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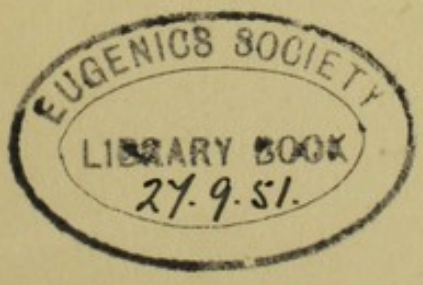

GENETICS IN OPHTHALMOLOGY

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GENETICS
IN
OPHTHALMOLOGY

ARNOLD SORSBY

RESEARCH PROFESSOR IN OPHTHALMOLOGY, ROYAL COLLEGE OF SURGEONS AND ROYAL EYE HOSPITAL; SURGEON, ROYAL EYE HOSPITAL, LONDON

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PREFACE

AT THE beginning of the last century, smallpox was the dominant cause of blindness and towards the end of the century it had been replaced by ophthalmia neonatorum. Some two-thirds of those who sought relief at the earliest institution for the blind —the one established at Liverpool in 1791—are said to have been blinded by smallpox, whilst an inquiry conducted in 1884 by the Ophthalmological Society revealed that some 30–41 per cent of all inmates at different institutions and schools for the blind had been blinded by ophthalmia neonatorum. In the nineteenth century, infections would therefore appear to have overshadowed all other causes of blindness.

During the present century, the picture has changed considerably. Admitting that there have been changes in criteria for registration as a blind person, it is clear that today the infectious diseases play a relatively insignificant part. In 1948, 0·4 per cent of those registered as blind were recorded as blind from ophthalmia neonatorum, and the incidence of other infectious diseases was also low. Sample analyses of the 75,000 or so persons registered as blind in Great Britain reveal cataract as the leading cause with some 25 per cent of cases, and glaucoma as the second cause with 15 per cent. Myopia accounts for some 10 per cent and the group of congenital, hereditary and developmental defects for a further 10 per cent, whilst senile macular lesions give an approximately similar percentage. Since cataract, glaucoma and the senile macular lesions account together for some 50 per cent of all cases, it is not unexpected that some 40 per cent of all registered blind are over the age of 69 years. The blind population as a whole is in fact an aged population, for some 77 per cent are over 49 years of age. The age distribution

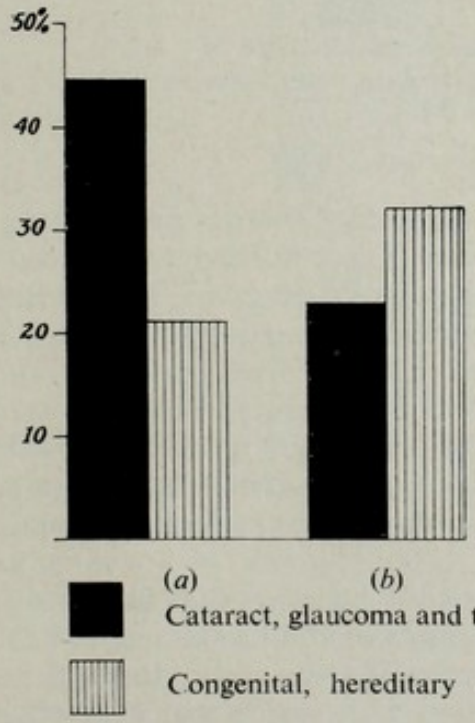


FIG. A.—Scheme to illustrate the fact that though the congenital and hereditary defects are not numerically the most significant causes, they are responsible for the greatest amount of blindness as measured in years.

(*a*) Percentage distribution of all cases.

(*b*) Percentage distribution computed on expected years of blindness (on the assumption that the expectation of the blind population is the same as for the general population).

of the blind does, however, tend to mask the fact that the burden of blindness, as assessed in years of blindness rather than in the number of blind individuals, falls most heavily on the numerically relatively less significant groups afflicted by myopia and by the congenital, hereditary and developmental defects. These two causes account for some 20 per cent of all cases of blindness, but as they affect the young and the middle-aged, they would appear to rank first in terms of years of blindness, overshadowing the causes operative in the aged. This is shown in Fig. A.

During the past hundred years the frequency of blindness has decreased greatly and in the space of the last quarter of a century the incidence of blindness in children aged 5–15 years has fallen from 37·0 per 100,000 in 1923 to 21·3 in 1948 (Fig. B). This decline reflects the elimination of the infectious causes of blindness,

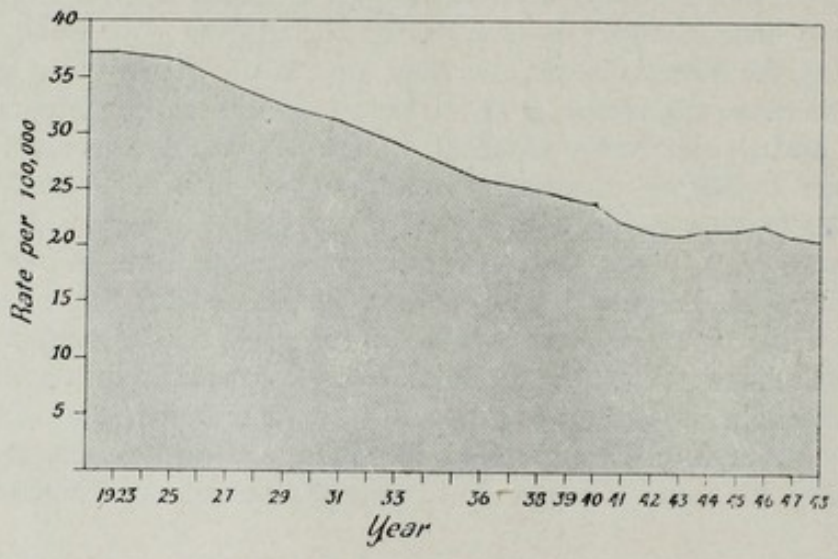


FIG. B.—Graph showing the steady decline in the incidence of blindness in children aged 5–15 years in England and Wales (from 37·0 per 100,000 in 1923 to 21·3 in 1948).

particularly ophthalmia neonatorum, and has brought into sharper relief the significance of the congenital and hereditary anomalies (Fig. C). There is no reason to believe that any such gratifying decline as has been observed in children applies to the population as a whole. There is nothing to suggest that cataract, glaucoma, the senile macular lesions, myopia, and the congenital, hereditary and developmental defects are declining. The causes of blindness as they are seen today and the age structure of the blind population as a whole give little reason to hope that any substantial further decline in the incidence of blindness may be expected in the immediate future from the measures that have proved so effective during the past hundred years.

The causes of blindness as seen today cannot readily be interpreted in terms of extraneous causative agents. Neither cataract, nor glaucoma, nor myopia, nor the senile degenerative changes, nor the hereditary anomalies are explicable in terms of bacteriology. The therapeutic revolution we have witnessed in our generation

has brought into relief a more complex and varied pathology than was envisaged by the pioneers of bacteriology or by our predecessors at the beginning of the century. Throughout the history of medicine there has been a shifting of emphasis, now on the extraneous factor, now on the constitutional factor, and whilst the results of bacteriology—with its stress on the extraneous factor—have been immense, it has become apparent that the constitutional factor, as opposed to the extraneous factor of disease, has now come to be the starting point for further advance.

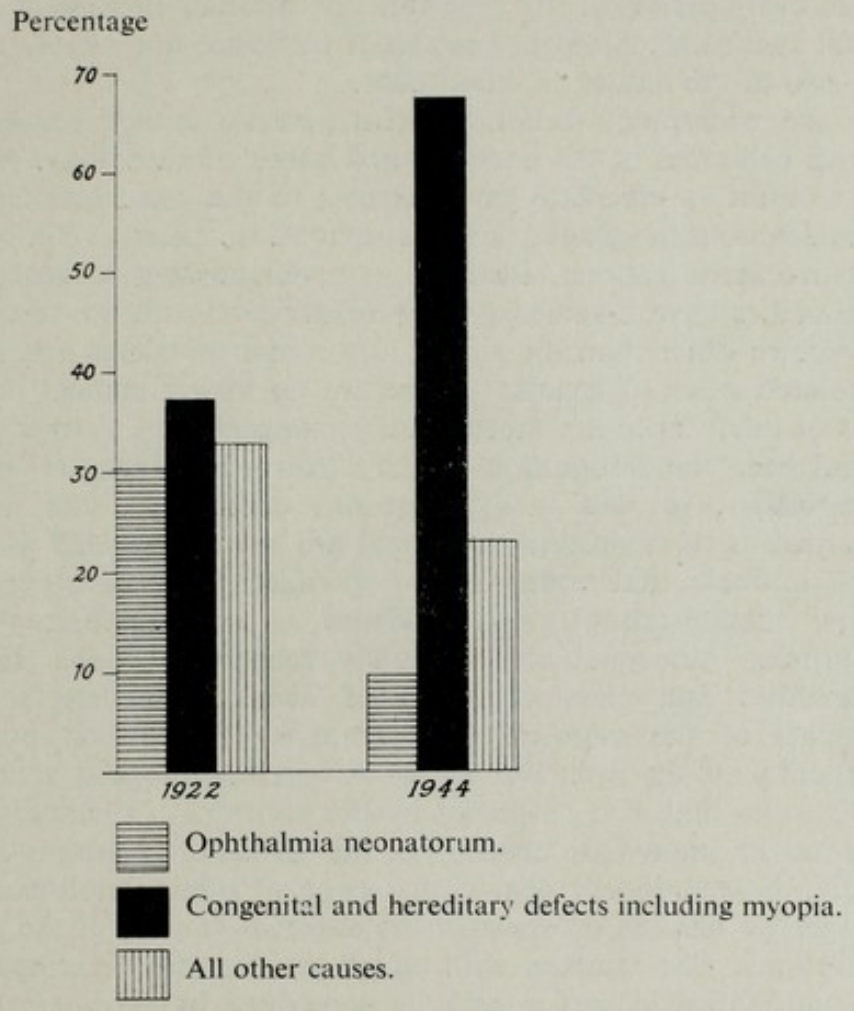


FIG. C.—Causes of blindness as seen in blind schools in England and Wales in 1922 contrasted with 1944.

Constitution is as yet an ill-defined concept. The reactions of an individual to his environment are likely to be a complex process, immensely difficult to unravel. An individual's reactions may be determined by the past experiences of his body, but also by his inherent anatomical and physiological structure. That, in turn, may have been conditioned by extraneous factors such as an abnormal maternal environment during development but also by an inherent genetic structure, and this, again, may well have been moulded by extraneous circumstances.

Medical genetics is an aspect of the study of constitution. The concept of the genetic constitution of an individual presents a sharp antithesis to the concept

of environmental factors. But disease is generally the result of the disharmonious interaction of constitution and environment, so that study of the genetic constitution of man is as significant as the study of the environmental pathogen. At the two extremes, either factor by itself may produce disease, as shown respectively by the lesions produced by mechanical injury and that produced by an inherited gene for retinitis pigmentosa. Frequently, however, other environmental or constitutional factors have to come into play for a disease process to become established. Not every individual exposed to tuberculous infection develops tuberculosis; not every carrier of the gene for, say, the Laurence-Biedl syndrome, develops the full syndrome. Medical genetics is therefore not merely a study of the modes but also of the nature of inheritance.

Contrary to the widespread belief, medical genetics is not concerned with collecting curious pedigrees of the unconsidered trifles of pathology. At the very least, it is an attempt to elucidate some aspects of the constitutional basis of disease. In some affections the genetic factor is obvious. In others, it can be revealed only by exhaustive investigations aided by an understanding of genetic theory. The genetic anomalies have assumed greater significance with the recognition of modes of inheritance other than the simple autosomal recessives and dominants of the past. Isolated cases of genetic disease are no longer clinical puzzles and unusual modes of inheritance are more readily recognized. A further significant development has been the recognition of the abiotrophic character of many of the genetic anomalies, so that many affections coming on late in life and previously regarded as of environmental origin are now recognized as genetic in type. It is not unlikely that some of the so-called senile degenerations are late abiotrophic manifestations, and evidence is accumulating that senile cataract and primary glaucoma are essentially genetic affections. Indeed, the congenital anomalies and classical forms of abiotrophic defects constitute only a small part of the inherited abnormalities or inherited potentialities towards abnormality of the eye. The scope of ophthalmological genetics is, in fact, very much wider than was suspected by the pioneers of the study, and this enlarged scope has an immediate bearing on the causes of blindness and ocular disease generally, as seen today. And if the scope of ophthalmological genetics has become larger, so has the prospect of the eventual control of the genetically determined affections. The fatalism with which genetic affections are generally regarded is as unfounded in reason as it is unjustified by achievement already reached.

It is more than an act of filial piety to pay tribute to the work of Edward Nettleship and C. H. Usher. Their pioneer efforts have done much to make ophthalmological genetics the most highly developed branch of medical genetics. The monumental volume by Julia Bell in *The Treasury of Human Inheritance* has been a constant source of help and inspiration, as have been the exhaustive ophthalmological surveys by A. Franceschetti and by P. J. Waardenburg, and the fascinating *Introduction to Medical Genetics* by J. A. Fraser Roberts.

My thanks are due to many workers for the use of pedigrees and other illustrations, and to Miss Muriel Attfield, M.Sc., and Mr. C. Martin for help with the drawings. Acknowledgement of borrowed illustrations is given under the appropriate figures.

To Dr. H. Kalmus and Dr. J. A. Fraser Roberts I am obliged for critical comments on the first section of this book. Dr. R. A. Burn has kindly helped with the proofs. Miss E. M. Gower and Miss P. M. Rowlatt have greatly facilitated an arduous task by their loyal secretarial help. The staff of Messrs. Butterworth & Co. (Publishers) Ltd. have almost succeeded in making the technical difficulties of book production an unalloyed joy.

December, 1950 ARNOLD SORSBY

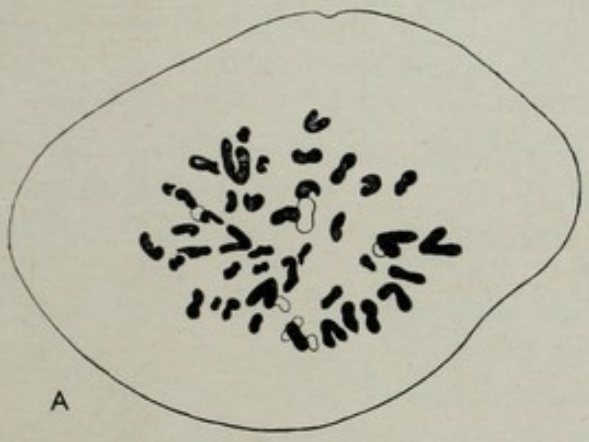
SECTION I
THEORETICAL

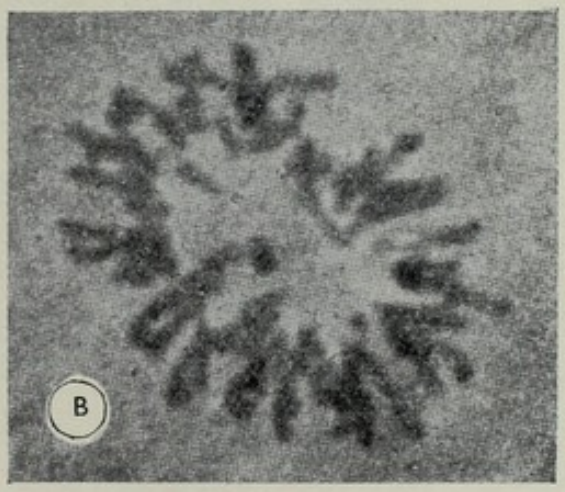
CHAPTER 1

MODES OF INHERITANCE

CHROMOSOMES AND GENES

STUDIES carried out towards the end of the last century on the behaviour of the nucleus during cell division established the fact that the changes taking place in the nuclei of somatic cells were different from those observed in the germ cells—spermatozoa and ova. When a human somatic cell divides into two, each of the 48 chromosomes (which are arranged in 24 pairs) can be seen to split longitudinally, so that each of the resultant two daughter cells contains the original number of chromosomes. Each of the two daughter cells is therefore a complete replica of the mother cell. When division takes place in the germ cells (*formation of gametes*) there is, in effect, no longitudinal splitting of the individual chromosomes. Instead, there is dissociation of the pairs of chromosomes; it is the pairing of chromosomes, but not the chromosome itself, which is split. In consequence the two daughter cells





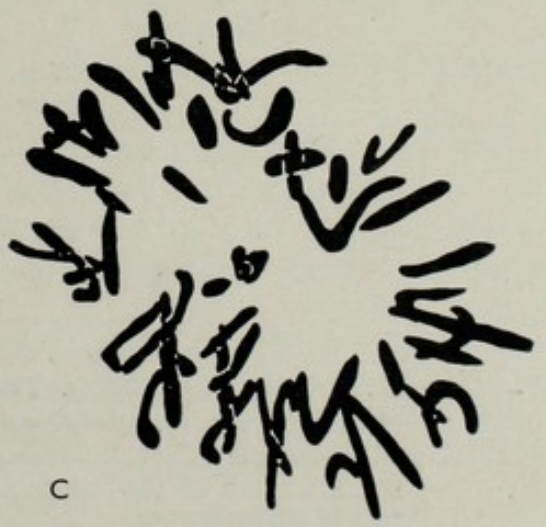


FIG. 1.—Chromosomes in the human cell.

(A) Diagrammatic representation of the 48 chromosomes in the resting stage before cell division (× 3000). The individual chromosomes can be counted. (*After P.C. Koller, Proc. Roy. Soc. Ed.*, 1937, **57**, 194.)

(B) Microphotograph (× ca 2500) of chromosomes in a dividing cell.

(C) Schematic representation of the microphotograph shown in (B). (*After T. Kemp, Zeitsch. f. Mikroskop-Anat. Forschg.*, 1929, **16**, 1.)

of a germ cell carry not 48 chromosomes, but 24 chromosomes (*reduction division*). In the process of fertilization, the head of the spermatozoon carries into the body of the ovum its complement of chromosomes. As each of the two gametes contains 24 chromosomes, the fertilized ovum now contains 48 chromosomes, that is the same number as a somatic cell. These 48 chromosomes do not lie haphazardly in the nucleus of the fertilized ovum, but arrange themselves in 24 homologous pairs, repeating the pattern of somatic cells (Figs. 1 and 2).

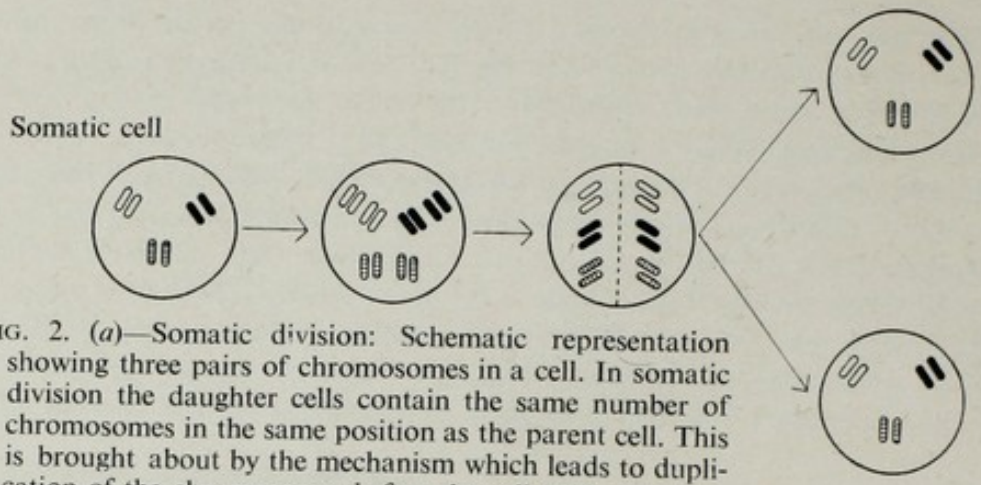


FIG. 2. (*a*)—Somatic division: Schematic representation showing three pairs of chromosomes in a cell. In somatic division the daughter cells contain the same number of chromosomes in the same position as the parent cell. This is brought about by the mechanism which leads to duplication of the chromosomes before the cell splits into two.

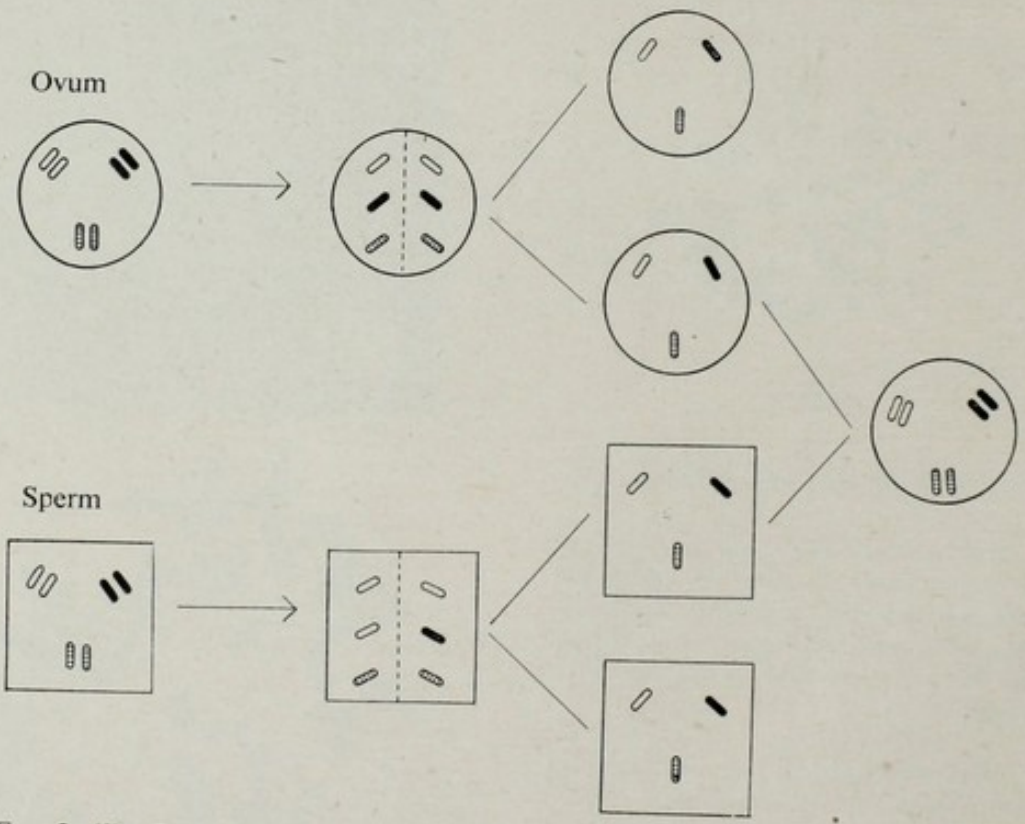


FIG. 2. (*b*)—Reduction division: In germ cells there is in effect no duplication of chromosomes prior to the splitting of the cell; there is, instead, separation of the two halves of a chromosome pair. Complete pairs of chromosomes are brought about by the fusion of two gametes each contributing one of each pair of chromosomes.

These marked differences in the behaviour of the chromosomes of somatic cells and of germ cells fitted well with Weismann's postulate in 1892 that the chromosomes of germ cells carry the hereditary material of the body. The mechanism whereby the chromosomes of germ cells do not split during cell division ensures that the number of chromosomes—and therefore of hereditary material—is not duplicated with each cell division, but remains constant.

