH WHEN BOTH MEMBERS OF A PAIR ARE AFFECTED (Unselected series only)

	Concordant	Discordant*	Total
Monozygotic – –	12	4	16
Dizygotic – – –	5	18	23
	17	22	39

* In two of these one partner had carcinoma of the stomach, the other of the intestine (*see* text).

It will be seen that amongst 16 monozygotic pairs, the same organ was affected in 12, whilst of 23 dizygotic pairs this was the case only in 5. Of the monozygotic pairs in which different organs were affected, two are of special interest; one member had carcinoma of the stomach, the other had carcinoma of the large intestine. One of the cases was reported by Kranz, the other by Busk, Clemmesen and Nielsen.

Table VI deals with cancer of the stomach as drawn from all the unselected data.

TABLE VI

CANCER OF THE STOMACH IN TWINS (Unselected material only)

Authors	(*a*) Monozygotic pairs			
	No. of pairs	Discordant	Same tumour	Different tumour
von Verschuer and Kober	6	4	2	—
Busk and his associates	6	5	—	1*
Others	7	3	3	1*
	19	12	5	2*

* These tumours were both in the large intestine.

Authors	(*b*) Dizygotic pairs			
	No. of pairs	Discordant	Same tumour	Different tumour
von Verschuer and Kober	17	13	—	4
Busk and his associates	8	6	—	1
Others	9	4	1	4*
	34	23	1	9

* One with tumour of large intestine.

It will be seen that in 7 of 19 monozygotic pairs both were affected, the stomach being the organ in 5 pairs whilst, as already mentioned, two partners had growths of the large intestine. In the von Verschuer and Kober series, two of the healthy partners had achlorhydria. Amongst 34 dizygotic pairs there were 10 in which both had tumours, but in only one (a case of Versluys) did both have cancer of the stomach. One of the healthy partners in the von Verschuer and Kober series had achlorhydria. Unfortunately, it is impossible to say whether the gross number of concordant cases is greater than expectation, but the difference between the monozygotic and dizygotic pairs is highly suggestive for the importance of genetic factors in the development of carcinoma of the stomach.

How closely carcinoma of the large intestine is related in aetiology to that of the stomach is difficult to say. The twin pairs quoted above do suggest some common factor which is not apparent from general statistical studies (*see* Table II). In the literature there are 12 monozygotic cases in which the notified twin had a colonic growth and in every case the partner was healthy. However, in one of these (reported by von Verschuer and Kober) the other partner had polyposis, and this is of particular interest for our present purpose. Here we have a gene that is well known to enhance the sensitivity of the intestinal mucosa to carcinogenesis. Clearly, non-genetic factors play their part in determining the time at which malignancy develops. This demonstrates the error in regarding " heredity " and " environment " as two mutually exclusive agents. It also shows the danger of drawing deductions from twin data as it stands today.

TABLE VII

MAMMARY CANCER IN TWINS (Unselected series only)

Authors	(*a*) Monozygotic pairs		
	No. of pairs	Discordant	Concordant
von Verschuer and Kober –	3	3	—
Busk and his associates –	12	11	1
Others – – – –	2	2	—
	17	16	1

Authors	(*b*) Dizygotic pairs		
	No. of pairs	Discordant	Concordant
von Verschuer and Kober –	9	8	1
Busk and his associates –	19	17	2
Others – – – –	8	5	3
	36	30	6*

* In only one of these cases did both partners have cancer of the breast.

Of the other sites, only mammary carcinoma will be dealt with separately. It will be seen from Table VII that as things stand at present there is little of a positive nature that may be deduced. In the single concordant monozygotic pair 16 years elapsed between the two cases. These figures have not been quoted to deny the importance of genetic factors in the aetiology of mammary cancer, but to assert the importance of non-genetic factors. As will be shown later, there is very considerable evidence that mammary cancer does show an excessive concentration in certain families. Some authors have taken it for granted that this must be due to a concentration of genes in such families and Jacobsen (1946) goes so far as to call mammary cancer an " endogenous " cancer. It is clear that the time of onset of mammary cancer is not entirely " endogenous ".