Chromosome division is an observable fact. The view that the chromosomes carry hereditary material is an assumption, and this assumption was carried further by Morgan in 1915, when he postulated isolated individual bodies—hypothetical genes—as the actual bearers of individual hereditary characteristics. In this view, a given simple character of body structure is determined by a particular gene at a particular place in a particular chromosome. Or rather, given simple bodily characters are determined by the action of two genes lying opposite each other in a given pair of chromosomes. Since each of the chromosomes is derived from one of the parents, both parents contribute to the development of hereditary characters by the chromosomes and the genes that these carry.

The gene theory of inheritance is, therefore, derived from microscopically observable changes. It is a working hypothesis which explains readily the facts of inheritance as observed in plants and animals. These facts, accumulated over centuries of observation, found a simple general statement in the studies of Mendel (1865) on inheritance in plants. Mendel's work, ignored in his lifetime, did not fructify till the beginning of the present century, when his fundamental findings were re-discovered independently by Correns, De Vries and Tschermak. In its simplest form, his work may be summarized in the following postulates:

(1) A given bodily character is determined by the joint action of two units of hereditary matter.

(2) These units may or may not determine identical somatic features or characters.

(3) These units are indivisible and do not blend. They separate from one another, or segregate, at the formation of gametes (Mendel's *law of segregation*).

(4) In fertilization, the combination of any pair of units of hereditary matter is a chance re-assortment (Mendel's *law of independent assortment*), that is each of the two units contributed by one of the parents has an equal chance of meeting either of the two units contributed by the other parent.

(5) This chance re-assortment may bring together units determining identical or dissimilar characters.

(6) In this mechanism of segregation and assortment there is combination and re-combination of the units of inheritance, but never any blending.

(7) When two units determine two dissimilar characters, one unit only is generally manifest: it is *dominant* to the other unit, which is designated as *recessive*.

(8) Where more than one character is under consideration, the units determining the different characters are subject (except under special circumstances) to the law of independent assortment. As an example yellow wrinkled peas may be given; dependent on the chances of assortment yellowness and wrinkling may or may not be associated in the same pea.

SOMATIC PATTERNS

Genetic theory helps to explain the emergence of different somatic patterns on the basis of a rearrangement of existing hereditary material—the dance of the genes as it has been called. The variety of somatic patterns is greatly increased by two circumstances.

Polygenic Inheritance

If a given bodily characteristic (character or trait) is determined by many pairs of genes, a fantastic number of new patterns can develop from the independent assortment of the different genes that contribute to that character. For most physiological traits—such as stature, or colour of hair or of iris—multiple genes (polygenic or multifactorial inheritance) come into play. Polygenic inheritance, discussed more fully later on, though of great importance in biology, has as yet little application in pathology.

Mutant Genes

Though ultra-microscopic, genes are highly complex bodies. They are also highly stable, but small changes may occur, and these influence greatly the traits that the gene determines. A changed or mutant gene may produce an effect which is innocuous, but it is more likely to be disadvantageous, or, in terms of human medicine, pathological. Genetic disease is therefore not due to any additional or any lacking gene, but to a disadvantageous mutation of an existing gene. The pathological effect will become apparent in the immediate offspring of an individual in whom the mutation has occurred if the mutant gene is dominant. If the mutant gene is recessive, the pathological effect may not become apparent until many generations have passed, when chance re-assortment of genes brings two recessive genes together in the same individual.

The study of pathological genetic features is as yet largely the study of abnormalities determined by a single dominant mutant gene, or by a pair of recessive mutant genes. Simple genetic situations, rather than the complicated situations of polygenic inheritance, therefore underlie the studies in inheritance of morbid conditions.

SOME TECHNICAL TERMS

Each chromosome in a pair of chromosomes is *homologous* to its companion, but not to any other chromosome. The 24 pairs of human chromosomes have theoretical numbers ranging from 1 to 24. As yet, little distinction can be made as between each of the first 23 pairs, and they are known under the generic name of *autosomal chromosomes* or *autosomes*. The twenty-fourth pair differs visibly from the others on microscopic examination in being different in the two sexes. In women, the two chromosomes are of the same length and cannot readily be distinguished from the remaining 23 pairs of chromosomes. In men, one of the pair of chromosomes is shorter than the other, giving this pair of chromosomes a distinctive pattern. The shorter of the two chromosomes is known as the *Y chromosome;* the longer of the two chromosomes is identical to the equal pair of

chromosomes in women (microscopically barely distinguishable from autosomal chromosomes), and is known as the *X chromosome*. Men therefore carry XY sex chromosomes and women carry XX chromosomes.

The position of a given postulated gene in a given chromosome is known as its *locus*. The gene at a given locus is called the *allelomorph* or *allele* of its counterpart in the homologous chromosome. If the alleles express the same character, the individuals are regarded as *homozygous*, and the genes as being in the *duplex* state. If one gene determines a different character from its allelomorph, the individuals are regarded as *heterozygous*, and the genes as being present in the *simplex* state. It follows that, if a mutant gene determines an abnormality, a homozygous individual must of necessity be abnormal, as there is nothing to balance the pathogenic genes. A heterozygous individual will be abnormal if the pathogenic gene is dominant, and will be clinically normal if the pathogenic gene is recessive.

A distinction must therefore be made between the genetic and clinical constitution. By *genotype* is meant the genetic constitution of an individual; by *phenotype* is meant the clinical appearance. An individual who manifests a genetic abnormality may be affected owing to the fact that he carries one dominant gene for the abnormality, or two recessive genes (or very rarely two dominant genes). An individual who is clinically normal may be genetically abnormal in so far as he may carry one recessive gene for the abnormality. A phenotypically normal individual may therefore be genetically abnormal, and a genotypically abnormal individual may be affected clinically because of more than one possible mode of genetic constitution.

An individual possessing a particular gene is of necessity a *carrier* or *conductor* of the gene. The term is, however, usually restricted to apply to individuals who carry a gene without manifesting it phenotypically, for example an individual carrying an autosomal recessive gene on one chromosome only.

AUTOSOMAL INHERITANCE

Theoretical Possibilities

A mutant gene determining a particular pathological abnormality ("pathogenic gene") may be carried by one or both parents, each of whom may be either heterozygous or homozygous. These possible situations are shown in Figs. 3 and 4 and in Tables I and II.

One parent carries the pathogenic gene

When this occurs the parent may be either heterozygous or homozygous for the pathogenic gene. Figs. 3 *a* and *b* and Table I illustrate the theoretically expected course on the Mendelian laws of segregation and of independent assortment. The emergence of genotypes is, of course, independent of dominance or recessiveness, which determines phenotypes but not genetic constitution.

Both parents carry the pathogenic gene

Both parents may be either heterozygous or homozygous for the abnormal gene. There is also the possibility of one parent being homozygous and the other

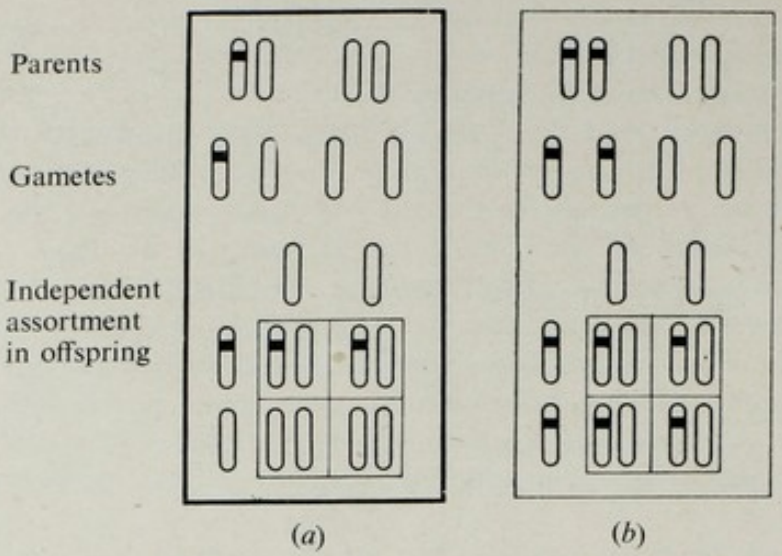


FIG. 3.—Inheritance of a pathogenic gene carried by one parent only. In these diagrams the gene determining an abnormality is shown as black in the drumstick figure which represents a chromosome. In reproduction there is first a dissociation of the two chromosomes carrying the genes determining the characteristic in each of the parents. In the constitution of the new individual any two of the four dissociated chromosomes may enter, resulting in a variety of patterns. (The arrangement of gametes at two sides of the square pattern gives an easy way of obtaining the four possible random combinations of four chromosomes.) This and Fig. 4 show the various theoretical possibilities. The common clinical situations are shown in the framed diagrams. Those with a heavy frame represent common situations with dominant inheritance; those with a light frame represent those with recessive inheritance.

(*a*) Parent is heterozygous. Fifty per cent of the children will also be heterozygous. If the gene is recessive neither the heterozygous parent nor the heterozygous children are affected. If dominant, the heterozygous parent and heterozygous children are affected.

(*b*) Parent is homozygous for the pathogenic gene. With one parent homozygous for the pathogenic gene and the other homozygous for normalcy all children are heterozygous. If the pathogenic gene is dominant all children are affected; if it is recessive all are unaffected. The parent homozygous for the pathogenic gene is clinically abnormal whether the condition is dominant or recessive, as he has no gene for normalcy.

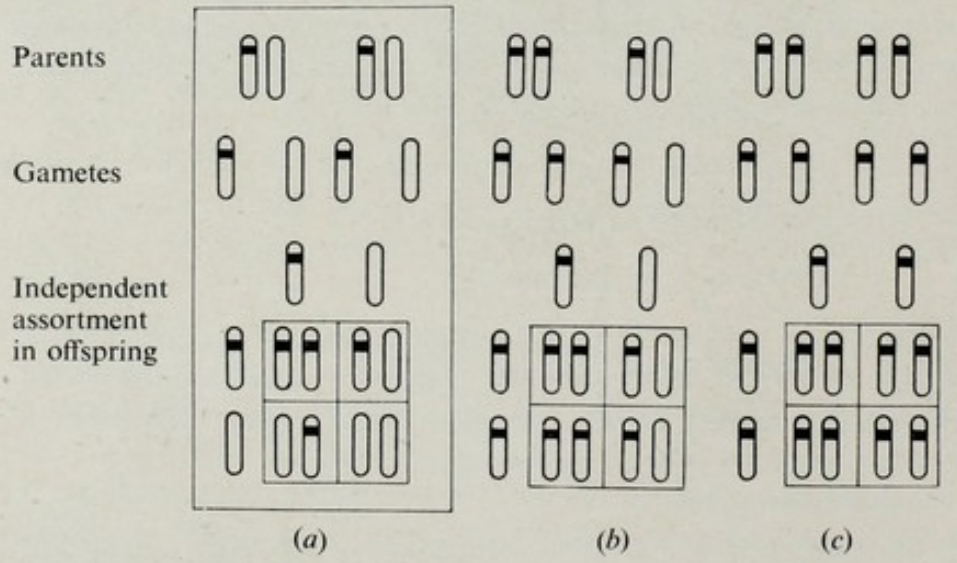


FIG. 4.—Inheritance of pathogenic genes carried by both parents. (*a*) Both parents are heterozygous. When both parents are heterozygous some children are homozygous for the pathogenic gene, some homozygous for normalcy, and some heterozygous. Where the pathogenic gene is dominant both the parents and 75 per cent of the children are affected. Where it is recessive, the parents are normal and 25 per cent of the children are affected.

(*b*) One parent is homozygous for the pathogenic gene and the other heterozygous. With one parent homozygous some children are homozygous and the others heterozygous. If the gene is dominant both parents and all the children are affected. If the gene is recessive the heterozygous parent and the heterozygous children are normal: the homozygous parent and homozygous children are affected.

(*c*) Both parents are homozygous for the pathogenic gene. With both parents homozygous all children are also homozygous. Irrespective of whether the gene is recessive or dominant, all individuals are affected.

heterozygous. Figs. 4 *a*, *b* and *c* and Table II illustrate the theoretically expected assortment under these circumstances.

Ratios of Affected Individuals

Figs. 3 and 4 show not only the genetic combinations, but the ratios in which these appear. These ratios are based on the assumption that the re-combination of chromosomes into pairs is a random process, and the ratios thus obtained are subject to the statistical vagaries of small numbers if individual families are studied. Bearing on the more common situations the essential features that emerge are as follows.

(1) When both parents are heterozygous, the gene being recessive, 25 per cent of the offspring are affected (Fig. 4 *a*)—the classical Mendelian ratio of 1 : 3.

TABLE I

Tabular presentation of relations shown in Fig. 3

Inheritance of pathogenic genes carried by one parent only

Parent		Offspring	
Genotype	Phenotype	Genotype	Phenotype
Heterozygous 	Normal if gene is recessive Affected if gene is dominant	50% heterozygous 	Normal if gene is recessive Affected if gene is dominant
		50% homozygous for normal gene 	Normal
Homozygous for abnormal gene 	Affected	All heterozygous 	Normal if gene is recessive Affected if gene is dominant

(2) When one parent is heterozygous, the pathogenic gene being dominant, and the other parent is homozygous for normalcy, 50 per cent of the offspring will be likewise affected (Fig. 3 *a*)—the classical 1 : 1 ratio.

Modes of Autosomal Inheritance

Dominant inheritance

Fully dominant inheritance is inheritance regularly from generation to generation. The essential feature in dominant inheritance is the fact that the affection can be and usually is derived from one parent only. It may be accepted that a pedigree shows autosomal dominant inheritance if the following criteria are satisfied.

(a) Direct transmission over three generations.

(b) A frequency of approximately 50 per cent of affected individuals.

(c) There is no predilection for either sex.

TABLE II

TABULAR PRESENTATION OF RELATIONS SHOWN IN FIG. 4

INHERITANCE OF PATHOGENIC GENES CARRIED BY BOTH PARENTS

Parents		Offspring	
Genotypes	Phenotypes	Genotypes	Phenotypes
Both heterozygous	Both normal if gene is recessive Both affected if gene is dominant	25% homozygous for pathogenic gene	Affected
		50% heterozygous	Normal if gene is recessive Affected if gene is dominant
		25% homozygous for normal gene	Normal
One homozygous for pathogenic gene and other heterozygous	Homozygous parent affected Heterozygous parent normal if gene is recessive Heterozygous parent affected if gene is dominant	50% homozygous for pathogenic gene	Affected
		50% heterozygous	Normal if gene is recessive Affected if gene is dominant
Both homozygous for pathogenic gene	Both affected	All homozygous for pathogenic gene	Affected

Certain variations occur in dominant inheritance:

(a) Generally one parent only is affected and carries a pathogenic gene on one chromosome only. As shown in Fig. 3 *a*, under these conditions 50 per cent of the offspring are affected. Rarely the affected parent carries the pathogenic gene on both chromosomes. In this case all offspring are affected (Fig. 3 *b*). Occasionally the dominant gene for abnormality is carried on one chromosome by each parent. In this case, 75 per cent are affected (Fig. 4 *a*).

(b) Inheritance over two generations, though suggestive of a dominant affection, is not conclusively so. It may happen that one parent is homozygous for a recessive gene, and is therefore affected, whilst the other parent is heterozygous for this

gene, and therefore clinically normal (Fig. 4 *b*). Since 50 per cent of the offspring of such parents would be affected, the suggestion of dominance would therefore be strengthened by the ratio of affected to unaffected children.

(c) Occasionally, for reasons unknown, a pathogenic gene produces no pathological effect in a particular individual—the clinically well-known phenomenon of irregular dominance, or "skipping a generation". In technical language, the gene is not expressed. Affections showing such irregular dominance are regarded as being due to genes which are not fully dominant.

Recessive inheritance

The diagnosis of recessive inheritance is frequently difficult. The parents being clinically normal, their genetic constitution is not obvious, and has to be deduced from indirect data. As for the offspring, single cases of the anomaly occur frequently in sibships, seeing that only 25 per cent of the offspring on the average show the anomaly, and that families are generally small.

The parents

As far as the parents are concerned, two possible factors may help in the diagnosis:

(a) The occurrence of the same affection in collateral branches of the family. Unless the pedigree is extensive, taking in many such branches, a history of such an occurrence is not often obtained, and in any case is not conclusive, as this occurs in irregular dominance too.

(b) A history of consanguinity. Consanguinity is of importance in recessive affections because two related individuals are more likely to carry the same pathogenic gene, which they will have derived from a common ancestor, than would two unrelated individuals.

It follows that in exceptionally rare diseases the incidence of consanguinity in the parents will be very high. In more common conditions the incidence of consanguinity will be considerably lower because the gene is widely scattered in the general population. The greater frequency of the proverbial village idiot in small communities is partly due to the fact that such communities are more inbred and therefore genetically more homogeneous than populations in towns.

As to the actual significance of consanguinity in recessive affections, it has been computed that if a recessive affection is present in one in a million of a population, it will be found that 38 per cent of the parents of affected individuals are first cousins, but if present in one in ten thousand, they are first cousins only in 6 per cent.

In most European countries the frequency of marriages between first cousins is $\frac{1}{2}$–1 per cent; it is always rather higher in country districts than in towns. Affections which carry a consanguinity rate of more than 2 per cent are suspect of being recessive.

The sibship

The occurrence of the same affection in more than one member of a sibship whose parents are normal is the criterion which draws attention to the possibility of a recessive condition. An isolated occurrence of the affection in the children of normal parents hardly raises the possibility of a genetic affection, unless the clinical condition is clearly recognized as such. As only 25 per cent of the offspring are

clinically affected, one requires, theoretically, a family of eight children before two cases would appear. Actually it may happen, because of the vagary of small numbers, that in a family of two children both would be affected, and likewise in a family containing more than four children none might be affected. It can be shown that with an expectation of one in four affected, a hundred families with four children in each family would give the following distribution of affected children:

Number affected	*Percentage*
None	31·6
One	42·2
Two	21·1
Three	4·7
All	0·4
	100·0

It follows, therefore, that many parents carrying a recessive condition may have no affected children, and likewise many such parents would have only one affected child, and the diagnosis of a genetic affection would be in doubt. Actually, as can be seen from this computation, with a hundred couples carrying a recessive gene and having families of four children, in no less than 74 per cent the evidence that the parents carry a genetic anomaly would not be obvious. Likewise there would be more isolated (sporadic) cases than familial cases, the ratio being 42·2 : 26·2, or roughly 60 per cent and 40 per cent respectively. The percentage of sporadic cases would be higher still with sibships containing less than 4 individuals and lower with larger sibships. In actual practice, published clinical reports are based largely on the exceptional statistical vagaries, which illustrate a high incidence of affected children; the sporadic cases in particular are not often recorded. For this reason most clinical reports on recessive conditions show an incidence considerably in excess of the expected 25 per cent.

SEX-LINKED INHERITANCE

Sex-linked inheritance is fundamentally the same as all other modes of inheritance; it has, however, two distinguishing features. In the first place, as already pointed out, the sex chromosomes differ from the autosomal chromosomes in being different in the two sexes. In women there are two X chromosomes, and these are largely indistinguishable from the autosomal chromosomes. In men, one of the sex chromosomes differs from its fellow in being shorter, the Y chromosome. Fig. 5 is a diagrammatic representation of the constitution of the X and Y chromosomes. It will be seen that both chromosomes have a segment that is complementary or

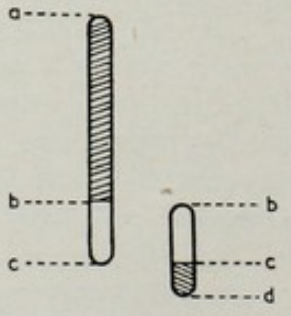


FIG. 5.—Diagrammatic representation of the constitution of the sex chromosomes. The two sex chromosomes have one homologous section, section *b* and *c* being present in both chromosomes; they carry corresponding genes.

The Y chromosome has no counterpart to the section *a*–*b* in the X chromosome, whilst the X chromosome has no counterpart of the section *c*–*d* in the Y chromosome.

homologous, indicated in the diagram by an unshaded area b–c. In the X chromosome there is segment a–b which has no counterpart in the Y chromosome, the non-homologous part of the X chromosome. Likewise the Y chromosome has a non-homologous segment c–d. The genetic constitution of a man is therefore different from that of a woman in so far as a portion of his X chromosome has no homologue. It also differs in that he possesses a small segment of the Y chromosome which has no counterpart in the X chromosome. The question of recessiveness and dominance therefore becomes a matter for special consideration, because a pathogenic gene on either that part of a man's X chromosome which has no counterpart in the Y chromosome or on the non-homologous part of his Y chromosome will express itself clinically irrespective of whether it is recessive or dominant. In a woman, a recessive gene on one X chromosome will not express itself as there is a dominant normal gene on the homologous X chromosome to inhibit it.

The other significant feature in sex-linked inheritance arises from the fact that the location of the pathogenic gene can be clearly placed in the sex chromosomes because of the obvious association of the affection with the sex of the patient.

Modes of Sex-linked Inheritance

Recessive X chromosomal inheritance

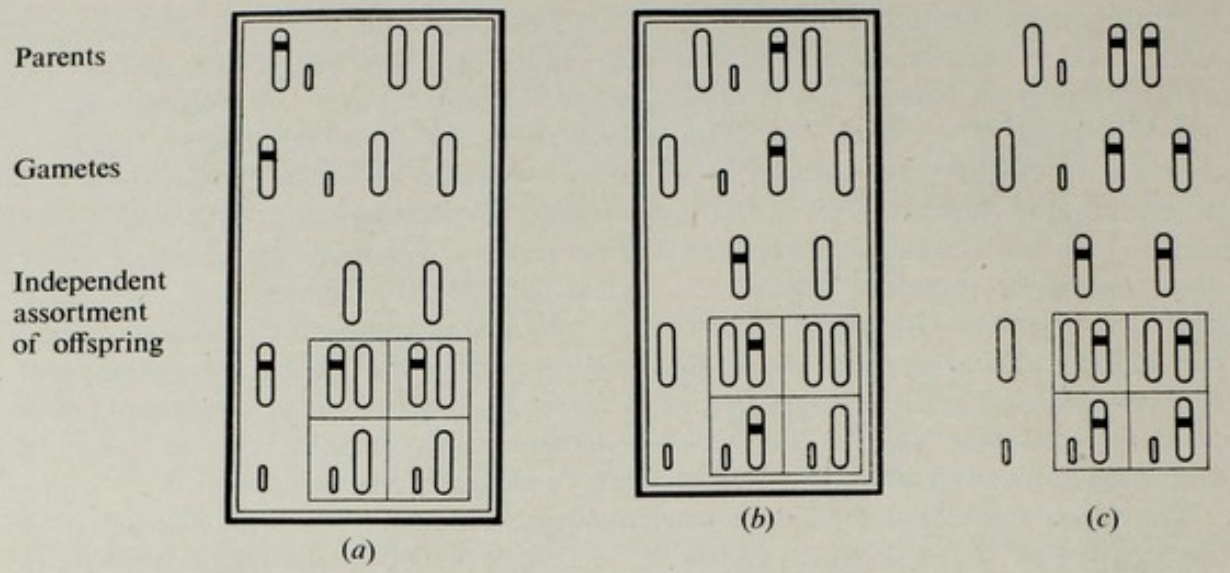
It is this mode of inheritance which is generally implied when the term sex-linked inheritance is used—a mode of inheritance well known to the older clinicians as inheritance according to Nasse's law. This stated that affected men transmit their affection never to, or through, their sons, but through their daughters, who themselves are unaffected but some of whose sons are affected. The genetic mechanism for this valid observation is explained in Fig. 6. It is assumed that the affection —say deuteranopia—is recessive and is carried by the X chromosome. In Fig. 6 *a*, the father is affected, as the Y chromosome does not carry any gene to counteract the abnormal gene located in his X chromosome. He is, therefore, a deuteranope. All his children are phenotypically normal, the sons being normal genotypically also (for their X chromosome is from their normal mother), while the daughters are all heterozygotes (for one of their X chromosomes is derived from the affected father). As the condition is recessive the daughters do not manifest it; they are carriers. A carrier daughter marrying a normal man (Fig. 6 *b*) has phenotypically normal daughters, half of whom are heterozygous; whilst there are equal proportions of normal and affected sons.