The data obtained from twins should cause no surprise to anybody acquainted with experimental work. One of the main difficulties has been the gathering of a sufficiently large unbiassed series. Whether it will be possible to follow the German series after the political upheavals in that country is uncertain, but it is to be hoped that the Danish workers will be able to resolve some of our doubts within a decade or so. The work is of importance since twins seem to offer the only possibility of answering some of the questions raised by ordinary statistical studies. For example, Jacobsen (1946) and Vidabaek (1947) claim that there is an increased incidence of cancer at various sites amongst the relatives of patients with mammary cancer and of those with leukaemia. If this is so, one should ultimately observe an enhanced concordance with all types of twins where one partner has either condition. Naturally, if the cause of this familial concentration is mainly genetic, the concordance should be considerably higher amongst the monozygotic group. In the case of mammary cancer, pairs of mixed sex will be

of great interest; if Jacobsen is correct in believing that some general susceptibility is inherited, cancer should be observed in a high proportion of male partners in whom the likelihood of mammary cancer is very small.

SOME INDIVIDUAL FORMS OF CANCER

The breast

Carcinoma of the breast is the tumour that has been most thoroughly studied from the genetical point of view. The earlier literature on the subject has been thoroughly reviewed by Jacobsen (1946).

There are numerous examples of pedigrees, some of which are too striking to be ignored. Broca (1866) published that of his own family; in 5 generations 1 man and 15 women died of cancer out of a total of 38 people, 10 of the deaths in women were with cancer of the breast. Smithers (1948) has given a preliminary report on work in progress at the Royal Cancer Hospital which includes some remarkable pedigrees. Another that would appear to be of some significance is that of a large kinship reported by Gardner and Stephens (1950) in which carcinoma of the breast appears to be concentrated in 1 branch.

Pedigrees however striking do not give sufficient information. As will be seen, in the case of other types of tumours there are certain rare genes that greatly enhance susceptibility to malignant disease. The example of polyposis intestini has already been mentioned. It greatly increased the risk of carcinoma of the colon but probably contributes but little to the total incidence of the disease. We therefore have to rely on systematic investigations in order to obtain a proper perspective.

Amongst the earlier work of this type mention may be made of that of Lane-Claypon (1926), Wainright (1931), Waaler (1931), Wassink (1935) and Martinova (1936). These studies differ from each other in method and in merit, but all agree that the incidence of mammary cancer is greater amongst the relatives of patients than can be accounted for by chance. More recently there have been notable contributions by Jacobsen (1946) and Penrose, Mackenzie and Karn (1948) with the same general result. Dissentient results have been obtained by Hanhart (1943) and Passey (1942). If the positive results are the consequence of some systematic error, the negative findings have not revealed it.

The work of Jacobsen and of Penrose, Mackenzie and Karn may be used to demonstrate the methods employed in problems of this kind. Jacobsen investigated the families of 200 probands with cancer of the breast and contrasted these with families of 200 controls. There would appear to be 2 methods of obtaining control material. For every patient one could choose another of the same age, social class and preferably from the same region of the country but leave their disease to chance. If this were done, some of the controls would have cancer including mammary cancer, but one should obtain figures that would represent the hospital population as a whole. The second method (as adopted by Jacobsen) is to take the first 3 precautions but not the last, in place of which he went to particular trouble to see that the controls did not have malignant disease. This particular method is open to criticism, since if it is true that some families have an excess of malignant disease (or any disease) others should show a deficiency. In Jacobsen's control material as a whole, the cancer incidence was definitely less than that of the general population. The question naturally arises whether this is due to inadequate ascertainment of cases in this group. This question was investigated by Busk, Clemmesen

and Nielsen (1948) who found that the deficiency was greatest in the more remote relations, whilst in the case of immediate relatives (parents and sibs) it was no longer statistically significant. It would therefore appear that the ascertainment was not satisfactory for the more remote relations of controls, since if the deficiency was genuine it would be expected to be most pronounced in the closer relatives. Amongst the patients' relatives Jacobsen found an excess of mammary cancer amongst the women which is in agreement with other work on the subject; in addition to this he found an excess of cancer at other sites—a point which will be dealt with again later. He also found evidence that the age of onset was earlier in familial than in sporadic cases. However, Busk, Clemmesen and Nielsen think this may be an artefact due to imperfect ascertainment concerning the relatives of older patients. Neither Smithers nor Penrose and his associates confirm Jacobsen's findings in this respect.