Some exceptional circumstances may occur:

(a) A woman who is a carrier married to an affected man will have both normal and affected sons, whilst of her daughters 50 per cent will be carriers, and 50 per cent affected (Fig. 6 *d*). Such a marriage is one of the explanations for the occasional appearance of women suffering from a recessive sex-linked defect such as colour-blindness.

(b) An affected woman marrying a normal man will have children who all carry one pathogenic gene, but only the sons will be phenotypically affected (Fig. 6 *c*). This is the classical situation of criss-cross inheritance: the daughters resemble the father and the sons resemble their mother.

(c) An affected woman marrying an affected man will have children who are all affected (Fig. 6 *e*).



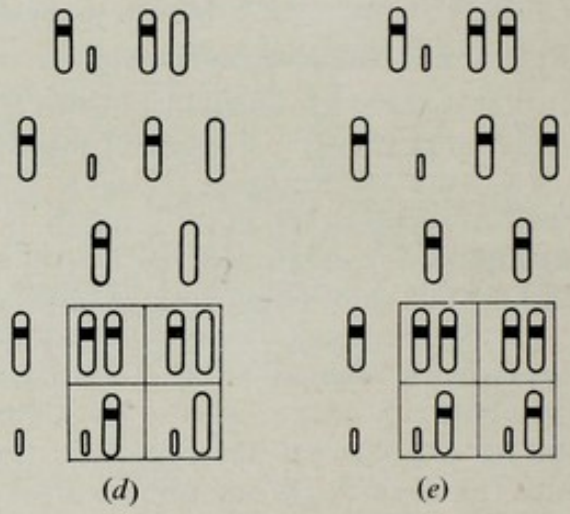


FIG. 6.—Inheritance of a sex-linked (X chromosomal) gene. The five possible theoretical situations are illustrated in diagrams (*a*)–(*e*). Diagrams (*a*) and (*b*) represent common clinical situations, and as shown by the heavy and light frames around them are significant for both dominant and recessive inheritance.

Gene carried by one parent

(*a*) The father is affected irrespective of whether the gene is dominant or recessive, as there is no counterpart on the Y chromosome to overcome the effect of the pathogenic gene on the X chromosome. Of his children, only the daughters will have the pathogenic gene. They will not be affected if the gene is recessive, but will be affected if the gene is dominant.

(*b*) The mother carries the pathogenic gene. If the gene is dominant she is affected, but is unaffected if it is recessive. Fifty per cent of both sons and daughters will carry the gene. If the gene is recessive, only the sons carrying this pathogenic gene will be affected. If it is dominant both the sons and daughters carrying it will be affected.

(*c*) The mother is homozygous for the pathogenic gene. She is affected whether the gene is recessive or dominant. All her children will carry the pathogenic gene: if the gene is dominant they will all be affected. If the gene is recessive, only the sons will be affected.

Gene carried by both parents

(*d*) The mother is heterozygous, and the father carries the gene on the non-homologous part of the X chromosome, and he will be affected irrespective of whether the gene is dominant or recessive. The mother will be affected only if the gene is dominant. All daughters will carry the gene, 50 per cent being heterozygous and 50 per cent being homozygous. With a recessive gene only the homozygous daughters will be affected; with a dominant gene all will be affected. Fifty per cent of the sons will carry the pathogenic gene and will be affected irrespective of whether the gene is dominant or recessive.

(*e*) The mother is homozygous and the father carries the gene on the non-homologous part of the X chromosome. Both parents and all the children will be affected.

Dominant X chromosomal inheritance

The theoretical possibilities in the case of a dominant gene situated on the non-homologous part of the X chromosome are illustrated in Figs. 6 *a* and *b*. If the father is affected (Fig. 6 *a*) none of his sons can be affected, for all his sons get their X chromosome from their mother (the father contributing the Y chromosome). All the daughters are bound to be affected, as all daughters would have an X chromosome contributed by the father carrying an abnormal gene. (This is another variety of criss-cross inheritance, the sex of affected children being opposite that of the affected parent.) If the dominant gene is carried by the mother (Fig. 6 *b*) sons and daughters would both fall into two types; one half would have a normal X chromosome, the other half an abnormal X chromosome; 50 per cent of both the sons and the daughters would, therefore, be affected. The ratio of affected to unaffected of each sex is 1 : 1, and this does not differ from the distribution observed in an autosomal dominant affection.

Y chromosomal inheritance

Just as the greater part of the X chromosome has no counterpart in the Y, so there is a portion of the Y chromosome (*c–d* in Fig. 5) which has no counterpart on the X chromosome. The genes it carries are few in number and consequently pathological conditions are very few. When such are present, they must be expressed and the affection will occur in men only, and will be transmitted from generation to generation, all the sons being affected. As there is nothing to balance the action of a gene in the c–d segment of the Y chromosome, the question of dominance or recessiveness does not arise.

Partial sex-linkage

It will be recalled that there is a portion of the Y chromosome (b–c) which has a counterpart in the X chromosome (*see* Fig. 5). The inheritance of a pathogenic gene situated on these homologous portions of the sex chromosomes is in some ways no different from that observed with two autosomal chromosomes, and for many years conditions now recognized as possibly due to partial sex-linkage were regarded as autosomal.

The possible theoretical situations are as follows :

(1) The pathogenic gene is carried by the mother only, either in the simplex or the duplex state (Fig. 7 *a* and *b*).

(2) A pathogenic gene is carried by the father only, either in the simplex state, when it may be on the X chromosome or the Y chromosome, or in the duplex state (Fig. 7 *c*, *d* and *e*).

(3) The pathogenic gene is carried by both parents. Here again the mother may be either heterozygous or homozygous; the father may carry the gene on either the X or the Y chromosome, or in the duplex state (Fig. 7 *f–k*).

Of the many possibilities shown in Fig. 7 only a few are likely to occur clinically.

Recessive genes

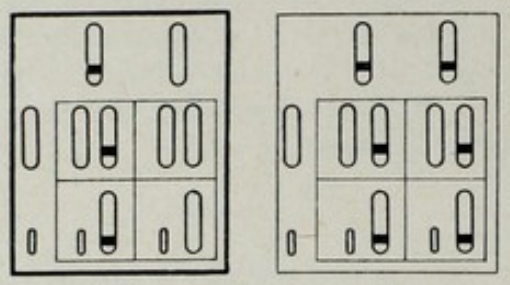
If only one gene is pathogenic and is recessive, it will obviously not manifest itself. In offspring of carriers the sex ratio will vary according to whether the gene is carried by the father on the homologous parts of the X or the Y chromosome (Fig. 7 *f* and *g*).

FIG. 7.—Inheritance of a partially sex-linked gene. The more significant clinical possibilities are indicated by the heavy frames for dominant and light frames for recessive affections. The genetic constitution of the parents is not shown separately, but can be seen from the chromosome diagram franking the squares.

Gene carried by the mother

(*a*) With a recessive gene on one chromosome in the mother she would not be affected and 50 per cent of her sons and daughters would carry the gene without showing it. With a dominant gene the mother would be affected and so would 50 per cent of her sons and daughters.

(*b*) The mother is homozygous and therefore affected whether the pathogenic gene is dominant or recessive. All her children would carry the gene. All would show it if the gene were dominant and none if the gene were recessive.



(*a*) (*b*)

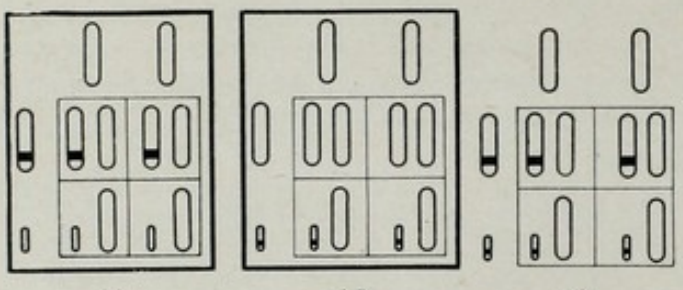
Gene carried by the mother

Gene carried by the father

(*c*) The father is heterozygous. He would be affected if the condition is dominant and unaffected if the gene is recessive. Only his daughters can carry the gene (in the absence of cross-over). These daughters would be unaffected if the gene is recessive and affected if dominant.

(*d*) The father carries the gene on the Y chromosome. He would not be affected if the gene is recessive. Only his sons can carry the gene (in the absence of cross-over) and they would be affected only if the gene is dominant.

(*e*) The father is homozygous (and affected). All his children would carry the gene and none show it unless the gene is dominant.



(*c*) (*d*) (*e*)

Gene carried by the father

Gene carried by both parents

(*f*) Both parents are heterozygous. Neither would be affected if the gene is recessive. Fifty per cent of the daughters would be homozygous and 50 per cent heterozygous. Of the sons 50 per cent would be heterozygous.

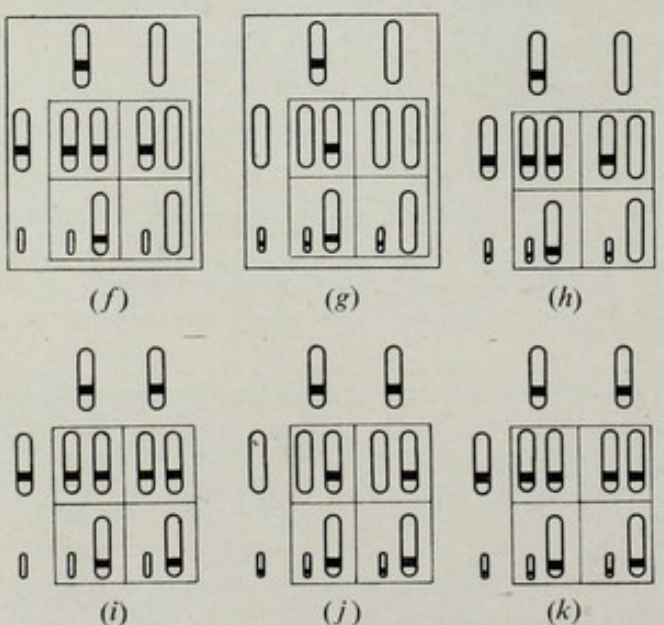
(*g*) The pathogenic gene is carried by the mother on one X chromosome and by the father on his Y chromosome. Neither would be affected unless the gene is dominant. Fifty per cent of the daughters will be heterozygous; 50 per cent of the sons will be homozygous, and 50 per cent heterozygous.

(*h*) The father is homozygous and the mother heterozygous. Fifty per cent of the sons and daughters will be homozygous and 50 per cent heterozygous.

(*i*) The mother is homozygous and the father heterozygous, carrying the abnormal gene on his X chromosome. All the daughters will be homozygous and all the sons heterozygous.

(*j*) The mother is homozygous and the father is heterozygous, carrying the pathogenic gene on his Y chromosome. All the sons will be homozygous and all the daughters heterozygous.

(*k*) Both parents are homozygous. All the children are homozygous.



(*f*) (*g*) (*h*)

(*i*) (*j*) (*k*)

Gene carried by both parents

If the father as well as the mother carries the pathogenic gene on his X chromosome (Fig. 7 *f*), daughters only can be affected—those that have one of the abnormal chromosomes of the mother in addition to the father's abnormal X chromosome. Some daughters are carriers. None of the sons is phenotypically affected though 50 per cent carry the gene. If the pathogenic gene is carried by the father on the homologous part of the Y chromosome (Fig. 7 *g*), no daughter can be affected phenotypically, whilst all sons carry the gene and 50 per cent are affected.

Dominant genes

If the gene is dominant there is a considerable difference in the outcome, dependent upon whether the gene is carried by the mother or by the father. If carried by the mother (Fig. 7 *a*), 50 per cent of the children are affected, and the sex ratio is the same for sons and daughters. If it is carried by the father there are two possibilities: If carried on his X chromosome (Fig. 7 *c*), none of his sons can be affected, for the sons get a normal X chromosome from their mother, but all the daughters must be affected as they will have one of their X chromosomes from their affected father—another instance of criss-cross inheritance. If the gene is situated on the Y chromosome (Fig. 7 *d*), none of the daughters but all the sons will be affected. As in dominant X chromosomal inheritance, transmission by the mother gives no special sex ratios, but transmission by the father gives unusual sex ratios.

These ratios are largely theoretical. The mechanism of crossing-over discussed in the next chapter, ensures some departure from these expectations.

MODES OF INHERITANCE OTHER THAN DOMINANT AND RECESSIVE

Intermediate Inheritance (Incomplete Dominance)

In the discussion so far, it has been assumed that genes are always clearly dominant or recessive. This is generally the case in domestic animals and in cultivated plants, but there are exceptions in which there is no clear dominance, and it is likely that in man such exceptions are not infrequent. When Mendel's work was re-discovered in the beginning of the century, Correns drew attention to what may be called incomplete dominance, or intermediate inheritance.

In the "four o'clocks" (*Mirabilis jalapa*), plants of a white flowering race crossed with those of a red flowering race produce offspring with pink-coloured flowers, that is, unlike those of either parent. There is no blending of the two genes here, as can be proved by the fact that self-fertilization of these pink-coloured plants produces red, pink and white flowers in the Mendelian genetic ratio of 1 : 2 : 1, that is, fundamentally the same as the familiar phenotypic ratio of 3 : 1 or three coloured to one white.

> "The colour of the hybrid four o'clocks might be compared to the pink light which would result if lights from red and white lamps were thrown on a screen at the same time. In this case there is no mixing at the source; the red and white lamps are themselves not changed. In the same way the normal and white alleles in the four o'clocks give rise to a mixed expression, but the alleles themselves do not mix; otherwise the hybrid could not produce pure red and pure white offspring." (Altenburg, 1945.)

In human pathology, an intermediate mode of inheritance is not readily recognized, except in the case of sex-linked genes. With such genes the full effect is

manifest in a man, because there is no allelomorph to modify its expression as there is in the case of a woman carrying one pathogenic gene and one normal gene. In consequence, pathogenic, intermediate, sex-linked genes determine different clinical pictures in the two sexes, as is seen in choroideremia.

An example of intermediate sex-linked inheritance in animals is the tortoise-shell colour seen only in female cats. Tortoise-shell is the intermediate effect of the presence of a gene for black and an allele for yellow carried on the non-homologous part of the X chromosome. In the case of a male cat, only yellow or black can be present.

With autosomal genes, an intermediate effect could only be recognized as such if individuals possessing two pathogenic genes were known, and showed a more severe affection. There is some evidence that the combination of two such pathogenic genes is lethal. Whether a particular affection showing dominance is due to a true dominant, or represents the intermediate effect of a pathogenic gene modified by a non-pathogenic gene is, as yet, undetermined in most so-called dominant affections.

Incomplete Recessiveness

By definition a recessive gene should be completely unexpressed unless present in the duplex state. This is generally the case, but the manifestations of a recessive gene may not be completely suppressed. The gene for deuteranopia is recessive and is carried on the X chromosome. As such it is always expressed in a man carrying the gene on his one X chromosome, and is generally not expressed by heterozygous women. Minor degrees of colour defect are, however not infrequent in such women and occasionally they show the full defect.

CONSANGUINITY IN GENETIC DISEASE

The significance of consanguinity is nowhere else so marked as in recessive affections.

In dominant affections, marriage to a related individual who is not affected would be of importance only if he happened to carry, but not show, an incompletely dominant gene. In sex-linked inheritance, recessive genes in the non-homologous portion of the X chromosome will manifest themselves irrespective of the constitution of the other parent; this likewise applies to genes on the non-homologous portion of the Y chromosome; and to dominant genes on either the homologous or non-homologous portions of the sex chromosomes. Consanguinity becomes of importance with a recessive gene situated on the homologous portion of the X and Y chromosomes. Here the sex ratios will be different from the sex ratios on autosomes. If the mother is a carrier and the pathogenic gene is carried by the father on his X chromosome, 50 per cent of the daughters and none of the sons will be affected; if the pathogenic gene is carried by the father on his Y chromosome, 50 per cent of the sons and none of the daughters will be affected.

CHAPTER 2

SOME GENERAL CONCEPTS

GENE MECHANISMS

MUTATION

THE EMERGENCE of new hereditary features in animals and plants under controlled conditions is the basis of the postulate of mutation. Though genes usually produce their likes, they are occasionally liable to produce unlike genes, which then multiply in the new fashion. Most mutations are biologically harmful, or actually pathogenic, and tend to be eliminated by natural selection. A few are beneficial, that is, they tend to give the individuals carrying them a greater survival value; such mutations may spread more widely through the community. Some are neutral in effect. Mutated genes may mutate back to normalcy, as has been observed in Drosophila. It must be stressed that a mutated gene is not a "new" gene, but a modification or mutant of a pre-existing gene with a consequent modification in the traits it determines.

Manifestation

Once a gene has mutated it has a life history of its own, which varies with its character and effects:

Autosomal recessives

As can be seen from Fig. 8 a recessive gene may remain hidden for many generations, and will become manifest only from a mating of heterozygotes, producing affected offspring. Having become manifest in a particular generation it again may remain latent for many successive generations. The duplex state may help to eliminate the gene because the homozygotes may fail to perpetuate it owing to infertility; and in the extreme cases homozygotes may never appear as the gene may be lethal in the duplex state. Obviously the number of heterozygotes carrying a recessive gene will always be greatly in excess of the homozygotes.

Sex-linked recessives

In contrast to autosomal recessives, sex-linked recessive mutants readily become unmasked. Such mutant genes become manifest as soon as they are carried on the non-homologous portion of the X chromosome of a man.

If the mutant gene is carried on the X chromosome of a woman, the affection becomes manifest only in the next generation among half her sons. An example of the appearance of such a mutation is seen in the case of the offspring of Queen Victoria; haemophilia occurred amongst her male descendants and spread through the former dynasties of Russia and Spain. Queen Victoria's antecedents did not show haemophilia, for it is unlikely that the condition would have escaped observation if it had occurred amongst men in previous generations, particularly in an

age when venesection was fashionable. A mutation of a recessive sex-linked gene must therefore have occurred in the gametes of one of her parents.

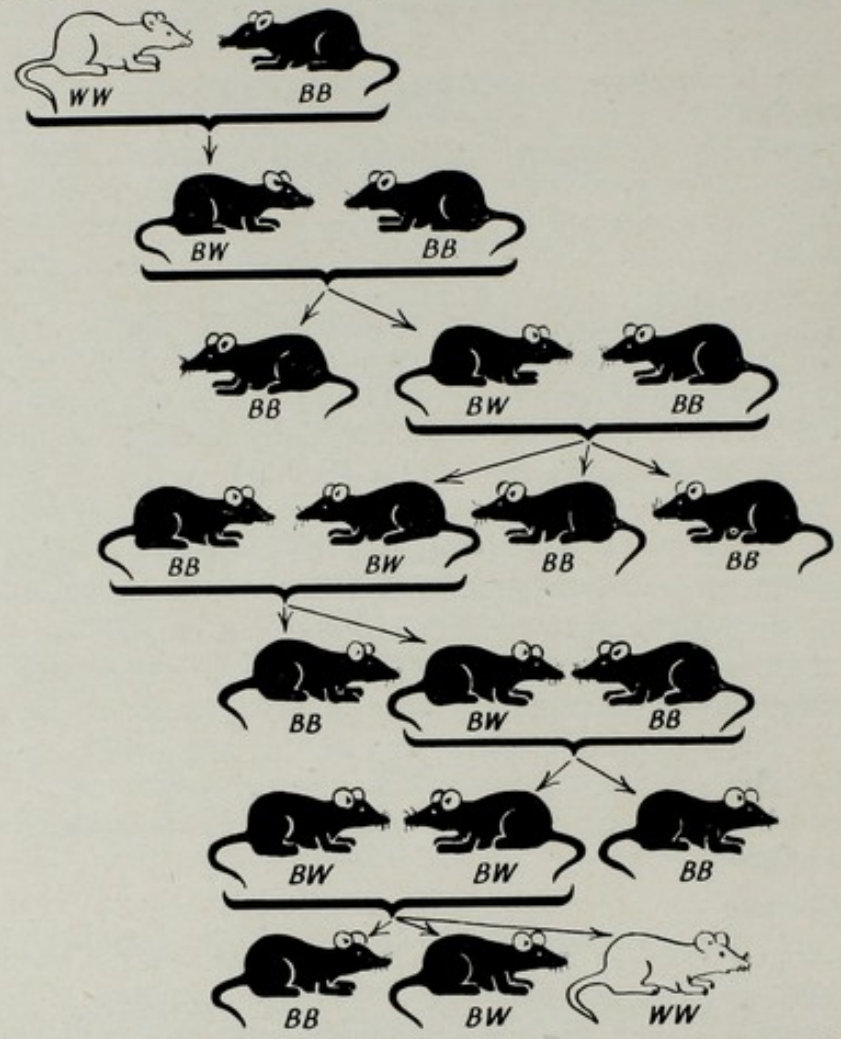


FIG. 8.—To illustrate that a recessive gene (W) may remain concealed for many generations of mating till two heterozygous individuals (BW) chance to mate. (*After G. Dahlberg. Race, Reason and Rubbish*, 1943. *London: Allen & Unwin.*)

Dominants

In the case of a dominant gene the life history of the gene will depend on its effects on the individual. If the manifestations of the gene are of no great personal consequence, such as, say, dominant inheritance of a moderate degree of hypermetropia, the gene perpetuates itself at the same rate as other genes. If, however, the condition is of serious import, such as the dominant inheritance of congenital optic atrophy, it is unlikely, because of social and perhaps also biological reasons, that there will be as many subsequent families, or that they will be as large as those of normal individuals. If the gene is of a highly lethal character, such as dominant glioma of the retina, the chances of the gene perpetuating itself become very slight indeed. On this basis one would expect dominant genes of serious import to have become eliminated from the community at large over the centuries of human existence. Actually there is good evidence that the frequency of serious dominant affections is very much the same in different generations, and it has been

postulated that normal and abnormal genes retain their relative frequency, that is, remain in equilibrium, owing to fresh mutations replacing the genes that are lost. On this basis it is easy to understand that in the case of less serious dominant affections, pedigrees extending over many generations backwards can readily be established, but no such extensive pedigrees can be obtained for the more serious dominant affections. Frequently only two generations can be clearly established, and it is possible that many rare affections of a severe character occurring sporadically—as glioma of the retina—are in fact examples of mutations in a gamete in one or other of the parents, and the starting point of a new and short line of transmission. Likewise miscarriages or stillbirths of monsters may perhaps be due to a dominant mutation in one of the parental gametes.