TABLE VIII

MAMMARY CANCER INCIDENCE IN DECEASED RELATIVES OF PROBANDS
(Abridged from Penrose and his associates (1948))

(*a*) Mothers: Expected carc. mamma 11. Observed 25. Expected other malignant tumours 49. Observed 51.

Cause of death	Age at death					
	20–39	40–49	50–59	60–69	70–79	80 +
Numbers observed:						
All causes – –	30	29	54	107	111	76
Malignant not carc. mammae	1	1	11	9	13	6
Carc. mamma – –	—	3	7	10	5	—

(*b*) Sisters: Expected carc. mammae 7. Observed 23. Expected other malignant tumours 25. Observed 19.

Cause of death	Age at death				
	20–39	40–49	50–59	60–69	70 +
Numbers observed:					
All causes – –	53	23	42	44	23
Malignant not carc. mammae	3	4	5	6	1
Carc. mamma – –	3	4	9	6	1

Whilst it may seem easy in theory to obtain satisfactory control material, in practice it is very difficult; some workers prefer to employ the general mortality figures in their place. In the case of carcinoma of the breast, these are probably sufficiently accurate to give significant figures. The disadvantage lies in the fact that we have no morbidity figures for malignant disease. This means that one can only draw conclusions from the frequency of the disease in relatives who are dead, though this is liable to give an underestimate for a small, but probably significant proportion of patients who are successfully treated and die of some other cause. There is no reason to suppose that this source of error will differ amongst the relatives of probands and the population as a whole. Penrose, Mackenzie and Karn began with a study of 510 probands; of the 510 mothers, 102 were still alive, 6 of these having mammary cancer; amongst 1,255 sisters 890 were still alive,

24 of whom had mammary cancer. The figures for deceased relatives is given in Table VIII, the expected incidence of various types of malignant disease being calculated on the basis of the Registrar General's figures for 1925–29. It will be seen that there is a significantly greater mortality from cancer of the breast amongst the mothers and sisters of probands, but no increased mortality in either sex for other types of malignancy.

Certain other points of interest arising in this investigation may be briefly mentioned. Amongst the 510 probands, 408 were married, but of these 91 (22·3 per cent) were childless, this is significantly greater than the figure of 17·3 per cent for women of the same age given by the Registrar General. This accentuates the association of low fertility with mammary cancer that has been found in numerous other investigations. When sibs were compared there was a high correlation in the age of onset of both mammary cancer and other types of malignancy. The authors point out that although their figures are significant in the statistical sense of that term, the result may well be misleading. Data on twins show that these misgivings are probably justified, since here the correlation in age of onset is certainly not very high. When sibs are affected at about the same age, they are more likely to come within a survey covering a short period of time. The surviving sisters of patients aged 40–50 years may develop carcinoma at 60 or 70 years of age. Furthermore, there was no significant correlation in the age of onset in mothers and patients. In this connexion we may allude to another possible influence in the aetiology of malignant disease, namely the age of the mother and birth order, some experimental work indicates that this might be of importance.

Since Bittner's discovery of the milk agent in mice, the possibility of a similar agent in man has arisen. Decisive experimental work is of course impossible, but if a virus is so transmitted there should be an excess of mammary cancer amongst maternal aunts and grandmothers as compared with those on the paternal side. Penrose's data are suggestive on this point, but there is no general confirmation.

As for Jacobsen's finding, that there is a general increase in cancer incidence amongst the relatives of probands as compared with the controls, it has already been mentioned that Busk, Clemmesen and Nielsen found reason to suppose that the data concerning the more distant relatives of the latter group was not entirely satisfactory. They therefore compared the findings obtained for both groups with the morbidity and mortality figures in possession of the Danish Cancer Registry, with the result shown in Table IX.

TABLE IX

CANCER INCIDENCE IN RELATIVES OF BREAST CANCER PATIENTS
(Jacobsen's data analysed by Busk and his associates)

Relatives	Number of cancer cases	
	Observed	Expected
Father – – – –	40	23
Mother – – –	55 (21)	29 (7)
Brother – – –	16	8
Sister – – – –	30 (13)	16 (5)

Figures in parentheses denote mammary cancer.

The figures for mammary cancer have already been discussed, and according to these authors the figures for cancer of other sites show a significant deviation from expectation amongst the parents and sibs of probands. Doubtless this is

correct statistically, but the possibility of diagnostic errors colouring these findings is real. It is noteworthy that Penrose and his colleagues failed to confirm Jacobsen's findings in this respect. It is true that the methods they employed were different, but it is difficult to see why their mortality figures for parents should fail to show a significant excess if it is present.

Even if Jacobsen's findings are valid his conclusions are open to question. He argues that since his probands were drawn from all strata of the population it is unlikely that infection, diet and other extraneous factors have any material influence on cancer of the breast, which must therefore be due to hereditary predisposition. Actually, one could obtain families with an excess of tuberculosis from various strata of most populations, but few would argue that this disease is determined by the genotype as irrevocably as the appearance of a blood group antigen. Does it mean that the population is sharply divided into those who are able to develop mammary cancer and those who are not? There is nothing to support such a contention which on *a priori* grounds must be regarded as unlikely. Furthermore, if mammary cancer were largely genetic in origin, it could hardly be a common tumour. A significant proportion of cases occur before the menopause, and the disease is significantly associated with a low fertility and thus natural selection would have lowered the frequency of such a genotype during the course of human evolution.

It would seem that whilst the view that mammary cancer is due to a hereditary predisposition is not substantiated by the available data, one cannot assert that an individual's genetic constitution plays no part in its development. It is quite likely that certain genes enhance the frequency of its appearance under adequate circumstances, and that the concentration of mammary cancer in certain families is due to a concentration of these genes in such families. If cancers of numerous sites are in fact concentrated in some families, my own guess (it is no better than a guess) is that such a concentration is probably non-genetic; one knows of chemical carcinogens that cause tumours at numerous different sites (acetyl-amino-fluorene and the di-ethyl stillbenes are examples) but there is no experimental evidence of general " cancer " genes.

The uterus

The question of cancer of the uterus has been fully reviewed by Brøbeck (1949). Some of the earlier writings suffer from the defect that no clear distinction is made between cancer of the cervix and cancer of the body, although the aetiology of the two conditions is clearly different.

TABLE X

THE CANCER INCIDENCE IN 5 GENERATIONS OF WARTHIN'S " G " FAMILY
(After Hauser and Weller (1936))

Generation	Number under the age of 25 years	Number over the age of 25 years	Number cancerous
1	—	10	6
2	8	54	27
3	30	104	7
4	87	5	—
5	6	—	—

Of the individual pedigrees published the " G " family originally described by Warthin is of outstanding interest. According to Hauser and Weller (1936) there were 174 members aged 25 years or more, and of these 41 had developed cancer at an average age of 48·3 years, in two cases there was more than one primary growth, making a total of 43 growths in all. Unfortunately not all the patients were thoroughly examined, and in many the diagnosis is based on clinical grounds alone. Twenty tumours occurred in males, all of which were classified as gastro-intestinal. Amongst the females there were 15 uterine tumours all affecting the corpus, with an accompanying carcinoma of the caecum in one case; in addition there were 5 other cases of gastro-intestinal cancer, and two tumours of " other sites ". The location of the gastro-intestinal tumours was not clear in all cases, but the majority appear to have affected the large bowel. Table X shows the cancer incidence in each generation. The findings in the first two generations are consistent with the assumption of a single gene effective when heterozygeous. The fact that the pedigree shows that cancer may skip a generation is no contradiction of this, since the variation in time of onset is certainly largely non-genetic. If we are dealing with a single gene it apparently has a different effect in the two sexes. This alleged gene must be excessively rare, since no similar family appears to have been reported.

Both Wassink and Waaler found that cancer of the uterus was more frequent in the relatives of patients than in the population as a whole. In the excellent study of Brøbeck (1949), based on 200 cases of cervical cancer and 90 of endometrial cancer, all of which had been verified histologically, the findings were to the same effect, but rather more complex.