Whilst it is true that dominant genes with severe consequences tend to be rapidly eliminated, there is one significant exception. If the gene manifests itself late in life, towards the end of the reproductive period, there is nothing to prevent the gene from becoming widely scattered through the population. This is exemplified by Huntington's chorea. Most of those affected develop the affection late in life, and the perpetuation of the gene is not influenced except in so far as there is voluntary abstention from parenthood amongst families affected. This is likewise the case with dominant retinal dystrophy manifesting itself late in life.

Mutation rates

Mutation rates have been calculated for several of the more severe pathological conditions. The mutation rate for haemophilia is amongst those that are particularly high, and for glioma it is probably higher still.

Somatic mutation

Occasionally a mutation occurs not in the germ cells but in somatic cells. The mutation will affect the individual but will not be transmitted. A somatic mutation will, therefore, affect bodily structure, and, depending upon the time in embryonic life when mutation occurs, the effect may be widespread or slight. There may be asymmetry of the body, unequal coloration on the two halves, or disturbances confined to one particular organ, one-sided in the case of bilateral organs. The rare cases of unilateral retinitis pigmentosa may perhaps arise in this manner.

Nature of mutation

Mutations are one of the basic factors in evolution with natural selection acting as the selective agency for fitness under particular conditions. Their existence emphasizes that the gene is not a rigid entity. The mechanism of mutation is unknown. Such environmental factors as heat, x-ray, radium, colchicum and mustard gas amongst others have been shown experimentally to increase the rate of mutations. The prospect of the widespread and uncontrolled use of radioactive substances carries grave genetic implications.

Multiple Effects of Gene Action (Pleiotropic Action)

The effect of a pathogenic gene may be relatively slight, as in colour-blindness, in which nothing else seems involved, or widespread as in the Laurence-Moon-Biedl syndrome, in which extensive anomalies are seen.

In the widespread syndromes, the temptation to incriminate more than one gene is strong, as it helps to explain partial syndromes. The ratios of full to partial syndromes do not, however, support any such reading. The fact that a pathogenic gene may have many effects is paralleled by the normal genes; these not only interact with each other to produce a bodily character, but have a number of effects in addition to the main effect. In the cat, for instance, one and the same gene produces a white coat, blue eyes, and deafness, and it is impossible to dissociate these features by selective breeding. In other mammals, conspicuous differences in fur colour may result in slight differences in weight and other quantitative characters. Partial syndromes are probably better explained as an incomplete expression of the particular gene than as a lack of an auxiliary gene.

Expression of a Gene

The examples of hereditary disease determined by a gene which is regularly expressed, that is, the effect of which is always manifest clinically, represent largely the efforts of the early workers in human genetics. Such examples were necessary to establish the fact that in human pathology the fundamental Mendelian conceptions and the gene theory were applicable. They are, however, somewhat misleading because of the suggestion that unless a gene is always expressed a genetic basis cannot be assumed. Actually, as genetic studies have developed, a mass of evidence has accumulated indicating beyond all doubt that a pathogenic gene may be present and yet not be expressed at all, or only partially expressed.

Incomplete expression

The evidence for total or partial failure of expression of a gene may be briefly summarized as follows.

Dominant genes

There is the well-established clinical fact that in dominant inheritance there may be "skipping of a generation". The gene is obviously present in the individual who transmits it to the succeeding generations, but is not expressed in that particular individual.

Incomplete expression of a gene is seen in some forms of irregular dominance; in these cases a careful search will reveal minor departures from the normal. Thus in the dominant transmission of acholuric jaundice there may appear a "skipped generation"; but the individuals in this skipped generation who transmit the affection are not altogether normal. On detailed examination in one particular family, two such individuals were found to possess abnormally fragile blood corpuscles; likewise the skipped generations of brachydactylous families do not have digits of normal length as assessed by actual measurement.

The variety of clinical manifestations that a family with, say, tuberose sclerosis may show—some individuals showing all the manifestations of tuberose sclerosis and others nothing more than minimal blemishes—is yet further evidence that though the gene is present its actual expression in different individuals varies considerably.

Recessive genes

The examples from dominant affections refer to a gene present in the simplex

state. The same, however, applies, though not so forcibly, to recessive affections in which the gene is present in the duplex state. Not all persons with the Laurence-Moon-Biedl syndrome show the complete syndrome, and, if it is accepted—and all the evidence points to this—that the affection is due to a single gene, the variability of expression of this gene is therefore considerable.

There is also some variability of expression of recessive genes in the simplex state. It has already been pointed out that in addition to the conception of complete recessiveness, there is also that of incomplete recessiveness. This, too, is well illustrated by the pedigrees on the Laurence-Moon-Biedl syndrome. It happens, not infrequently, that amongst ascendants a partial aspect of the syndrome is expressed in a mild form such as occasional polydactyly or occasional obesity. This is hardly the Laurence-Moon-Biedl syndrome, but it would appear that the gene in the simplex state in the antecedents is not altogether silent. Similarly some of the apparently healthy relatives of diabetic patients show abnormal blood sugar levels (Fig. 9).

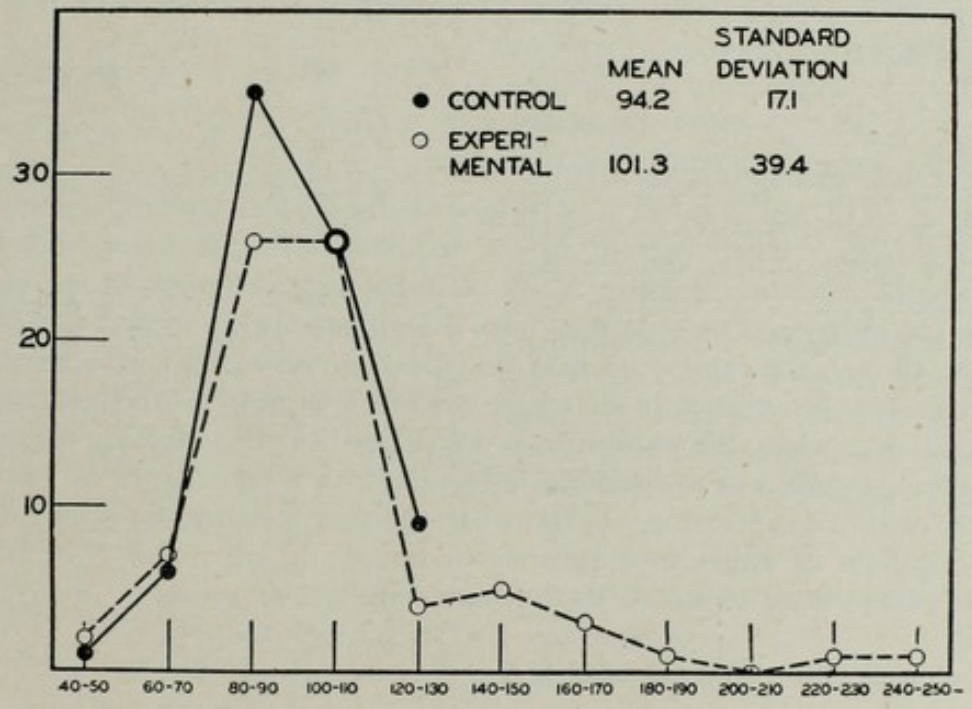


FIG. 9.—Showing the greater frequency of individuals with abnormal blood sugar curves amongst relatives of diabetics. (*After G. Pincus and P. White* (1934). *Amer. J. med. Sci.*, **188**, 783.)

In contrast to partial expression is the opposite phenomenon of a gene occasionally expressing itself when normally it is unexpressed. This is seen in the occasional occurrence of colour-blind women in families in which the affection is transmitted as a simple sex-linked recessive. Some 3 per cent of women in such families are colour-blind. This cannot be always explained on the assumption that they are the daughters of mothers who are carriers and fathers who are affected, for sometimes the fathers are normal, so that the daughters cannot be homozygous. Here a recessive gene is fully expressed in the simplex state.

As a gene may have—and generally has—more than one effect, it follows that variability in expression readily explains partial syndromes in such affections that have more than one "main" feature. It also follows that any conception of the gene as a rigid and immutable entity with invariable effects is fallacious. Such a conception has served a useful purpose in the past. At the present the broader conception of gene action emphasizes the fact that the gene is susceptible to both environmental and genetic influences. The appreciation of this phenomenon opens wide the possibility of the control of gene action by planned effort.

Sex limitation

The phenomenon of sex limitation is not infrequent. Some hereditary anomalies are seen more frequently in boys than in girls—the Laurence-Moon-Biedl syndrome is an example. Less commonly, affections are more frequent in girls, as in the case of congenital dislocation of the hip. Auxiliary genes have been postulated for such a sex-distribution, but like most multi-factorial explanations for pathological states this is not tenable. For the present, sex limitation can be explained only in general terms as an aspect of partial expression under certain genetic or environmental conditions.

Penetrance of a Gene

Penetrance and expression are frequently, but wrongly, used as synonyms. Penetrance is a statistical concept and refers to the regularity with which a gene produces its effect when present in the requisite homozygous or heterozygous state. Expression is the measure of the variable manifestation of the state from individual to individual. A gene may have a high penetrance in that it is frequently expressed, though the expression may be partial or very slight. In contrast a gene may have a low penetrance in that it is not often expressed, and expression may be high in that when the condition is expressed its full effect is present. Thus leukaemia is regarded as a dominant affection with a penetrance as low as 1 per cent and a variable expression, so that when the gene is expressed it may determine the development of either myelogenous or lymphatic leukaemia—for both these conditions have been observed in the same family.

Bi-factorial and Multi-factorial Inheritance

Most of the physiological characters such as colour of skin and stature in man are the product of the effects of more than one gene. These multiple genes may be on one chromosome, but are more frequently distributed over different chromosomes. They therefore tend to segregate and to re-assort independently. The colour of skin in man is illustrative of this. The offspring of a white man and a negro woman, or a black man and a white woman, are, as is well known, neither white nor black (mulatto). The offspring of two mulattoes are generally very much like their parents, but in extreme cases an almost completely white individual, or an almost completely black individual, may be seen. The explanation is shown in Fig. 10. It is assumed that blackness of skin is determined by two dominant genes—carried on different chromosomes—in association; and whiteness is determined by two similar recessive genes. The blacked-out symbols (◆ and ●) are used to designate the two dominant black genes, and the corresponding unshaded symbols

the two recessive white genes. From a negro-white cross (◆ ◆ ● ● × ◇ ◇ 0 0) the resultant mulatto hybrid is genotypically ◆ ◇ ● 0. A cross between two mulattoes involves gametes carrying: ◆ ●, ◆ 0, ◇ ●, ◇ 0. The chess board pattern shows the possible combinations of these gametes and of zygotes. It will be seen that there are extreme instances of individuals possessing only black, or only white, genes (square 1 and square 16 respectively). As against single individuals possessing only black or white genes the remaining individuals possess one black or one white in 4 instances each, and two black or two white genes in 6 instances. Thus in a total of sixteen individuals, one is completely black and one completely white; six have white and black genes in equal proportions, four have one black gene and four have three black genes. The depth of colour will depend on the

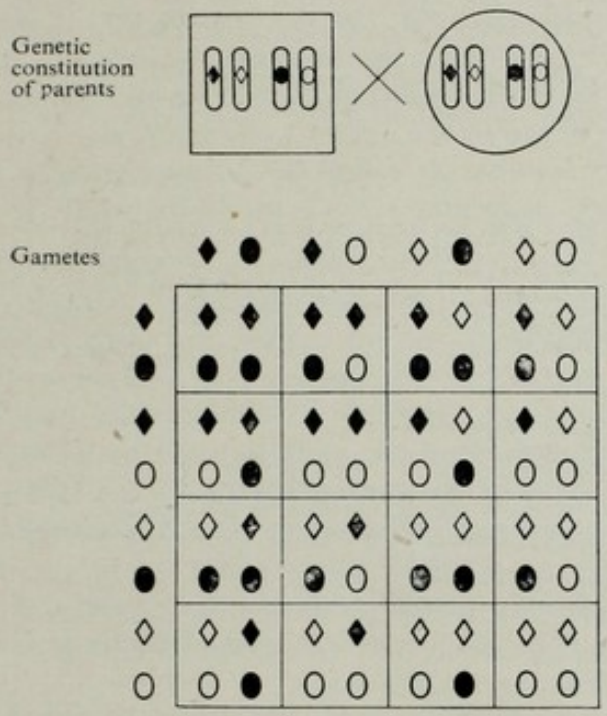


FIG. 10.—Cross between two mulattoes showing the possible types of offspring (after Davenport).

On the assumption, largely valid, that the dark skin of the Negro is determined by two sets of dominant genes, and the white skin of the Caucasian by their recessive alleles, the mulattoes carry both dominant and recessive genes. Segregation and independent assortment of these genes produced in a cross between two mulattoes show offspring some of whom have only dominant genes and others only recessive genes, but most have both genes in variable combinations. The theoretically expected reassortment is shown diagrammatically in this figure, in which the blacked-out symbols represent the dominant genes and the unshaded symbols their recessive alleles.

◆ = one of the two dominant genes determining the dark colour of the
● = the other of the two dominant genes. [Negroes.
◇ = one of the two recessive alleles determining the white colour of the
0 = the other of the two recessive alleles. [skin of the Caucasian.

number of black genes in the individual. Actually there are minor additional genes which tend to affect this distribution, but only to a slight extent. Moreover, a negro differs from a white man in other respects than colour of skin, such as the shape of the skull, and the nares, and the waviness of the hair. It would take a considerably larger number than sixteen offspring of a mulatto mating for independent assortment of the different genes to produce a completely black, or white, individual.

It is conceivable that pathological conditions may be determined by the influence of more than one pathogenic gene, but there is no concrete support for this view. Such a conception has been advanced for the inheritance of cancer, and of diabetes, and would explain the unusual ratios of affected to unaffected seen in families

showing these affections. As yet, human pathology has not succeeded in disentangling the genetics of affections due to more than one gene.

Multi-factorial inheritance in continuous variations

Stature, colour of iris and colour of skin are physiological examples of variations in individuals in whom differences are not sharply contrasted—these are continuous variations, as opposed to the discontinuous variations represented by a sharply defined pathological lesion, such as say retinitis pigmentosa. Between individuals with a normal retina and patients with retinitis pigmentosa there are no intermediate gradients, but some pathological features in man do show such intermediate gradients. Between the extreme myope and the extreme hypermetrope there stretches an extensive range of intermediate refractive states. In refraction, as with other continuous variations, multiple genes may be postulated, and it is reasonable enough to conceive of different genes as determining axial length, corneal refraction, and other components of total refraction. But these individual components, too—the cornea, the lens, the depth of the anterior chamber, and the axial length—all show a considerable and continuous range of variation, and it is not known whether these variations are determined by a mono-factorial or multi-factorial mechanism.

Other Aspects

Multiple allelomorphs

A gene may mutate to produce more than one effect. A particular gene may therefore have more than one allele. The term multiple allelomorphs or poly-alleles is applied when a gene at the same locus in the same chromosome has two or more alternative forms. The existence of multiple alleles has been established experimentally in a wide range of animals and plants.

In man, blood grouping is an example of multiple allelomorphs. Group A and group B represent two dominant allelomorphs to group O. Group AB contains these two dominants in exclusion, and both are expressed.

In pathology, haemophilia, epidermolysis bullosa, colour-blindness, and a number of other conditions may appear in severe or in mild forms. It is assumed that the abnormal gene may have several forms, and, dependent upon which particular allele is present, the condition will be mild or severe. The alternative possibility is that different genes may be responsible. These are still largely unresolved difficulties in human genetics.

Parallel to these difficulties is the difficulty inherent in the belief that the same clinical picture may be produced by different genes. In support of this view is the fact that such conditions as retinitis pigmentosa may be sex-linked or autosomal in different families. This would suggest a different gene on a different chromosome. This argument is, however, not conclusive, as it is theoretically possible for an autosomal gene to get transposed on to a sex chromosome by translocation as explained below. In animal genetics, however, apparently identical clinical pictures (such as "shaker" in mice) have been shown to be due to two separate genes. There also remains the possibility that apparently identical clinical pictures (such as autosomal or sex-linked retinitis pigmentosa) may differ in finer detail from each other.

The significance of multiple allelomorphs is best shown by an example. In the various anomalies of dichromatic vision three distinct groups can be isolated—deuteranopia, protanopia and tritanopia, the last being very rare.

Deuteranopia and protanopia are determined by two different genes, both carried on the non-homologous part of the X chromosome. Should a man carry, say, the gene for deuteranopia, and his wife the gene for protanopia, their daughters may carry both these genes but would not be affected as the genes are not alleles. Within the deuteranopic range there is deuteranopia, deuteranomaly and extreme deuteranomaly—and these are alleles, that is, different mutants of the same gene. In consequence 50 per cent of the daughters of a deuteranopic man married to a woman who is also a deuteranope would be affected, but such daughters would also be affected if one of their parents were a deuteranope and the other showed either deuteranomaly or extreme deuteranomaly. Such daughters would be deuteranopes, and not deuteranomalous, as the gene for deuteranopia is dominant to both deuteranomaly and extreme deuteranomaly.

Lethal factors

It has already been indicated that the presence of two dominant genes for an abnormality in an individual may either lead to a more marked affection, or to stillbirth. Experimentally the combination of two dominant genes leading to stillbirth is well shown by the classical example of Cuénot's yellow mice. In the mouse yellow is dominant, but yellow mice never breed true. They always produce 1 non-yellow to 2 yellows. The 2 yellows are less than the expected 3 yellow on the classical Mendelian ratio. Actually the two yellows represent the heterozygotes, whilst the third yellow, which is homozygous, is never born, but becomes a macerated foetus, as shown by actual observation (Fig. 11 shows this development diagrammatically). These observations have this bearing on human pathology: the incidence of miscarriages and stillbirths may be high in some genetic affections owing to the emergence of a lethal combination of genes.

Modifying genes and genic balance

In animal and plant experiments the existence of modifying genes is a proved

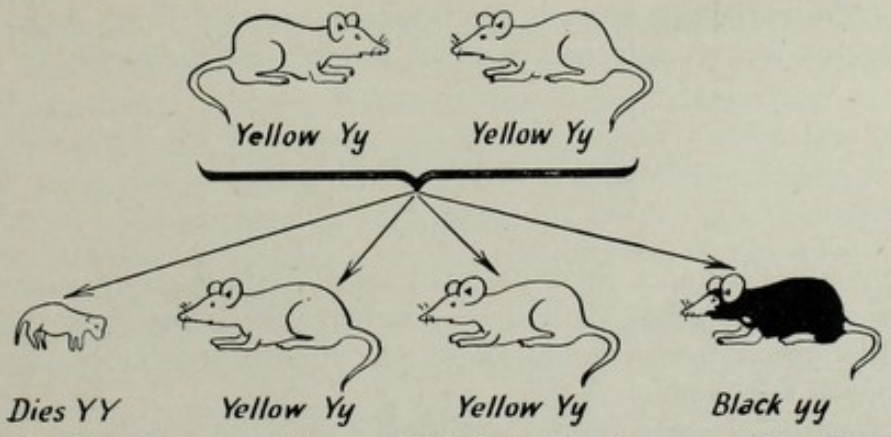


FIG. 11.—Diagram to illustrate the lethal effect of two genes for yellow coat in the mouse. The homozygous yellow mouse is never born. It can be recovered as a macerated foetus. (*After Cuénot from G. Dahlberg. Race, Reason and Rubbish*, 1943. *London; Allen & Unwin.*)

fact. The conception of modifying genes has been used in human genetics to explain irregular dominance as opposed to the assumption that environmental influences suppress the manifestation of the dominant gene. It is assumed that in addition to the main gene responsible for an abnormality there is an auxiliary gene which itself has physiological or slight effects and is widely scattered throughout the population. A gene for a dominant abnormality would be expressed in the presence of such an auxiliary gene and suppressed in its absence. Alternatively it is assumed that the modifying gene contributes an effect which brings out the manifestation of the dominant gene. Proof for these conceptions is lacking in human genetics.

Actually every gene is subject to modifying influences from every other gene, for a gene exerts its effect in a community of genes. The significance of the total genic environment has been brought out experimentally in a number of different ways. In the first place the actual position of the gene in the chromosome is of importance, as seen when chromosomes are experimentally damaged by x-rays, and exchange of segments between non-homologous chromosomes occurs; there result substantial somatic changes. Secondly, the addition of a segment of the X chromosome at a particular stage in the development of Drosophila will determine the development of females. Thirdly, there is the evidence from the formation of intersexes as in the chocolate moth, studied by Goldschmidt, in which X chromosomes are expressed differently in different autosomal environments.

Change in Mode of Inheritance

A gene is so subject to total genic balance that the conception of dominance and recessiveness serves well for particular individuals or generations only, but not as an absolute measure. A gene, by itself, is neither recessive nor dominant. These states are the result of the interaction with the other genes and with environmental factors. Under experimental conditions one and the same gene in two different genetic environments may be either recessive or dominant. There are good grounds for believing that a mutant gene is frequently dominant on its first appearance, but becomes either completely eliminated or steadily more recessive as the accumulation of modifying factors by natural selection aids the necessary conditions which prevent the dominant mutant from expressing itself. The gene reaches full recessiveness when it can express itself only in the duplex state.

CHROMOSOME MECHANISMS

Linkage

If each chromosome is transmitted intact, it carries a whole group of genes *en bloc*. Should two of these genes determine dominant abnormalities, the offspring possessing this chromosome would show two clinical conditions—gene linkage producing linked affections.