The data obtained were compared with a control group and with data in the possession of the Danish Cancer Registry. Over 50 per cent of the control group consisted of the same material that Vidabaek (*see below*) used as controls in his study of leukaemia, for the remainder the families of patients were chosen by Brøbeck himself. The method of selection was the same in principle as that of Jacobsen.

In the case of cervical cancers it appeared that the sisters of patients had an increased tumour incidence contributed entirely by an increase in uterine cancer. Amongst the cancers found in female relatives of probands 24 per cent were uterine, as against 17 per cent for Denmark as a whole. Unfortunately, in over 33 per cent of the cases in the former group the type of uterine cancer was not specified. In those in which it was specified, the ratio of cervical to endometrial cancer was about 8 : 1, whereas in Denmark as a whole it is about 3 : 1—as it is in England. Amongst the male relatives the most striking finding was an increased incidence of cancer of the oesophagus in the fathers of patients. Both cancer of the cervix and cancer of the oesophagus tend to be concentrated in the same social strata. At present it is not possible to say whether their concentration in certain families is due to a community of environmental factors, of genes or of both.

In the case of cancer of the corpus uteri Brøbeck found that there is a significant increase in the general cancer incidence for both male and female relatives. In the latter case this can be accounted for by an increased incidence in cancer of the uterus, which in this case accounts for 21 per cent of all cancers. In the case of male relatives there is no significant increase in any particular site and the author is inclined to invoke the existence of some general cancer gene to account for the observed results.

In both the male relatives of propositi and of controls, there is an apparent excess of oesophageal and gastric cancers as compared with the figures of the Danish Cancer

Registry. Expressed as percentages of all cancers, for the probands the percentages are 12·3 oesophageal, 39·7 gastric, for controls 11·4 and 43·1 and for the Cancer Registry 3·8 and 23·3 respectively. The totals in the first 2 groups are small, there being only 14 oesophageal growths between them. However, those for gastric cancer are more suggestive although presumably not statistically significant. It is possible that there may exist genes similar in nature but less extreme than that postulated for the " G " family.

On the other hand, one may apply the same argument here as in the case quoted by Jacobsen. It is quite likely that certain environmental factors shared by a family may favour the incidence of several types of tumour. Endometrial cancer is associated with a low fertility and a high standard of living. A high standard of living is just as " environmental " as a low standard.

The alimentary canal

Oesophagus

Mogensen (quoted by Brøbeck and by Clemmesen, 1951) has investigated cancer of the oesophagus in Denmark, and is inclined to doubt whether the familial concentration observed by him is strictly genetic.

Stomach and intestines

As for other sites in the alimentary canal—where there is considerably more doubt as to diagnosis—the findings of Kober and von Verschuer on gastric cancer in twins have already been discussed. Martinez (1927) described 2 remarkable families with gastritis, achlorhydria and gastric cancer, whilst Levin and Kuchur (1937) reported that the relatives of patients with gastric cancer showed a higher incidence of achlorhydria than did controls and that the incidence increased with age.

Large intestine

Polyposis intestini is described elsewhere (page 419). McFeeters (1939) described the familial distribution of various morbid conditions in an isolated rural community. Polyposis was not encountered but it did appear that carcinoma of the colon was concentrated in certain families. Unfortunately, his data have not been published fully.

The leukoses in relation to cancer

Vidabaek (1947) found but 1 case of leukaemia amongst the relatives of his controls as against 17 amongst those of his probands (10 in males and 7 in females). There were 149 neoplasms of other types amongst the males of this group and 170 in females, therefore leukaemia amounted to about 6·6 per cent and 4 per cent of all neoplasms in the proband group. The Danish Cancer Registry gives 3·0 per cent for males and 1·5 per cent for females. This is highly suggestive, but one would very much like to know the incidence of leukaemia relative to the population, as well as that relative to other neoplastic diseases. Vidabaek also holds that there is an increased incidence of neoplastic disease in general amongst his proband material, but his data are not convincing. Busk, Clemmesen and Nielsen (1948) have re-examined his figures, and found a significant excess only amongst the fathers and sisters of patients. Once again the need of a statistical measure really adequate for the material is apparent.