Fig. 12 shows the two possibilities with linked genes on autosomes. In Fig. 12 *a*, the two genes are carried on the same chromosome. In the absence of cross-over (discussed below) the offspring resemble their parents, that is, if one parent is a double heterozygote for two dominant genes (shown in capital letters), and the

other a double homozygote for their recessive alleles (shown in small type), 50 per cent of the children will have a chromosome carrying both dominant genes. If, however, the two dominant genes are placed each on one of the pair of chromosomes (Fig. 12 *b*), the individual carrying them will be phenotypically indistinguishable from the individual carrying two dominant genes on one chromosome; but amongst the offspring independent assortment of the chromosomes will produce individuals none of whom carry both dominant genes (that is, the parent carrying the two genes on two different chromosomes cannot possibly contribute both chromosomes to any of his offspring). Linkage of genes must be understood in the sense that a particular chromosome carries two genes determining two particular characters. The fact that one of the characters may be pathological (that is, a variant or mutant of the normal) helps to locate the gene on that particular

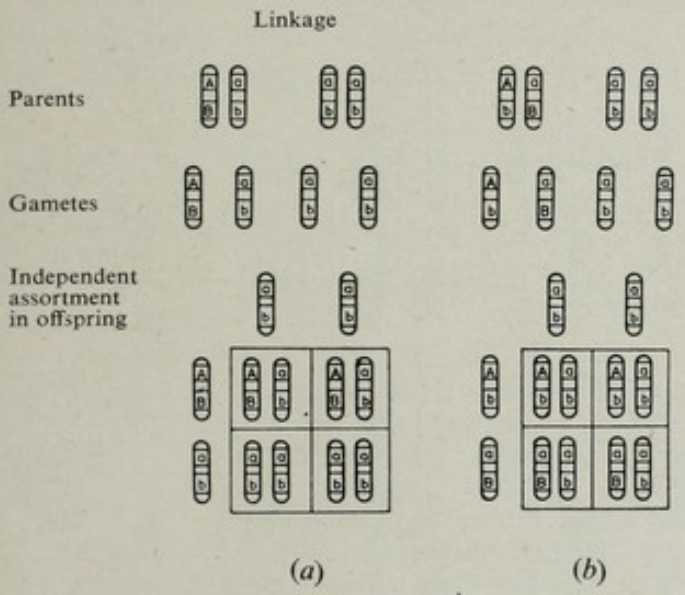
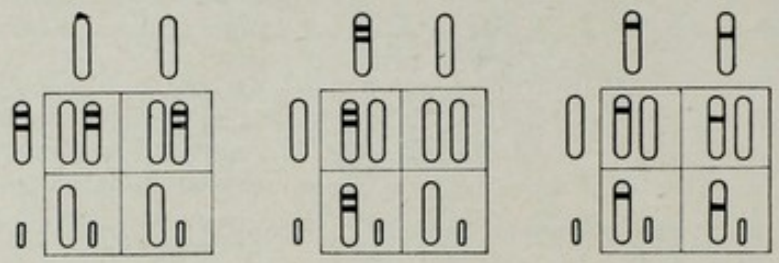


FIG. 12.—Inheritance of two dominant pathogenic genes carried by one parent only.
(*a*) One parent is normal (aabb), the other is affected for two abnormalities (AaBb). The two genes for dominant abnormalities are linked, that is they are on the same chromosome. Of the offspring 50 per cent will show both abnormalities and 50 per cent will be normal (in the absence of cross-over).
(*b*) One parent is normal (aabb) the other is affected (AabB) for two abnormalities. The two genes for dominant abnormalities are carried on different chromosomes. Of the offspring 50 per cent will show one abnormality and 50 per cent the other abnormality.

chromosome pair. Whether carried by the one or the other chromosome is immaterial to a large extent, as crossing over may place it on one or other of the pair of chromosomes.

In human genetics the opportunity of seeing two dominant pathological states together is rare. This makes it all the more important to attempt to relate the pathological state with a sharply defined and clearly transmitted normal trait. Three such normal traits have been clearly established. One is the transmission of the genes for blood grouping; the recessive O and the dominant A and B are alleles similar in a simple manner. The genes for the M and N precipitins are a similar group situated on another pair of chromosomes. The gene for the capacity to taste phenyl thiocarbamide is yet a third normal trait. A few other normal characters have also been isolated, but they are not quite so useful, mainly because of certain genetic complications, though some of the recently isolated blood groups such as Rh., P. and Lewis may prove satisfactory, as may also the capacity for tongue curling. There are, therefore, "markers" to at least three autosomal chromosomes. Since sex itself can be regarded as a linkage system, it has been possible to place a number of pathogenic genes on to the sex chromosome. Sex is, in fact, the easiest and most studied of all "markers".

Linkage of two genes on the X chromosome produces a situation somewhat different from that with an autosome. The theoretical possibilities are shown in Fig. 13. If the two genes are carried on the non-homologous part of the X chromosome of a man (Fig. 13 *a*) the situation does not differ in any way from that seen if only one gene were so carried. Whether recessive or dominant they would manifest themselves in the man and would be transmitted to all his daughters, who would not be affected unless the genes were dominant. If on the other hand the genes are carried on the X chromosome of a woman, two situations arise. If both genes are carried on one and the same X chromosome (Fig. 13 *b*) the mother will be unaffected if the genes are recessive, and will show both affections if dominant; 50 per cent of her sons and, in the absence of cross-over, 50 per cent of her daughters will likewise carry both genes. The daughters will show the two



(*a*) (*b*) (*c*)

FIG. 13.—Inheritance of two pathogenic genes carried on the non-homologous part of the X chromosome.
(*a*) The father carries the pathogenic gene on the X chromosome and is affected. The mother is normal. All daughters will carry both genes and will be affected only if the genes are dominant. The sons are normal.
(*b*) The mother carries two linked pathogenic genes and will be affected if the genes are dominant. The father is normal. Half the sons (carrying both genes) will be affected whether the genes are dominant or recessive. Half the daughters will carry the gene and will be affected only if the genes are dominant.
(*c*) The mother carries the two pathogenic genes, one on each of the two X chromosomes, and will be affected only if the genes are dominant. The father is normal. All the children will carry one or other of the genes. The daughters will be affected only if the genes are dominant. All the sons will be affected with one or other abnormality regardless of whether the genes are dominant or recessive.

affections only if the genes are dominant, whilst the sons will show the two affections irrespective of whether the genes are recessive or dominant. Should the genes be carried by the mother, one on each X chromosome (Fig. 13 *c*), she would once more show both affections if the genes were dominant and neither if the genes were recessive. All her children will, however, be carriers. The daughters would be affected with one condition only if the gene were dominant, and would be altogether unaffected if the gene were recessive. The sons would show one or other affection only, irrespective of whether the gene were recessive or dominant.

Crossing Over

The normal mechanism of separation of a pair of chromosomes involves some coiling of the two chromosomes over each other. In the process of separation a chromosome may get broken and the two chromosomes may become reconstituted in such a manner that portions have been exchanged between the two. In consequence there is exchange of blocks of genes (Fig. 14 *a*). Occasionally a double cross-over occurs, giving a different type of exchange (Fig. 14 *b*). A cross-over is more likely to occur with genes lying far apart, say at the two ends of the chromosomes. The relative frequency with which dissociation of linked genes takes place, and association occurs, is therefore a measure of the distance between them. Clinically crossing over will produce dissociation of two linked conditions, so if a particular pedigree recording two linked clinical conditions shows a number of individuals with only one or other condition, the relative frequency with which this is observed is a measure of the distance between the genes. This occurrence

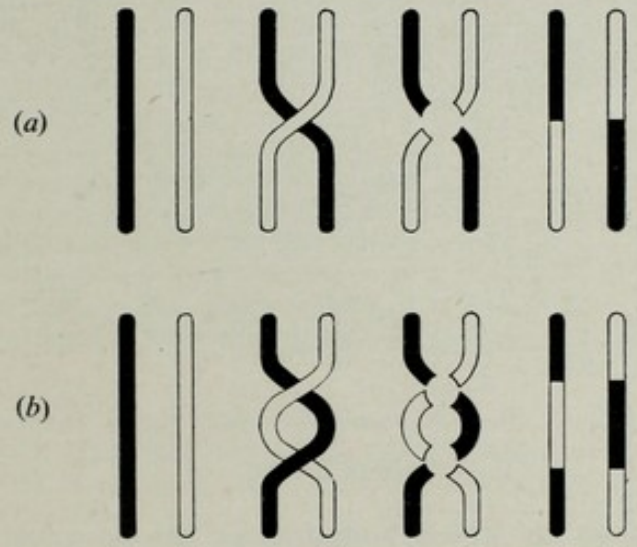


Fig. 14.—Drawings illustrating the interchange of segments in crossing over between the members of a chromosome pair: (*a*) simple cross-over; (*b*) double cross-over. (*After J. A. Fraser Roberts. An Introduction to Medical Genetics*, 1940. *Oxford Medical Publications.*)

is the basis for calculating cross-over values and placing genes at their loci in the chromosome, that is, it is the basis for chromosome mapping.

The potential practical value of chromosome mapping lies in this: if it is known that a particular gene lies in an autosomal chromosome, which normally carries an innocuous gene (such as one determining a particular blood group), the presence or absence of the innocuous character suggests whether or not the patient also carries the gene for the abnormality. In addition the cross-over value will indicate the likely error in the assumption that the pathogenic gene is present. Such information is of obvious value in judging the likelihood of an abiotrophic condition becoming manifest later on.

Non-disjunction

Non-disjunction—failure of the two chromosomes to separate at the formation of gametes—has been observed histologically in Drosophila and has been used

to explain abnormal sex ratios in human genetics. It is assumed that occasionally the two X chromosomes do not separate in gamete formation. In the course of fertilization, zygotes with three X chromosomes, or with two X chromosomes and one Y, will therefore be formed. The three X chromosome zygotes are non-viable, and the non-disjointed X chromosome and the Y occur in outwardly normal women. Such phenotypically normal women do, however, transmit their non-disjointed X chromosomes to successive generations. It is they who give the Y chromosomes to their sons, whilst the father contributes a Y chromosome to daughters possessing a non-disjointed chromosome. This phenomenon has been used to explain the transmission of colour-blindness by women, themselves affected and transmitting it to their daughters only (Fig. 15).

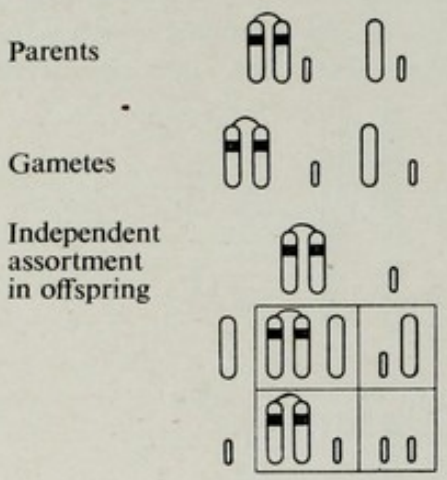


FIG. 15.—Non-disjunction of the two X chromosomes. This mode of inheritance, for which there is experimental evidence in drosophila, has been postulated but not proved in human genetics. The unusual situation arises that the Y chromosome of sons is derived from the mother and the X chromosome from the father. The daughters repeat the unusual chromosome pattern of their mothers; they derive their disjointed X chromosomes from their mother and their Y chromosomes from the father. It is unlikely that the daughters carrying three X chromosomes are viable; it is certain that individuals with two Y chromosomes are not viable.

TRANSLOCATION

In contrast to cross-over, in which homologous chromosomes are concerned, there is the phenomenon of translocation. By means of x-rays it is possible to break non-homologous chromosomes in Drosophila and when re-union takes place, segments from different pairs may become united, involving a segmental interchange. Under experimental conditions various degrees of translocation have been studied. The more severe forms are incompatible with life, and anomalies ranging from mild to severe disturbances occur in the less severe translocations. There is evidence that translocation occurs in nature. Indeed it may be one of the varieties of mutation affecting a chromosome as a whole.

ENVIRONMENTAL FACTORS

ENVIRONMENT AS A DETERMINING FACTOR

Genetic potentialities are susceptible not only to their total genic environment, but also to external environmental factors. Environmental factors may inhibit or release a genetic potentiality, or they may reverse a genetic trait that is already established, as shown by the following examples.

Suppression of a genetic potentiality

Genetically, tadpoles are destined to become frogs, but if they are kept in water and on a diet in both of which there is no trace of iodine, they never fulfil their genetic destiny: the thyroid mechanism which determines the change from tadpole into frog cannot function in the absence of the environmental factor represented by iodine. A less striking, but more common, effect is illustrated in Fig. 16.

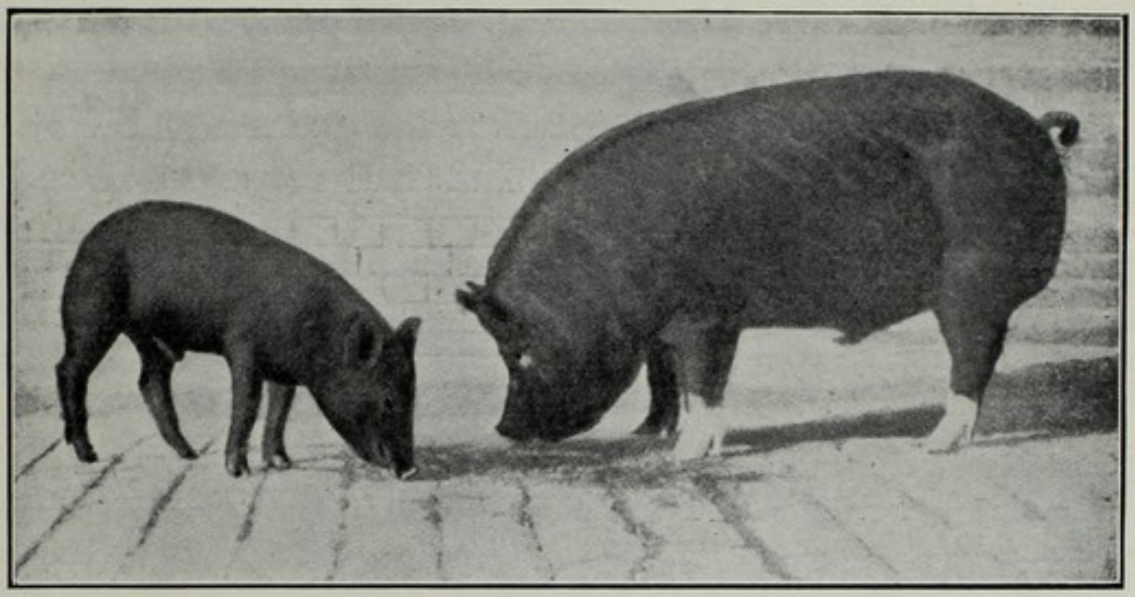


FIG. 16.—Suppression of a genetic potentiality. Two pigs from the same litter of an extremely uniform breed (Berkshire). One fed normally, and the other on an insufficient diet. (*After Mathusius. In E. Baur, E. Fischer and F. Lenz. Human Heredity. London: Allen & Unwin*, 1931.)

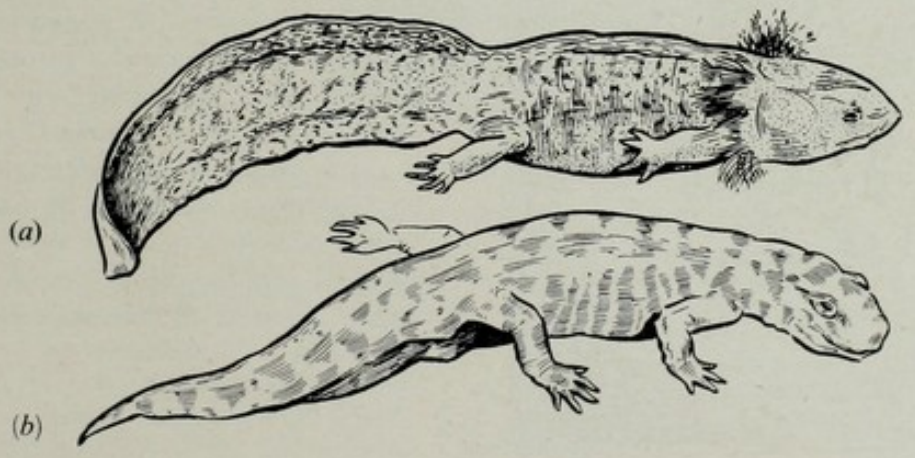


FIG. 17.—Release of a genetic potentiality. The axolotl breeds in the aquatic form (*a*) from generation to generation. It becomes a terrestial newt (*b*) if fed on thyroid gland: it loses its gills and develops legs. (*After A. Brehm Thierleben, Bibliographishes Instit. Leipzig and Vienna*, 1912.)

Release of a genetic potentiality

A local race of the American newt, found in the neighbourhood of Mexico City, never grows up. It breeds from generation to generation in the aquatic form, but will become a terrestial newt if fed on thyroid gland (Fig. 17). Likewise the variety of tropical domestic fowl known as the "Frizzle", a bird practically devoid of feathers throughout the first year of life, and so delicate that it is difficult to rear outside the tropics, can be reared in temperate regions under special conditions; develops complete plumage within three weeks if it is maintained in a woollen jacket and kept in a warm room.

Modification of a genetic tendency

Some chickens have white shanks and others yellow shanks; chickens having either feature can be bred true to form, so that the difference is genetic and not environmental. Yet chickens of the yellow shank variety fed on white corn instead of green food have white shanks. Likewise there are two genetically distinct strains of rabbits, some with yellow fat and others with white fat. Rabbits of the yellow fat variety will deposit only white fat if their food lacks green stuff. Modification which amounts to suppression of a pathogenic tendency is illustrated in Fig. 18.

Reversal of an existing trait

The reversal of a process that is already established is shown by observations on the Himalayan or Russian rabbit, which has black paws, black eyes, and a black snout, but is otherwise white. The black pigment is here the effect of the gene in the relatively low temperature in the peripheral parts of the body. Experimentally,

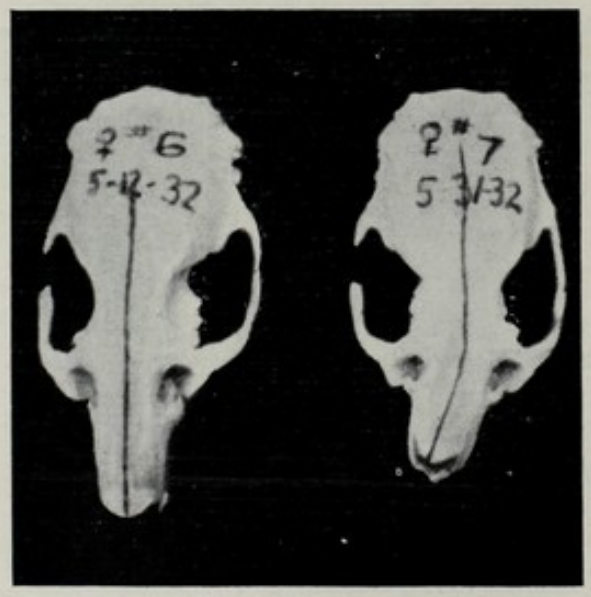


FIG. 18.—Suppression of a pathogenic potentiality. "Bent nose" is a genetically determined skeletal anomaly in a particular strain of rat, developing only when the mother is deficient in vitamin D and kept on a diet with an unbalanced calcium-phosphorus ratio. The development of these anomalies can be avoided by an adequate diet for the mother during pregnancy. (*After W. E. Heston* (1939) *J. Hered*, **29**, 437.)

if the hair of the back of a rabbit is shaved off in mid-winter, and the rabbit is kept in the open air, the hair which grows gradually on the shaven region exposed to cold becomes black (Fig. 19). A further example is shown in Fig. 20.

Influence of maternal environment

An example of maternal influence on the developing animal is seen in the size of offspring of a cross between allied animals differing in size. A cross between a Shetland pony and a Shire horse has the same type of genes whether the Shetland pony is the mother or the father. If the mother is the pony, the foal at birth is of the size of a newborn pure Shetland pony. If the mother is the Shire horse, the foal is almost as big as a pure-bred Shire foal. Here the maternal environment determines the size at birth. After birth the rate of growth in the two types of foal is different, and the end-result is the same.

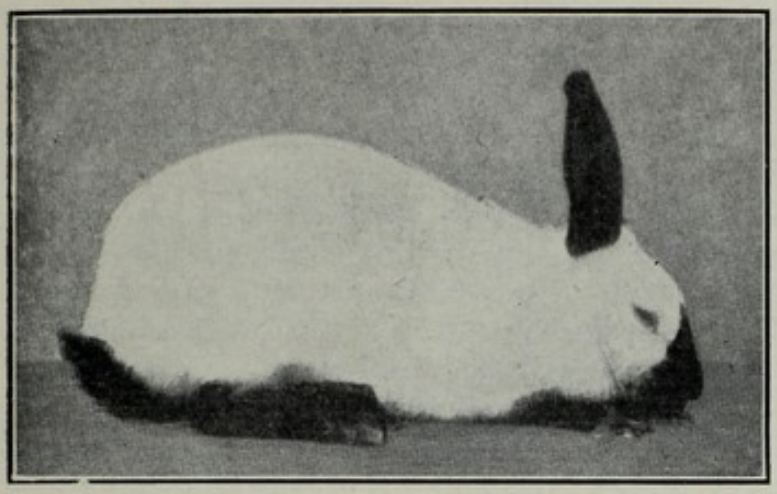
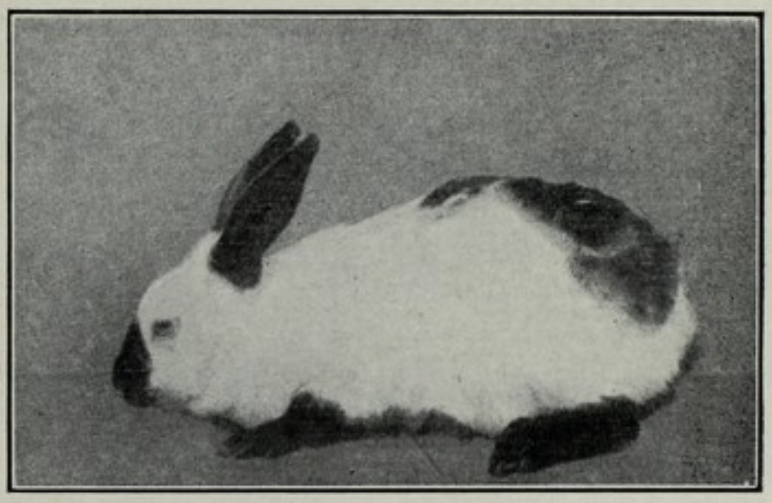
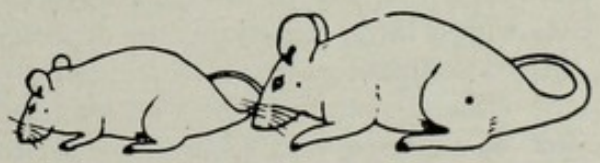


FIG. 19.—Reversal of an existing trait. The Himalayan rabbit is black at its extremities, presumably from the somewhat lower temperature at the periphery. If the hair on the back is shaved off, and the rabbit kept in a cold atmosphere, the newly grown hair has a dark colour. (*After E. Baur, E. Fischer and F. Lenz. Human Heredity. London: Allen & Unwin*, 1931.)



In human pathology, mongolian idiocy illustrates the significance of maternal environment. There is much evidence that the affection is dominant, but it is

FIG. 20.—Reversal of an existing trait: a further example. The dwarf mouse is an established genetic strain due to inherited pituitary deficiency. Daily grafting with pituitary tissue can induce almost normal development. (*From Stern, Curt. Principles of Human Genetics. W. H. Freeman and Co.*, 1949.)



also established that maternal age is an important factor for the actual appearance of the affection. Mongolian idiocy is more likely to occur in the younger members

of large families, or in the offspring of aging mothers. In both cases it is the maternal environment correlated with age which determines the expression of the gene.

Heredity in Environmental Affections

Theoretical genetics largely produces artificial situations, very much as the study of isolated vitamins under laboratory conditions does. The emphasis in such studies is on the genetic factor unhampered by other influences. Inevitably also human genetics has as yet isolated extreme cases in which the genetic factor is outstanding. A truer perspective which, as yet, can only be dimly seen, would embrace at least three possibilities. In the first place there are those affections in which the genetic factor is outstanding; secondly there would be affections which would appear only from the interaction of suitable genetic and environmental factors; and thirdly those affections which, though genetically determined, are easily suppressed by environmental agencies and are not readily appreciated as genetic anomalies.

The first of these three possibilities needs no further elaboration. The line of demarcation between the second and third possibilities is hazy, and, theoretically, these two possibilities can cover almost every aspect of pathology; tuberculous infection may be given as an example. The role of the bacillus of tuberculosis is unquestionable; social and hygienic factors are also undoubted; but in addition there is also an undoubted genetic factor. Clinically, tuberculosis frequently affects many members of a family. This in itself is no evidence for a genetic predisposition, but that this is real has been shown experimentally in rabbits; in these animals genetic strains highly susceptible, or highly insusceptible to tuberculosis can be reared. Such considerations raise the larger issues as to whether immunity shown by whole groups and races to particular infections, and other environmental disturbances are genetically determined.

Studies on Twins

Studies on twins have a particular value in human genetics. In contrast to bi-ovular twins, uniovular twins have the same genetic constitution. Inherited anomalies will therefore be identical in uniovular or identical twins, except in so far as they are modified by environmental conditions.

Genes with high penetrance and high expression will manifest themselves in the requisite homozygous or heterozygous state irrespective of any environment. Genes with a lesser penetrance or expression will be modified by such differences in the environment as two identical twins may experience. The degree of difference in the clinical manifestations of identical twins is therefore a measure of the degree of expression in relation to environment.

Studies on identical twins are also of value in abiotrophic conditions. Vogt has paid special attention to the appearance of anomalies which come on late in life, and found that many ocular anomalies and defects tend to appear and follow the same course in old age in uniovular twins. Similar types of pinguecula and similar forms of cataract are amongst the features he found in aging uniovular twins.

THE NATURE OF THE GENE AND OF ITS ACTION

One view of the gene stresses its similarity to the virus. Both are ultra-microscopic, both probably consist of nucleo-proteins, both live inside cells, and both have the faculty of self-perpetuation with widespread biological effects. It is suggested that they both represent the most primitive form of life: the virus is regarded as an "uncivilized" gene with a predatory parasitical existence on other forms of life. The gene is its "civilized" counterpart, and lives in an organized community.

Chemically the gene is regarded as a giant molecule in which each radical has a characteristic effect. Re-arrangement of the radicals can produce isomers in the same way as these are produced in simpler molecules with extensive changes in the chemical and physical properties of such molecules. Mutations may therefore be "isomeric" in character, and x-ray study of genes suggests that a mutation is essentially the effect of ionization confined to one atom. The discontinuity presented by mutations has its counterpart in the "jumps" of present-day quantum mechanics.

Gene action is being visualized in terms of enzymes. Each gene is assumed to produce a specific enzyme. Albinism may be used as an illustration. Normal pigmented individuals produce melanin in pigmented areas; this pigment is derived from phenylalanine, an amino-acid derived from food. A complicated series of chemical reactions lie between phenylalanine and melanin; each of these steps requires the presence of a specific enzyme. The normal individual possesses all these enzymes; an albino cannot, however, convert one of the intermediate products (3, 4-dihydroxyphenylalanine—also known as "dopa") into the next compound in the chain of reactions. Likewise in Tay-Sachs disease the patient lacks the necessary enzyme for oxydizing the lipoid sphingomyelin.

In some lower animals, any of the cells composing the developing fertilized ovum before growth can be separated artificially and induced to develop into a complete young animal. This is no longer possible once differentiation has taken place. Development is visualized as consisting of the following sequence of events. All cells contain their full complement of chromosomes and genes, but different cells differ in the chemical stimuli ("organizers") that they liberate activating the genes. Thus in the cells that ultimately form skin, only those genes are stimulated which cause the development of pigment, hair and other features of the skin. The remaining genes lie dormant, but can be stimulated artificially to produce their specific effects. Thus, if the developing eye is grafted on to the abdominal wall, it will stimulate the skin of the abdomen to produce a lens.

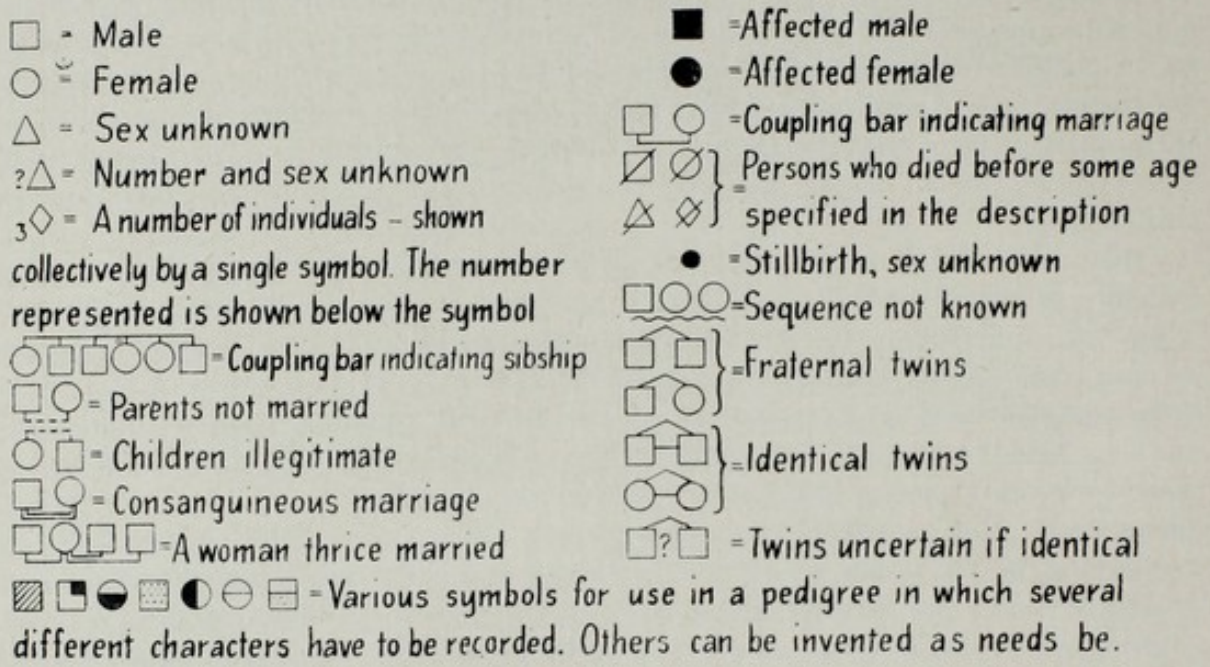
These changes can be induced only in the early stages of development. Once the organizers have induced differentiation of the tissue the process proceeds independently of environment, so that experimentally the embryonic bud which will form, say, the leg of a developing chicken, will continue to grow and develop into a leg with normal bone development if kept in an artificial nutrient medium.

CHAPTER 3

HUMAN PEDIGREES

SYMBOLS USED

SOME standardization of human pedigrees has been achieved in recent years. The following symbols are now widely used.



In a pedigree extending over several generations, Roman numerals are used to indicate the different generations, for example, I—IV. Arabic numerals may be used to frank the individuals in any generation and so indicate their relative positions. An individual is identified by the Roman number giving his generation and the Arabic number his place in it, for example, IV, 5. The patient who is the starting point of an inquiry is generally designated as the propositus or proband.

THE FAMILY HISTORY

At the very least the family history must contain information on the parents and on the patient's sibship. If either of the parents is affected by the same disturbance as the patient, the tentative suggestion of dominant inheritance emerges. If neither parent is affected, but the parents are first cousins, or blood relatives of lesser degree, the possibility of recessive inheritance arises. In neither case need any of the patient's sibs be affected, though in both cases the suggestion of an hereditary affection is strengthened by such a finding.

A history bearing on the parents and sibs only is never conclusive evidence as to any particular mode of inheritance. The affection may appear in two generations and yet be recessive, though this is exceptional in human genetics, but would come about—as already explained—if one parent were homozygous and the

other heterozygous. The absence of the affection in either parent is not conclusive evidence of lack of dominance, as the condition may be irregularly dominant—"skipping a generation"—in the case of one of the parents. The importance of consanguinity in unaffected parents as a criterion for recessiveness has already been stressed.

A pedigree confined to two generations is likely to miss recessive sex-linked inheritance. In such conditions the mother is a carrier, and this fact would not emerge unless it were established that her father, and possibly some of his brothers, were affected; alternatively her mother's brothers might be affected (if the mother inherited her carrier state from her mother). The possibility of a recessive sex-linkage suggests itself if in a particular sibship only boys are affected. Obviously the sibship would have to be fairly large, as otherwise it may be merely fortuitous that, say, in a sibship of three boys and two girls, two boys were affected and none of the girls.

All pedigrees should therefore cover at least three generations. If there is direct transmission over three generations without any sex predilection, the diagnosis of autosomal dominance is beyond dispute. A pedigree extending over three generations will likewise establish in most cases the possibility of sex-linked inheritance. A pedigree over three generations can readily be adapted to show the presence of consanguinity in the parents.

ILLUSTRATIVE PEDIGREES

Dominant

Fig. 21 shows clearly dominant inheritance, the condition being congenital stationary night-blindness. Transmission is by either men or women over successive

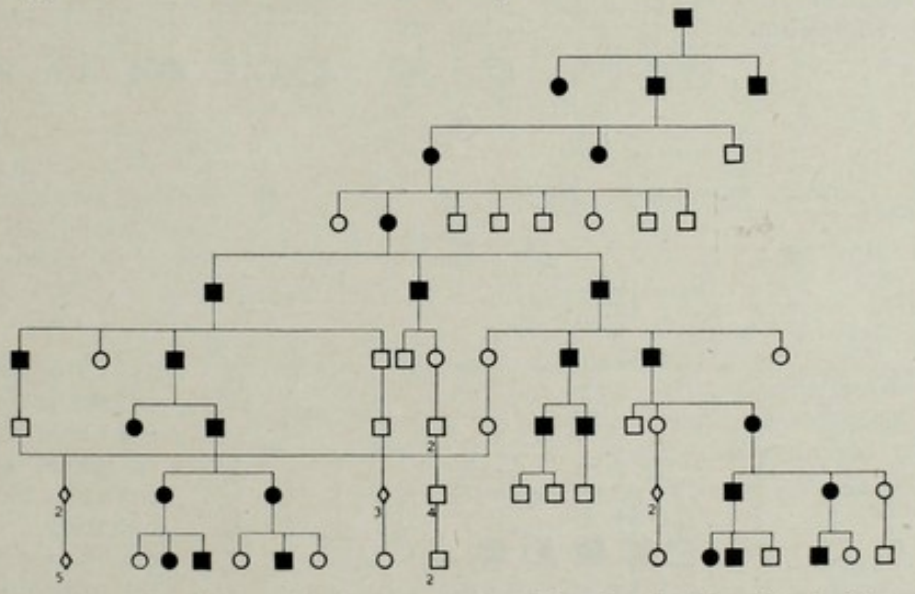


FIG. 21.—Dominant inheritance. Part of the Cunier-Truc-Nettleship pedigree of congenital stationary night-blindness. (*After E. Nettleship. Trans. Ophthal. Soc. U.K.*, 1907, **27**, 269; *and in Treasury of Human Inheritance* (1933), *Ed. by K. Pearson, Vol.* 2 (*by Julia Bell*), *Pedigree No.* 317. *London; Cambridge University Press.*)

generations, and there is no tangible difference in the numbers of men and women affected. This is seen from the following analysis of the numbers and the sex distribution of the affected and unaffected in this pedigree.

OFFSPRING OF AFFECTED INDIVIDUALS

	Affected			*Unaffected*		
	M.	F.	T.	M.	F.	T.
II	2	1	3	–	–	–
III	–	2	2	1	–	1
IV	–	1	1	5	2	7
V	3	–	3	–	–	–
VI	4	–	4	2	4	6
VII	3	2	5	2	1	3
VIII	1	3	4	3	1	4
IX	4	2	6	1	4	5
	17	11	28	14	12	26

It will be seen that there are 28 affected against 26 unaffected. This corresponds closely to the expected ratio of 1 : 1. The slight excess of affected men over unaffected men and the slight deficiency of affected women to unaffected women do not represent a significant statistical deviation from the expected 1 : 1 ratio.

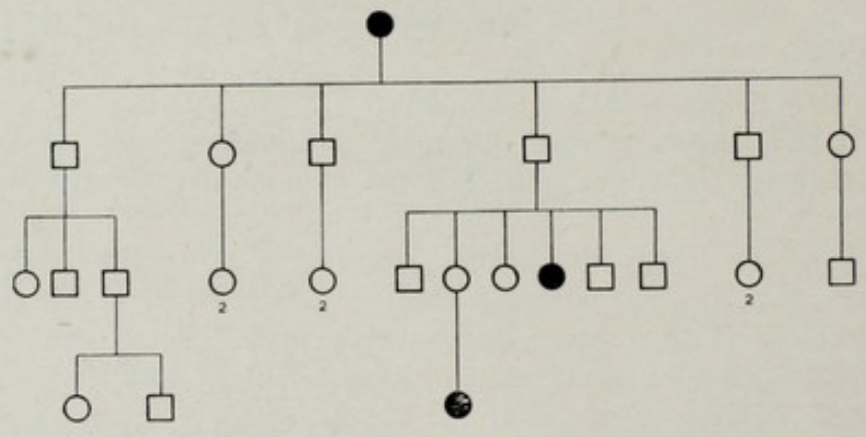


FIG. 22.—Irregular dominance. Epicanthus. (*After C. H. Usher. Biometrika*, 1935, **27**, 24.)

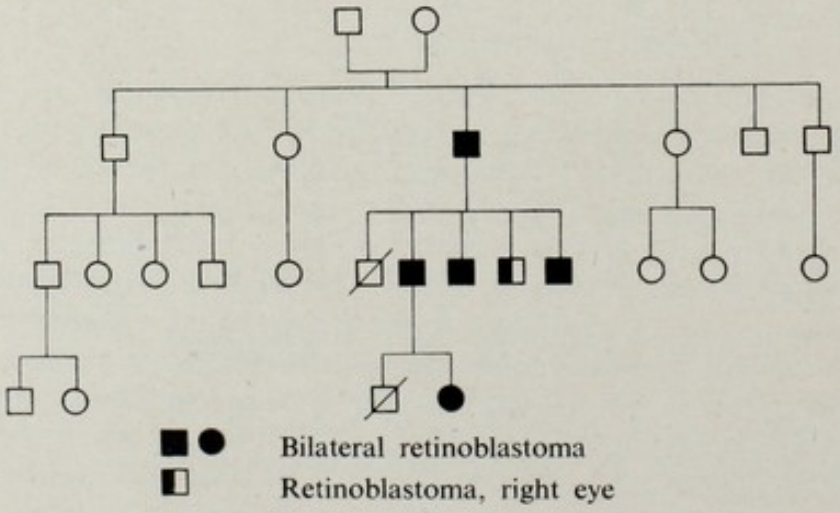


FIG. 23.—Mutation. In the second generation there is an isolated occurrence of retinal glioma, presumably due to a fresh mutation. Dominant inheritance is seen from the subsequent course. (*After A. D. Griffith and A. Sorsby. Brit. J. Ophthal.*, 1944, **28**, 279.)

Some unusual features

Irregular dominance.—The phenomenon of skipping of a generation is illustrated in Fig. 22. The dominant character of the affection is suggested by the pedigree as a whole.

A fresh mutation.—Since a dominant mutation with severe manifestations generally has a short life and equilibrium is established by fresh mutations, it follows that pedigrees showing severe dominant affections extending over many generations are less likely to be established than pedigrees of dominant affections that have no serious consequences. In human genetics it is not unusual to meet with findings such as those shown in the pedigree in Fig. 23 illustrating transmission of glioma of the retina. The affection began with an individual none of whose sibs was affected. It has been transmitted over three successive generations.

Recessive

The following pedigrees (Figs. 24–28) are illustrative.

Fig. 24.—The parents were normal and were first cousins. Of their 5 children, 2 were affected with the Laurence-Moon-Biedl syndrome.

Fig. 25.—The parents were second cousins. Of their 3 children, 2 were affected with congenital cataract.

Fig. 26.—An unaffected man married successively two sisters, who were his cousins and were both normal. Albinos occurred in the offspring of both marriages. The man and his two cousins must have carried the recessive gene for albinism.

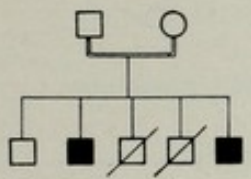


Fig. 24. — Recessive inheritance: (1) A pedigree of the Laurence-Moon-Biedl syndrome. The parents were first cousins. (*After A. Sorsby, H. Avery and E. A. Cockayne. Quart. J. Med.*, 1939, **8**, 51.)

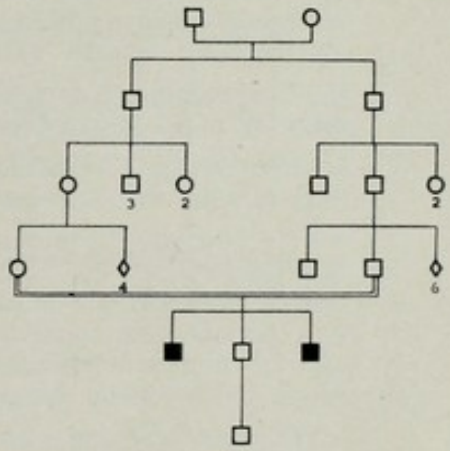


Fig. 25.—Recessive inheritance: (2) A pedigree of congenital cataract. The parents were second cousins. (*After J. Saebø. Brit. J. Ophthal.*, 1949, **33**, 601.)

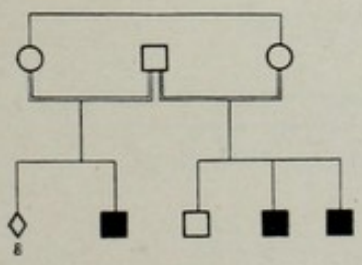


Fig. 26.—Recessive inheritance: (3) A pedigree of albinism. A man marries successively two sisters, his first cousins. They must all be presumed to have been carriers. (*After J. Heidenreich, Fig.* 455 *in A monograph on Albinism in Man, by K. Pearson, E. Nettleship and C. H. Usher* (1913). *London: Cambridge University Press.*)

Fig. 27.—A pedigree confined to the immediate relatives of IV, 4 would suggest that the affection—albinism—was sporadic, occurring in only one individual in a particular sibship, in none of the two ascendant generations, and in none of the offspring of the two members of the sibship who had children. The full pedigree, reveals two collateral branches with 13 affected individuals.

Fig. 28.—Both parents were affected with albinism and were therefore homozygous for a recessive gene. Their two children were both affected.

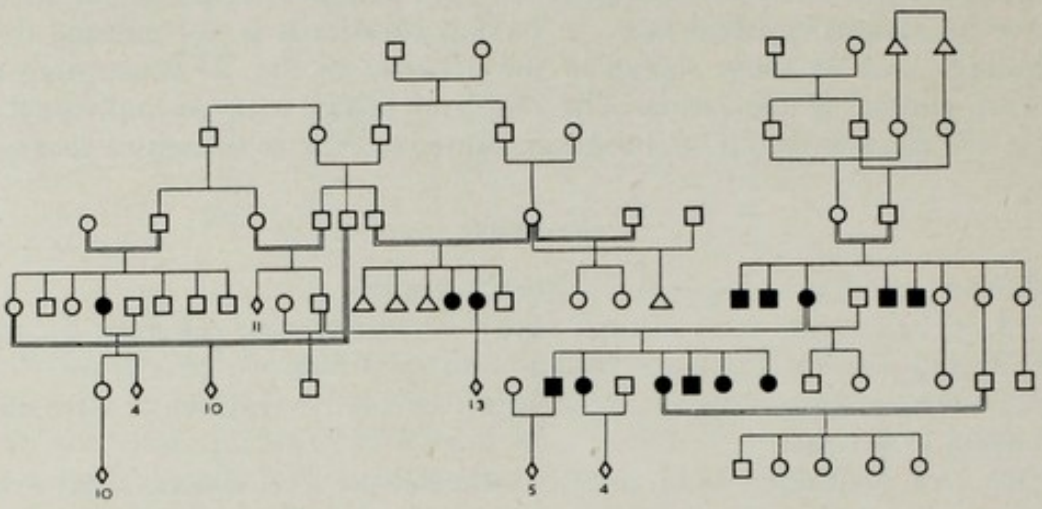


FIG. 27.—Recessive inheritance: (4) A pedigree of albinism illustrative of the following points:

(*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 F. W. Marlow and W. L. Faxon. Fig.* 412 *in A monograph on Albinism in Man, by K. Pearson, E. Nettleship and C. H. Usher* (1913). *London: Cambridge University Press.*)

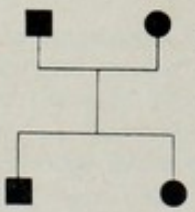


FIG. 28.—Recessive inheritance: (5) A pedigree of albinism. Both parents affected. Their two children were also affected. (*After G. C. and C. B. Davenport.* 1910, *Amer. Nat.*, **44**, 705.)

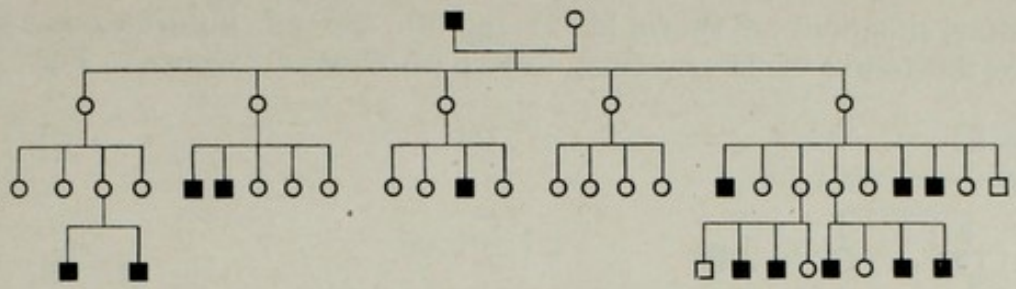


FIG. 29.—Recessive sex-linkage: (1) A pedigree of red-green blindness. (*After W. D. Horner* (1876) *quoted in Treasury of Human Inheritance*, 1933, *Ed. by K. Pearson, Vol.* 2 (*by Julia Bell*), *Fig.* 420. *London: Cambridge University Press.*)

RECESSIVE SEX-LINKAGE

The theoretical possibilities with a recessive gene on the non-homologous part of the X chromosome discussed on page 77 may be summarized in the following scheme, in which a heavy **X** stands for a chromosome which carries a pathogenic gene.

(A) *Affected father* (**X**Y)

(1) **X**Y × XX — Affected father and normal mother

→ **X**X **X**X XY XY — Daughters: all carriers; Sons: all normal

(2) **X**Y × **X**X — Affected father and carrier mother

→ **X**X **X**X **X**Y **X**Y — Daughters: 50% affected, 50% carriers; Sons: 50% affected, 50% normal

(3) **X**Y × **X**X — Affected father and affected mother

→ **X**X **X**X **X**Y **X**Y — Daughters: all affected; Sons: all affected

(B) *Normal father* (XY)

(4) XY × **X**X — Normal father and carrier mother

→ **X**X **X**X **X**Y **X**Y — Daughters: 50% carriers, 50% normal; Sons: 50% affected, 50% normal

(5) XY × **X**X — Normal father and affected mother

→ **X**X **X**X **X**Y **X**Y — Daughters: all carriers; Sons: all affected

The usual situations are shown in (1) and (4), and are illustrated in Fig. 29. Pedigrees illustrative of the remaining three possibilities are shown in Figs. 30–32.