SOME GENERAL CONSIDERATIONS

Some less controversial views

Polyposis intestini, xeroderma pigmentosum and other such conditions as retinoblastoma and neuro-fibromatosis discussed elsewhere, all give more or less satisfactory fits to mendelian expectations. From a genetical point of view, xeroderma is probably the least complex. In the other 3 conditions one has to deal with sporadic cases as well as hereditary ones, and since all are highly disabling there is a tendency to regard these isolated cases as mutants. So far as polyposis is concerned, it is impossible to be certain. Of neurofibromatosis it seems unlikely that all sporadic cases are mutants since there is apparently an excess of males among them, but not in those families where the disease behaves as a dominant gene. Retinoblastoma is generally considered to be due to a dominant gene which occasionally skips a generation. This is the simplest explanation, but there are grounds for misgiving.

Griffith and Sorsby (1944) found that in those families with direct inheritance, 60 per cent of the children were affected. Where the father was the affected parent there were 53·5 per cent affected; only 17 children were borne by affected mothers, but of these 13, or 76·5 per cent, had the disease. Where there was an affected uncle or aunt, or where there were clear antecedents the percentages of pathotypes were 49 and 46 respectively. In general the number of pathotypes is too high. In the last 2 crosses there is a fair approximation to 50 per cent of pathotypes, the number expected for a gene of full penetrance, but here we have to postulate diminished penetrance to account for the behaviour of the disease, and the expected value is then something less than 50 per cent. As so often happens in human genetics, the figures may be influenced by biassed reporting. The disease is so rare that further data are likely to be slow in accumulation; in the meantime one should treat the genetic interpretation with some reserve and the status of sporadic cases must remain in doubt. It is difficult to regard them all as mutants owing to the lower incidence of bilateral cases amongst them. Some of the former may really be metastatic neuroblastomas (*see also* Weller, 1941.)

It will be seen that even in those cases where the role of heredity is most clear, many points remain to be cleared up.

The contributions that have been made by genetics to experimental cancer research have been so striking that the somewhat doubtful results reported here may come as a disappointment. It must be remembered that even in experimental work many years had to be spent in the building up of pure strains of animals and in elaborating satisfactory techniques of study. It could hardly be claimed that the methods used in the statistical study of human cancer have yet reached a satisfactory stage.

It has already been pointed out that cancer of the liver showed a statistically significant social gradient in women. These figures undoubtedly signify something, we can only be certain that they do not represent the incidence of primary carcinoma of the liver. Statistical freaks of this kind may be more common than we think, which is an additional reason for not paying too much attention to orthodox tests of significance. This being so, it is always desirable to see how far different bodies of data are consistent with each other. Some doubt has been expressed concerning the claim of certain Danish workers concerning the concentration of cancers at numerous sites in the same families. Jacobsen, Vidabaek and Brøbeck all agree that this occurs—and yet one may question whether

their findings are entirely consistent with each other. If one were dealing with a situation that was analagous to Warthin's G family—though of course of less severity—it would not matter if one began with a case of cancer of the corpus uteri or a gastro-intestinal tumour, we should find that both types of tumour were unduly common in the families concerned. Therefore, if cancer of the breast and cancer of the corpus uteri are both endogeneous cancers (in Jacobsen's sense of that term), one might expect that Jacobsen would have found the latter unduly common in his families, whilst Brøbeck would have found the former, and similarly with Vidabaek in his study of leukoses.

The general accuracy of cancer statistics is likely to advance slowly as is the elaboration of useful tests of significance. This being so, it would appear that the study of twins is the most promising method of obtaining a check on the study of family histories. However, it must be done systematically and the twins must be observed for several decades. The publication of selected cases or appeals for data through medical journals are worse than useless.

Except for the rare special cases, attempts to specify the number of genes concerned in susceptibility to various forms of cancer, are at best futile and may be misleading. It must be remembered that even in mice we do not yet know the number of genes concerned in susceptibility to any neoplasm. With a common condition in mankind, a person of sufficient mathematical ingenuity can undoubtedly obtain some sort of agreement with mendelian expectations. This may distract attention from important environmental factors. Properly considered, the study of the familial concentration of various kinds of tumours should be regarded as part of the epidemiology of the neoplastic diseases.

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