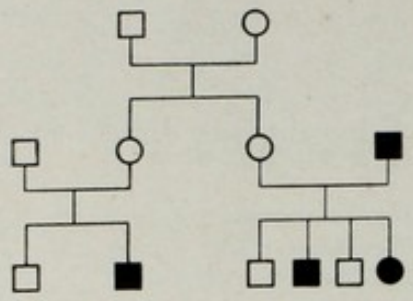


FIG. 30.—Recessive sex-linkage: (2) A pedigree of red-green blindness. The father affected and the mother a carrier. (*After A. Vogt and R. Klainguti. Arch. Rassen.-u. Ges. Biol.*, 1922, **14**, 129.)

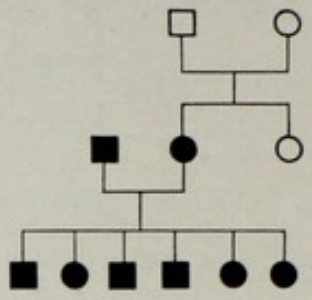


FIG. 31.—Recessive sex-linkage: (3) A pedigree of deuteranopia (green blindness). Both parents affected and all the children affected. (*After G. F. Göthlin, Acta Ophthal.*, 1925, **2**, 15.)

There is one further exceptional situation. Occasionally heterozygous women, who theoretically should not manifest the affection, are affected. An example of this occurrence is seen in Fig. 33. What is uncertain is whether such heterozygous and affected women have daughters who also show the affection.

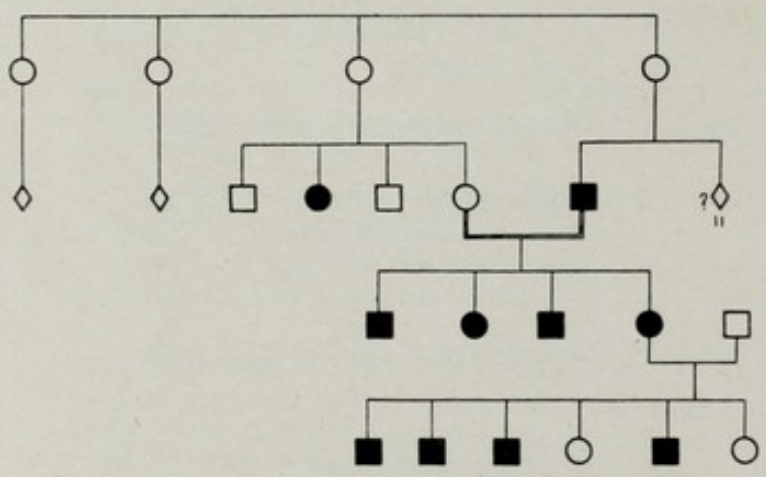


FIG. 32.—Recessive sex-linkage: (4) A pedigree of colour-blindness. Illustrating (*a*) father affected and mother presumed a carrier; (*b*) mother affected and father normal. All the sons are affected. (*After I. Schiötz., Klin. Mbl. Augenheilk.*, 1922, **48**, 498.)

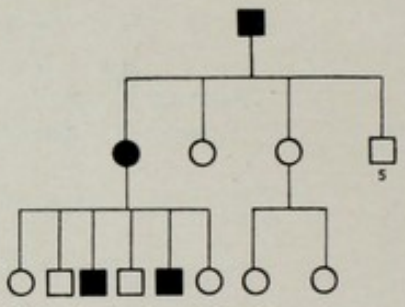


FIG. 33.—Recessive sex-linkage: (5) Manifestation in a heterozygous woman. A pedigree of colour-blindness. (*After Julia Bell in Treasury of Human Inheritance* (1933), *Ed. by K. Pearson, Vol.* 2 (*by Julia Bell*), *Fig.* 583. *London; Cambridge University Press.*)

DOMINANT SEX-LINKAGE

The behaviour of a dominant sex-linked gene is illustrated by Fig. 34. Fifty per cent of the children of affected women are affected, and both sons and daughters may be amongst the affected and the normals. An affected man transmits his X chromosome carrying the pathogenic gene to his daughters only, so that all the daughters are affected, but none of his sons. This is brought out in generation IV of the pedigree. The affection was defective enamel of the teeth.

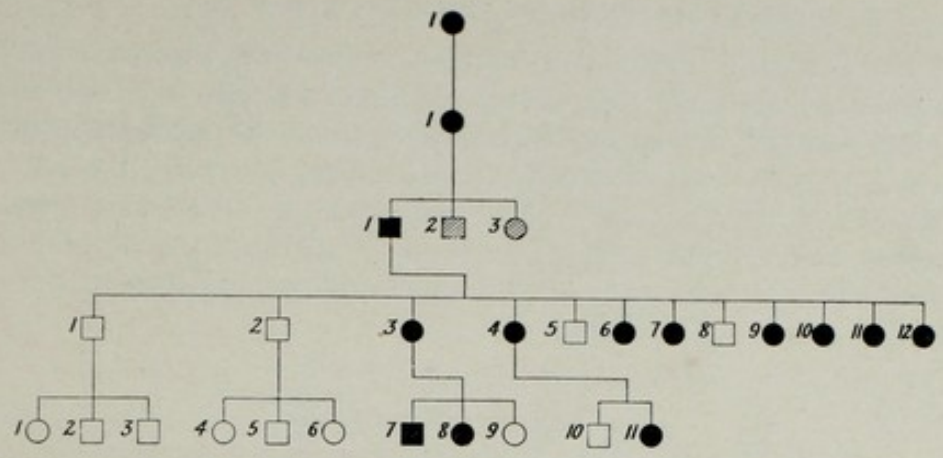


FIG. 34.—Dominant sex-linkage. A pedigree of defective enamel of the teeth. (*After E. H. Bampton. Sixth International Dental Congress, London*, 1949.) (The shaded symbols refer to individuals on whom information is uncertain.)

Y CHROMOSOMAL INHERITANCE

Fig. 35 illustrates transmission over four generations with men only affected. The abnormal gene could only be situated on the non-homologous portion of the Y chromosome. The affection here was webbed toes. There is no clearly established ophthalmological condition showing this mode of inheritance.

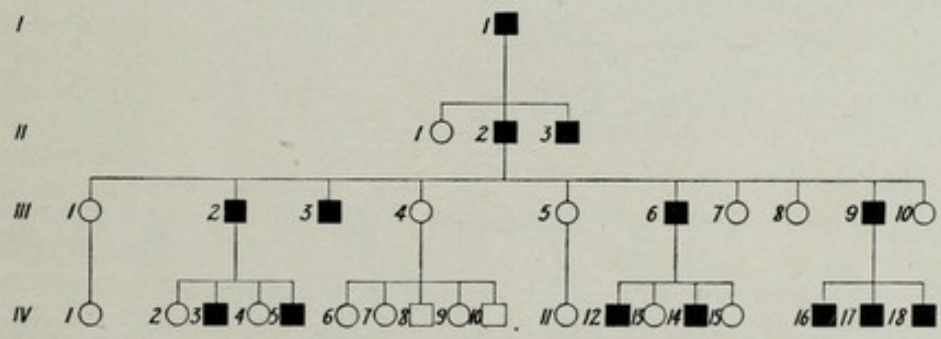
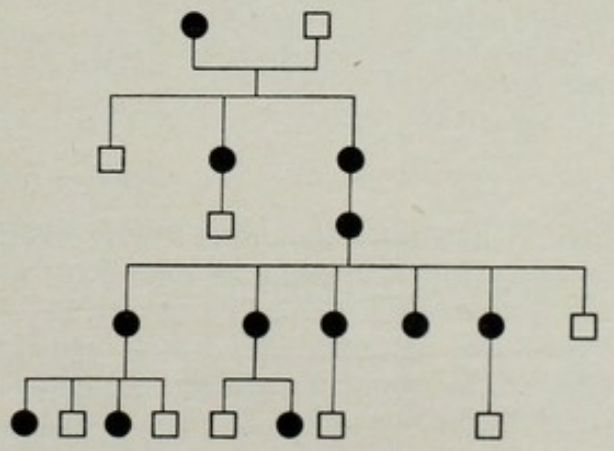


FIG. 35.—Y Chromosomal inheritance. A pedigree of webbed toes. (*After R. Schofield, J. Hered.*, 1921, 12, 400.)

FIG. 36.—A pedigree of colour-blindness transmitted exclusively in the female line. 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 F. Cunier* (1839) *in Treasury of Human Inheritance* (1933), *Ed. by K. Pearson, Vol.* 2 (*by Julia Bell*), *Fig.* 431. *London; Cambridge University Press.*)



Direct Transmission through Women only

In one of the pedigrees for colour-blindness (Fig. 36), transmission occurred through women to their daughters only. The normal chromosome mechanism cannot explain this and by analogy with observed data in Drosophila, it is postulated that such women are of the XXY constitution, and carry the affected gene on their double X chromosome. They contribute to their sons their normal Y chromosome, and as these sons get a normal X chromosome from their father, the sons are unaffected; whilst the daughters who all get the disjointed X chromosome from their mother are affected.

Intermediate Inheritance

The difficulty in distinguishing intermediate from dominant inheritance in human genetics has already been stressed. In the case of a gene carried on the non-homologous part of the X chromosome this difficulty is less real, for an intermediate gene would show its full effect in a man, and a considerably lesser effect in a woman. Fig. 37 is a pedigree of choroideremia which is blinding in men, and shows itself in women by minor ophthalmoscopic anomalies with little effect on vision.

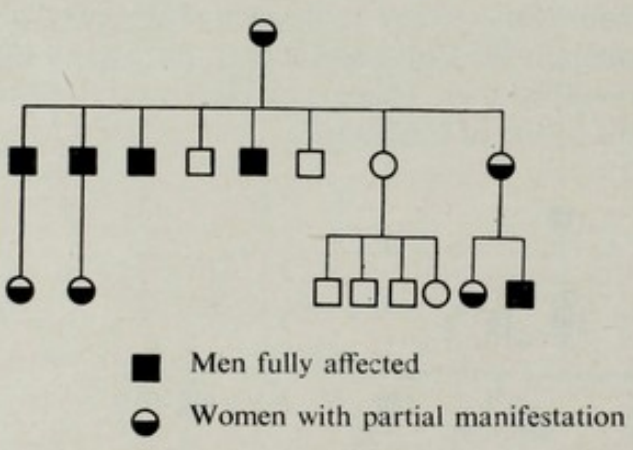


Fig. 37.—Intermediate sex-linkage: a pedigree of choroideremia. Abbreviated. Choroideremia manifests itself fully in men. In women the fundus appearances are incomplete, ranging from normalcy to "atypical retinitis pigmentosa". (*After C. and R. J. P. McCulloch. Trans. Amer. Acad. Ophthal. Otolaryng.*, 1948, **53**, 160.)

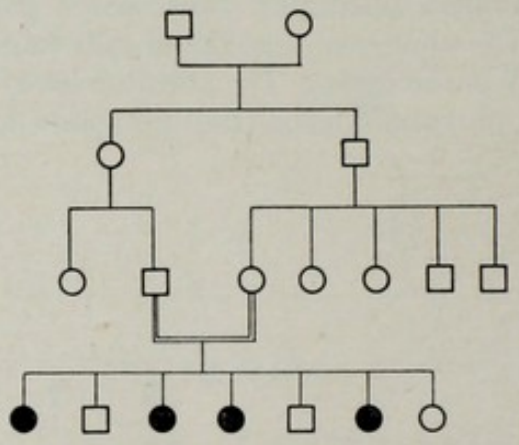


Fig. 38.—Presumed recessive partial sex-linkage: a pedigree of total colour-blindness. The sons should all be normal and 50 per cent of the daughters should be affected on theoretical expectations. By itself the pedigree is inconclusive. (*After Komai from J. B. S. Haldane. New Paths in Genetics* (1940). *London; Allen & Unwin.*)

Partial Sex-linkage

Fig. 38 illustrates that total colour-blindness (day-blindness) might possibly be inherited in a manner consistent with recessive partial sex-linkage. The parents are first cousins, and are presumed to carry a recessive gene on their X chromosomes. The sons are all normal, whilst 50 per cent of the daughters should be affected. By itself the pedigree is hardly conclusive. This sex distribution might occur fortuitously in an autosomal recessive.

A pedigree consistent with dominant sex-linked inheritance is shown in Fig. 39. The affected man in the first generation cannot have affected sons, but all his daughters would be affected because the father contributes an X chromosome with a dominant gene. The woman in the second generation transmits the affection to 50 per cent of her children, the sex ratio being the same for sons and daughters.

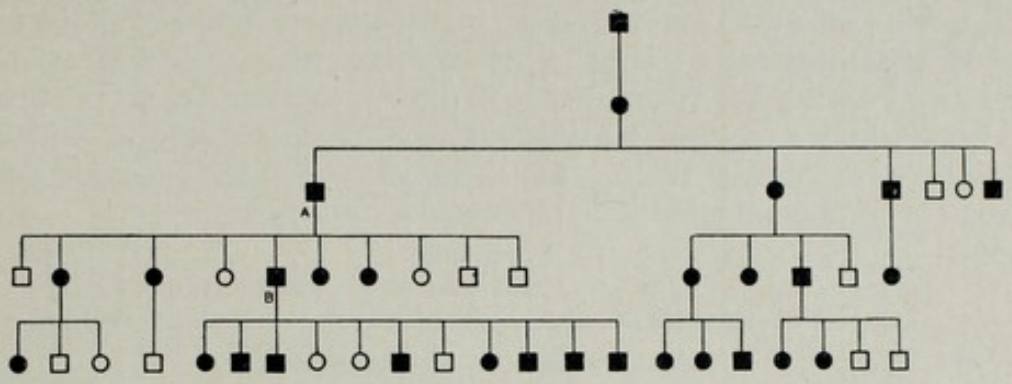


FIG. 39.—Presumed dominant partial sex-linkage: A pedigree of retinitis pigmentosa.

On the assumption of dominant partial sex-linkage the affected man in the first generation carried the dominant gene on his X chromosome and can have only affected daughters. Such daughters in turn can 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 S. Snell, Trans. Ophthal. Soc. U.K.*, 1903, **23**, 68.)

In subsequent generations the same pattern would repeat itself. Affected men transmit the affection to all their daughters ; affected women transmit the affection to 50 per cent of their sons and 50 per cent of their daughters. There are, however, exceptions in this pedigree which might arise from cross-overs. Thus it may be postulated that in the third generation three cross-overs occur in the first sibship of 10 children leading to one affected son and two normal daughters (the crossing occurring at gamete formation in A). The affected son, B, now carries the gene on the Y chromosome and transmits it to his sons only: this is seen by the fact that 6 of his 7 sons are affected. Of the 4 daughters none should be affected; actually 2 are affected here. Three cross-overs explain the anomalous sex distribution.

CRISS-CROSS INHERITANCE

This may occur in several distinct modes of sex-linked inheritance. The theoretical possibilities are shown in Table III.

Recessive sex-linkage.—An affected woman married to a normal man has affected sons and carrier daughters. The daughters are, therefore, phenotypically like their father (*see* Fig. 32).

Dominant sex-linkage.—An affected man married to a normal woman has daughters who possess his X chromosome, whilst the sons have a normal X chromosome from their mother. The daughters here are therefore both genotypically and phenotypically like their father, whilst the sons are like their mother (*see* III and IV, Fig. 34).

Partial sex-linkage.—A dominant partially sex-linked gene on the X chromosome of a man will lead to the appearance of the affection in him and in his daughters, whilst the sons receiving a normal X chromosome from their mother are normal (*see* III and IV, Fig. 39). If the dominant gene is situated on the X chromosome of a woman there is no criss-cross inheritance for 50 per cent of both sons and daughters will be affected. (In the case of partially sex-linked genes these criss-cross arrangements only hold good in the absence of cross-overs.)

TABLE III

SHOWING THE THEORETICAL POSSIBILITIES AS TO CRISS-CROSS INHERITANCE
(Criss-cross inheritance is indicated by heavy symbols against offspring)

TOTAL SEX LINKAGE (*X Chromosomal*)

Father affected	Parent		Phenotypes in offspring				Disturbance of sex-ratio of offspring owing to cross-over
	Genotype	Phenotype	Daughters		Sons		
			50%	50%	50%	50%	
Recessive		+	—	—	—	—	Not applicable
Dominant		+	+	+	—	—	
Intermediate		+	±	±	—	—	
Mother affected							
Recessive		+	—	—	+	+	
Dominant		+	+	—	+	—	
Intermediate		±	±	—	+	—	

PARTIAL SEX LINKAGE (*X and Y Chromosomal*)

Mother affected							
Recessive		+	—	—	—	—	Not applicable
Dominant		+	+	—	+	—	
Intermediate		±	±	—	+	—	
Father affected							
Recessive		+	—	—	—	—	Disturbed ratios are to be expected
Dominant		+	+	+	—	—	
Intermediate		±	±	±	—	—	
Dominant		+	—	—	+	+	
Intermediate		±	—	—	±	±	

NON-HOMOLOGOUS PART OF Y CHROMOSOME

Father affected		+	—	—	+	+	Not applicable

LINKAGE OF GENES

Red-green blindness is a common condition, and the gene is carried by the X chromosome. Though it is not a normal feature it can be used as a marker for the X chromosome because it happens to be so common. Fig. 40 illustrates an actual occurrence. In Fig. 40 *a* I, 1 must have carried the gene for haemophilia on one chromosome and the gene for red-green blindness on the other X chromosome.

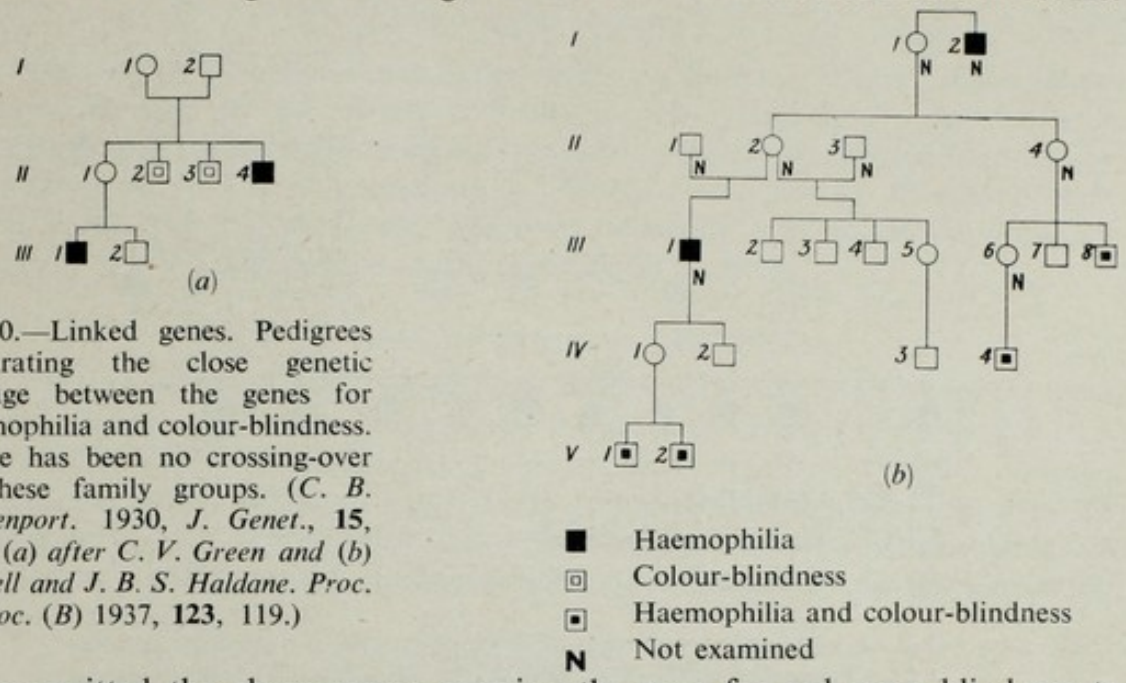


FIG. 40.—Linked genes. Pedigrees illustrating the close genetic linkage between the genes for haemophilia and colour-blindness. There has been no crossing-over in these family groups. (*C. B. Davenport.* 1930, *J. Genet.*, **15**, 401. (*a*) *after C. V. Green and* (*b*) *J. Bell and J. B. S. Haldane. Proc. R. Soc.* (*B*) 1937, **123**, 119.)

She transmitted the chromosome carrying the gene for red-green blindness to II, 2 and II, 3, and the X chromosome carrying the gene for haemophilia to II, 4. Her daughter, II, 1, must have received the chromosome carrying haemophilia from her mother and the normal X chromosome from her father. This is shown by the fact that one of the sons of II, 1 was normal, carrying the normal X chromosome, whilst the other son, III, 1, was a haemophiliac as he received the X chromosome carrying the gene for haemophilia. In Fig. 40 *b* it is obvious that IV, 1 must have carried the gene for haemophilia and the one for colour-blindness on the same chromosome. She must have derived this chromosome from her father, III, 1, who was known to be a haemophiliac, but whose colour vision could not be tested as he was no longer alive when the investigation was carried out. The assumption that his X chromosome carried both these genes is confirmed by the fact that his maternal aunt transmitted an X chromosome carrying both these genes to one son, and a normal X chromosome to another son. Here, therefore, the two genes were situated on the same X chromosome. The 6 family groups on which this investigation was based all showed linkage, the abnormal gene being situated either on different chromosomes as in Fig. 40 *a* or on the same chromosome as in Fig. 40 *b*. There was, however, a single example of crossing over, indicating a cross-over value of about 5 per cent—suggestive of the fact that the two genes, or their mutants, are situated close to each other on the X chromosome. This is an instance illustrating a closer approach to chromosome mapping in so far that the relative situation of the two genes can be shown, over and above the fact that they are carried by the same chromosome.

Fig. 41 is a pedigree of a family in which three abnormal conditions were observed, congenital total colour-blindness, otosclerosis and vascular hypertension. In the first three generations only otosclerosis and hypertension are seen. Both these conditions are dominant with a high degree of penetrance and should therefore appear in most individuals carrying the trait. They appear together in II, 2

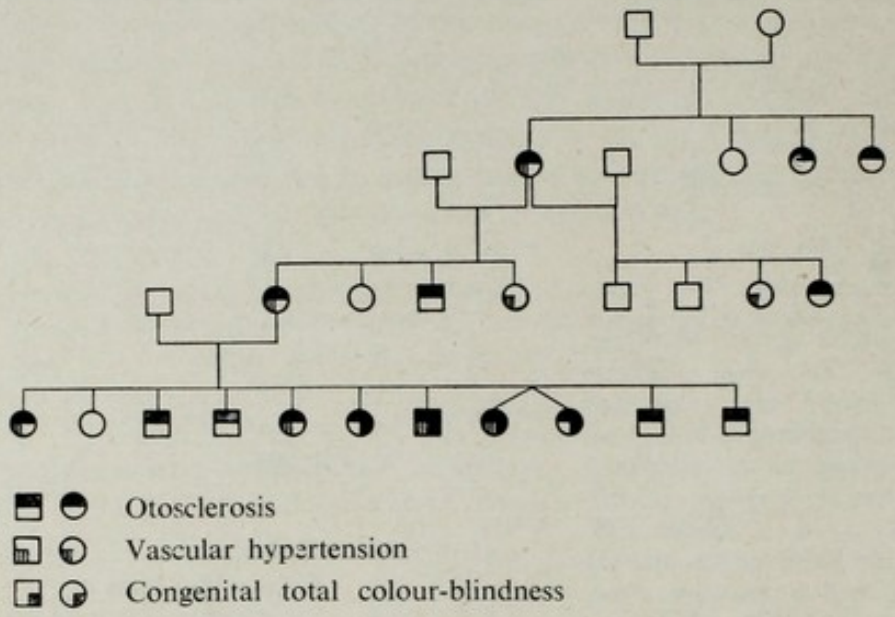


FIG. 41.—Clinical association of three affections in a sibship. *See* text for a discussion on the possibility of linkage. (*After W. J. W. Ferguson and A. C. Macgregor. Trans. Ophthal. Soc. U.K.*, 1949, **69**, 249.)

and in III, 2, but separately in 6 more patients. In the fourth generation they appear together 4 times and separately 6 times. There are therefore altogether in this family 6 instances of the two conditions appearing together and 12 in which they appear separately. This fits in better with the assumption that the two conditions are carried on separate pairs of chromosomes than carried on the same pair of chromosomes. They obviously cannot be carried on the same chromosome as there is an excess of patients in whom the conditions are dissociated. The assumption that they would be carried on the two different chromosomes of a given pair, and that cross-over would bring the two affections on one chromosome in one-third of the number of affected patients is theoretically possible, though it would imply a high cross-over rate, and there is nothing to support this mode of location of genes against the more likely assumption that the genes are carried on different pairs of chromosomes. In the fourth generation 4 patients appear with total colour-blindness. This is a recessive condition, and could possibly be carried by the same chromosome that carries the dominant gene for otosclerosis. This is suggested by the fact that all the 4 patients with total colour-blindness have otosclerosis. The 6 patients in this generation with otosclerosis without total colour-blindness would presumably receive the chromosome carrying the gene for this affection from their mother together with the recessive gene for total colour-blindness, but would receive a normal chromosome from their father. Here again, there is no reason to assume this, as against the more likely hypothesis that

the genes for these two abnormalities are carried by two different pairs of chromosomes. One thing can clearly be excluded. It is impossible to postulate that the same chromosome pair carries both otosclerosis and total colour-blindness on the two different chromosomes; if this were the case the two affections could never occur together in any of the individuals in generation IV.

STATISTICAL NOTE*

Apart from statistical considerations the ratios on human pedigrees have to be assessed in the light of the clinical difficulty in getting full family histories and examinations. Additional difficulties may arise from a heavily affected branch of a family readily submitting to examination, whereas a less heavily affected branch may not do so. When dealing with affections occurring later in life the difficulty of establishing a full pedigree becomes particularly marked.

The 1 : 1 Ratio in Dominant Inheritance

The 1 : 1 ratio in dominant inheritance can be established only on relatively large numbers. Human pedigrees are generally small, and deviations from the 1 : 1 ratio are to be expected as chance occurrences. It is therefore a matter of some importance to assess whether a particular pedigree departs from the expected ratio by more than a chance occurrence. The statistical significance may be tested by calculating "chi squared" (for one degree of freedom) by the arithmetically simplified formula of Fisher:

$$\frac{(\text{Difference}-1)^2}{\text{No. of observations}}$$

The chances of the observed values occurring as a sampling fluctuation are then (from the chi squared distribution) as follows:

$\frac{(\text{Difference}-1)^2}{\text{Number of observations}}$	Probability Once in :	
0.5	2	trials
1	3	,,
2	6	,,
3	12	,,
4	22	,,
5	39	,,
6	70	,,
7	123	,,
8	214	,,
9	370	,,

Probability of once in less than 20 trials is regarded as not significant statistically. On the formula

$$\frac{(\text{Difference}-1)^2}{\text{No. of observations}}$$

an answer of less than 4 may therefore be taken as not significant.

* This section is based largely on J. A. Fraser Robert's *Introduction to Medical Genetics*.

Example:

In the pooled sample of 4 pedigrees showing a fundus lesion that develops at the age of 40 years, the total number of individuals aged 40 years and over was 106, of whom 61 were affected and 45 unaffected.

$$\frac{((61-45)-1)^2}{61+45} = \frac{(16-1)^2}{106} = \frac{225}{106} = 2{\cdot}1$$

The distribution of affected and unaffected can therefore be regarded as a chance variation of no significance, and consistent with the 1 : 1 ratio.

The Sex-ratio

In pooled pedigrees the number of men and women should be about equal, that is, a 1 : 1 ratio. Any apparent inequality in the distribution of affected individuals can therefore be tested by the same procedure as the 1 : 1 ratio in dominant affections.

The 3 : 1 Ratio in Recessive Inheritance

The 3 : 1 ratio theoretically expected in recessive affections is, as already pointed out, not frequently observed in human genetics, because the selection of cases tends towards a bias in recording sibships with large numbers affected, whilst the sibships with only one individual affected are not often recorded. Pooled figures therefore give an excess of affected individuals, and these of an artificial type. There is a considerable mathematical literature which aims at correcting this bias in sampling and most of it is best left to an expert.

TABLE IV

(*After J. Saebø. Brit. J. Ophthal.*, 1949, **33**, 601.)

Serial No. of family	Number of children in sibship (S)	Number of affected (A)	Weinberg's reduction method	
			A (S—1)	A (A—1)
1	3	2	4	2
2	2	1	1	0
3	4	2	6	2
4	2	1	1	0
5	1	1	0	0
6	3	2	4	2
7	9	2	16	2
8	5	1	4	0
9	3	1	2	0
10	1	1	0	0
11	2	1	1	0
12	11	4	40	12
13	4	2	6	2
14	8	1	7	0
15	5	1	4	0
16	2	2	2	2
17	5	2	8	2
Total	70	27	106	26

A widely used method is the reduction or proband method of Weinberg. An actual example of its use is the following:

In an investigation on the recessive inheritance of congenital cataract, 27 in a total of 70 sibs in 17 different families were found to be affected. This represents 38 per cent as against the expected 25 per cent. If the material is analysed as in Table IV, a computed incidence of 26 in 106, or 24·5 per cent, is obtained.

The Weinberg method, as all the other methods evolved for this purpose, can only be applied to pooled material. The difficulty inherent in these methods is the lack of uniformity with which such pooled material is collected.

Frequency of Recessive Genes

It has already been seen that a recessive gene may remain latent for many generations until it happens that two heterozygous partners have offspring to whom each parent contributes the chromosome carrying the pathogenic gene. It is therefore obvious that in any community the number of heterozygotes will always be considerably more than the number of homozygotes. If one assumes a frequency of occurrence of the gene as 1 : 100 in the general population, the chances of any individual carrying the gene are 1 : 50, for he may get the gene from either of his parents. The chances of any individual getting the gene from both his parents are 1 : 100 × 1 : 100, or 1 : 10,000. With a gene frequency of 1 : 100 the number of heterozygotes is therefore 200 times as high as the number of homozygotes. The frequency of a simple recessive gene in the general population can therefore be estimated by the frequency of affected individuals. If a particular recessive affection is seen once in every 10,000 individuals, the frequency of the gene is of the order of 1 : 100. If it is seen once in every 1,000,000 individuals the frequency would be 1 : $\sqrt{1{,}000{,}000}$, which equals 1 : 1,000. Most recessive conditions are not so rare as 1 : 1,000,000, and perhaps not so common as 1 : 1,000. The frequency of most recessive genes is therefore certainly more than 1 : 1,000 and probably less than 1 : 100 for most cases. In any given affection a rough approximation can be computed by establishing the frequency of the affection in the general populations.

Frequency of Consanguinity in Recessive Disease

Two distinct problems are involved. In the first place, there is the question of the chance of an affection cropping up in the offspring of consanguineous parents. Secondly, there is the question of how frequently consanguineous marriages are observed in recessive affections.

Frequency of recessive disease in the offspring of consanguineous parents

In Fig. 42 if it is assumed that III, 1 is heterozygous for a recessive affection, she must have received a recessive gene from either her father or her mother. The chances that it was her father who carried the gene are therefore 1 : 1, that is, $\frac{1}{2}$, and the same chance applies to his sister II, 3. The combined chance that both are heterozygously affected is $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$. If II, 3 is heterozygous, the chance that

her son III, 2 is also heterozygous is again 50 per cent, so that if III, 1 is heterozygous the chance that her first cousin is also heterozygous is $\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} = \frac{1}{8}$. If, therefore, a person heterozygous for a recessive trait marries a first cousin, the chance is 1 : 8 that the cousin will carry the same trait. A first-cousin marriage thus involves the risk that if one partner carries a recessive gene the chance of the other partner

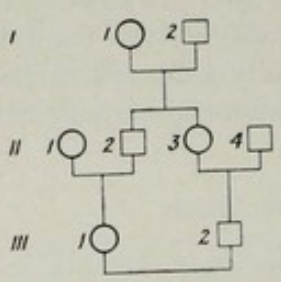


FIG. 42.—Scheme showing that first cousins have a 1:8 chance of carrying the same gene. (*After J. A. Fraser Roberts, Introduction to Medical Genetics* (1940). *London: Oxford University Press.*)

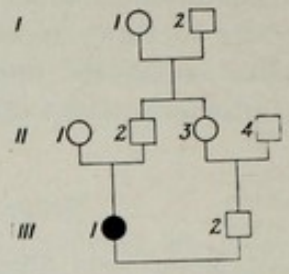


FIG. 43.—Scheme showing that the chance of the same gene being carried by both parents is 1:4 if one parent is affected and marries a first cousin. (*After J. A. Fraser Roberts, Introduction to Medical Genetics* (1940). *London: Oxford University Press*, 1940).

also carrying it is not dictated by the frequency of the gene in the general population, but by the much closer ratio of 1 : 8. If III, 1 is homozygous, and therefore affected, the chance of her offspring being affected is double the ratio of 1 : 8, for now it is clear that it was her father II, 2 who carried the gene, and the chance that his sister also carried the gene is 1 : 1. The chance that III, 2 carries the gene is now $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$. The offspring of III, 1 and III, 2 are therefore exposed to a 1 : 4 chance of being affected (Fig. 43).

The frequency of consanguinity in recessive affections

If it is assumed that a particular recessive gene is present once in 100 times in the general population, then the chance that any individual has of receiving it on one or other of his chromosomes is 1 : 50. In the general population the chances of a sibship derived from random mating being affected are 1 : 50 × 1 : 50, that is 1 : 2,500. One marriage in 2,500 will therefore produce children who are affected, and as the incidence of affected to normal is 1 : 4, 1 in every 10,000 individuals will be affected. In a first-cousin marriage, the chances will be increased considerably, for if one partner carries a recessive gene the chances of the other also carrying it will be 1 : 8. The occurrence of affected sibships would therefore be $1 : 50 \times \frac{1}{8} = 1 : 400$, that is, one marriage in each 400 will give affected offspring if the marriage is between first cousins; one in every 1,600 individuals will be affected.

In the general population recessive affections will therefore come from two

distinct types of marriages—random marriages and first-cousin marriages. First-cousin marriages are, on the whole, infrequent (about 1 per cent of all marriages) and the following situation will arise. Out of, say, 40,000 marriages, 39,600 would be random marriages and 400 between first cousins. The chances of affected sibships cropping up among the 39,600 marriages are 1 : 2,500, that is, 16 sibships would be affected. The chance that in the 400 first-cousin marriages there would be affected sibships is 1 : 400, that is, one sibship. With a gene frequency of 1 : 100, therefore, there would be 16 non-consanguineous marriages and 1 first-cousin marriage amongst 17 family groups. The frequency of consanguineous marriage would therefore be about 6 per cent.

If it is assumed that the frequency of the gene is 1 : 1,000 instead of 1 : 100, then the chance that there would be an affected sibship in random marriages would be $1 : 500 \times 1 : 500 = 1 : 250{,}000$, that is, in the offspring of one marriage in every 250,000. The chance of affected sibships from a first-cousin marriage would be $1 : 500 \times \frac{1}{8} = 1 : 4{,}000$. Out of every postulated 40,000 marriages, 39,600 random marriages would therefore give only a small chance of an affected sibship: $\frac{39{,}600}{250{,}000} = 0\ 16$, and 400 first-cousin marriages would give also a small chance, $\frac{400}{4{,}000} = 0{\cdot}1$. The ratio of affected individuals derived from non-consanguineous marriages to those from consanguineous marriages is therefore 16 : 10, that is, approximately 62 per cent of the sibships would be derived from non-consanguineous parents and 38 per cent from parents who are first cousins.

The lower the frequency of the gene the higher does the rate of consanguinity become amongst parents of affected sibships. With a frequency distribution of 1 : 10,000 the proportion of affected sibships derived from non-consanguineous parents becomes very small (about 1·6 per cent).

Clinically Indistinguishable Conditions Due to Different Genes

The frequency of a recessive gene in the general population can therefore be assessed by establishing not only the frequency of the affection in the general population but also the frequency of first-cousin marriages amongst the parents of affected individuals in a random sample.

In albinism the frequency of first-cousin marriages is about 20 per cent, and in retinitis pigmentosa about 17 per cent; this implies that the genes for albinism and retinitis pigmentosa are rare, and that considerably fewer than 1 : 10,000 individuals in the general population would be affected by either of these disorders. Actually neither affection is particularly rare and considerably more than 1 : 10,000 individuals are affected. These contradictory results suggest that in albinism, as in retinitis pigmentosa and in many other conditions, more than one gene is responsible for clinically indistinguishable affections: though the clinical conditions are fairly common, the different individual genes are fairly rare.

In clinical practice it is found that when a recessive affection is less common than the incidence of one affected individual in 2,000–3,000 of the general population, the incidence of first-cousin marriages amongst the parents is above that in the general population.

CHAPTER 4

CLINICAL VARIETIES OF GENETIC DISEASE

A SHARP antithesis between environmental and hereditary affections is fallacious and misleading. 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. None the less, it would be merely an exercise in logic to stress the genetic factor in conditions in which environmental factors are the main causative agents. Moreover, such exercises would be clinically misleading, particularly if the environmental factors are readily amenable to correction, and the hereditary factors are not—or, rather, not as yet.

Such considerations do, however, emphasize the fact that only in extreme cases can hereditary and environmental factors be clearly disentangled in the effect they produce. At the one extreme there are clinical conditions, such as, say, Tay-Sachs disease, which are always genetic in origin; at the other extreme there are such lesions as a stab wound which are always environmental. In many clinical conditions both environmental and genetic factors may be equally significant, and—what is as important—the appearances of an affection definitely of genetic or definitely of environmental origin may be 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. Lamellar cataract may be genetic in origin or caused by nutritional disturbances in the mother: a macular lesion cannot always be readily distinguished as of genetic or environmental origin.

Broadly speaking the following varieties of genetic affections may be recognized:

Congenital anomalies
Abiotrophic anomalies
Phakomatoses
Neoplasms
Metabolic disorders
Functional derangements
Syndromes

In some, at least, of these groups there are examples which merge on to the disturbances of environmental origin, or are indistinguishable in appearances.

CONGENITAL ANOMALIES

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 is the classical example of intra-uterine infection. It is one of the exceptions to the general rule that maternal infections are kept back by the placental barrier from reaching

the embryo. Depending upon the stage of development at which intra-uterine infection with syphilis occurs, and the severity of the infection, the range of effects extends from miscarriage, stillbirth, or a child born with all the stigmata of congenital syphilis, to a child apparently normal at birth and developing the manifestations of congenital syphilis later in life. Congenital anomalies that may be present in a child born at term include opacification of the cornea from intra-uterine interstitial keratitis, gross malformation of the eye, and possibly chorioretinal lesions. Buphthalmos has occasionally been observed. Recently the role of the virus of German measles as a cause of congenital anomaly has been clearly recognized. German measles contracted by the mother in the first two months of pregnancy may lead to widespread congenital anomalies including microphthalmia. Toxoplasmosis is yet another environmental factor that produces congenital fundus lesions, generally a central chorioretinal reaction, but occasionally more diffuse reactions, including that seen in macular coloboma.

Apart from infection, prematurity itself may be a cause of serious congenital defect. Retrolental fibroplasia is merely the ocular counterpart of a wide variety of congenital defects seen in the premature infant kept alive by the fine methods developed in recent years.

Experimentally a great variety of ocular abnormalities have been produced ranging from cyclopia and anophthalmos to less marked anomalies. Such anomalies have been particularly studied in the developing fish, where relatively slight changes in the temperature, oxygen, and salt concentration of the fluid in which the embryo grows give widespread effects. The younger the embryo is, 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. With fuller knowledge the clinical appearance of the lesion might be used as a time scale indicative of the height of activity of the disturbing factor. 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 mass of congenital anomalies for which no infective agent can be established.

The clinical similarity of many of the congenital anomalies of genetic origin with those of environmental origin—such as buphthalmos and lamellar cataract, to mention only two—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. For the present all that can be done is to distinguish in extreme cases those anomalies that are clearly of one or other type. 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 the two eyes and inflammatory reactions are lacking. Symmetry is, however, not conclusive; in a frank pedigree of anophthalmos one eye may show microphthalmia and the other anything ranging from normalcy to anophthalmos.

ABIOTROPHIES

Abiotrophic lesions have not been studied to any extent in animal genetics. Abiotrophy is, however, an undoubted clinical phenomenon: a classical example is 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. 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. In general medicine Huntington's chorea stands out as an important example of an abiotrophic process frequently coming on in middle life. The blood dyscrasias (as distinct from Rhesus factor disturbances and haemophilia which are congenital anomalies) are less clearly recognized as genetic anomalies of late onset. In ophthalmology there is some evidence that macular dystrophy may develop in middle life and later, and there is proof of a widespread chorioretinal dystrophy which begins as a macular lesion at about the age of 40 years and leads to total or subtotal blindness by the age of 70 years. 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. Outstanding amongst these are the corneal dystrophies, the macular dystrophies, Leber's optic atrophy, and the group of affections known as retinitis pigmentosa. It is also likely that many cases of optic atrophy, and some, if not the bulk, of glaucoma and senile cataract and ill-differentiated fundus lesions are genetically determined abiotrophies.

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 macular dystrophy. 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

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

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, unmistakable 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 abiotrophies, but any suggestion that the abiotrophies have specific and characteristic reactions is an oversimplification and a diagnostic pitfall.

Anticipation

Glaucoma 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 such affections as are not readily diagnosed (such as chronic glaucoma) 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 affected ancestors, but the opposite has also been observed.

PHAKOMATOSES

The classical examples of the phakomatoses (Van der Hoeve) are neurofibromatosis, tuberose sclerosis, and the haemangiomatosis group. Here 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 parallel 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 gliomas are malignant phakomas for there are no associated general conditions as in phakomatoses. Direct transmission of glioma over two generations has been observed repeatedly, and there is at least one authenticated example of transmission over three generations. It is possible that there may also be transmitted a tendency towards intracranial tumours.

The line of demarcation between simple and malignant melanomas of the iris and choroid is not always clear. There are several pedigrees on the occurrence of choroidal sarcoma; there is as yet little information on the genetic background of melanomas generally.

THE LIPOIDOSES

Disturbances of lipoid metabolism giving rise to ocular lesions have been known for many years in the relatively simple forms of xanthelasmas of the skin of the lids in diabetes mellitus and of arcus juvenilis seen in young adults with hypercholesteraemia—a condition also observed experimentally. Ocular changes of a graver character are seen in the group of generalized hereditary lipoid dystrophies such as Gaucher's disease, Niemann-Pick disease, and Christian-Schüller disease.

Pathologically these three affections have in common the widespread storage of excessive amounts of lipoid within large cells derived from the reticulo-endothelial system. Clinically they constitute distinct entities with many points of similarity. As hereditary lesions developing in apparently fully differentiated tissues, they fall into the abiotrophy group and are inherited in a recessive manner. Chemically the type of lipoid disturbance is different in the three affections, kerasin, phosphatide, or cholesterol excess being characteristic.

The relationship of Tay-Sachs disease (infantile amaurotic idiocy) and of Batten-Mayou disease (juvenile amaurotic idiocy) to each other, and to the recognized lipoid dystrophies, still requires elucidation. While juvenile amaurotic idiocy falls in the group of abiotrophies—for the children are normal until about the age of the second dentition—it is not certain whether the infantile variety may not in fact be a congenital anomaly.

The occurrence of a congenital variety of lipoid dystrophy is most clearly seen in the case of gargoylism. Here the child is abnormal at birth, and the metabolic disturbance is of the lipoid variety. This affection, too, appears to be recessive.

FUNCTIONAL ANOMALIES

Colour-blindness and night-blindness are generally hereditary. The eyes are apparently normal in structure, and the reason for hereditary failure in function

is not known. Two considerations emerge: in the first place parallel failures in function can be observed in environmental conditions; secondly, the concept of hereditary disease, broad as it is with the inclusion of congenital, abiotrophic, phakomatous, neoplastic and lipoid reactions, has to be extended to cover functional as distinct from immediate or late structural changes. These considerations emphasize once more that in the effects such reactions produce there is no sharp demarcation between the affections of hereditary and 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. The syndrome of macular coloboma and apical dystrophy of hands and feet is 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, 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.

CHAPTER 5

PROSPECTS IN THE CONTROL OF GENETIC DISEASE

CONTROL OF GENETIC DISEASE AS A NATURAL PHENOMENON

THE ESTABLISHED clinical fact of irregular dominance and the conceptions of penetrance and of low expressiveness are in themselves ample proof that under natural conditions the appearance of genetic disease may be suppressed in particular individuals. It is true that only the manifestations of the disease process are suppressed and not the tendency to the affection itself, for individuals who do not manifest the affection may still transmit it. It is, however, clear that under certain conditions, ill-defined at present, spontaneous suppression of the manifestation of a genetic affection does occur, so far as the individual is concerned.

Translated into general terms, the manifestations of a pathogenic gene are suppressed in an individual in whom there is an accumulation of other genetic factors or of environmental factors, which inhibit its action.

As yet only the most imperfect understanding of these inhibiting factors has been reached. Theoretically there are three possibilities. In the first place it is conceivable that a minimal change takes place in the structure of the gene disturbing its pathological action. This is unlikely, for a change in a gene would affect not only the individual but his descendants. It would, in fact, correspond to a mutation which introduces a whole series of fresh properties. Secondly it can be conceived that the pathogenic gene in a particular individual exists in a total genetic environment which influences the manifestation of the gene. This conception is well grounded experimentally, and in the results of matings in animal stock; it implies the accumulation of modifying genes in an individual influencing the behaviour of a particular gene. The fact that under experimental conditions one and the same gene can be made to appear as a dominant or recessive, depending upon the total genetic constitution in which it is operative, is clear proof that no gene acts as an isolated unit. One may therefore visualize the patient in whom a genetic manifestation is suppressed as the possessor of a genetic constitution which is unfavourable for the expression of the particular genetic abnormality. Finally there is the possibility that ill-understood environmental factors have suppressed the manifestation of the gene. This possibility, too, is based on extensive experimental evidence for it is well established that such factors as temperature, moisture, and other environmental agencies can bring out or suppress certain genetic potentialities. It is, of course, also possible that both the total genetic constitution and environmental factors may in combination be effective in particular cases.

The significant conclusion that emerges from these considerations is this: though the gene is inherently stable, and tends to express itself with a high degree of regularity and effect, no gene acts as an isolated and independent unit; it is part of a complex internal and external environment and is susceptible to modifications in either environment. Genetic disease is therefore never merely the

expression of a pathogenic gene; it is the expression of a pathogenic gene in a particular internal and external environment. This is, of course, parallel with the modern conception of infective disease. Infections are never merely the result of a pathogenic organism; they are the result of the action of pathogenic organisms in relation to the patient's resistance and environmental conditions.

THE EXPERIMENTAL CONTROL OF GENE MANIFESTATIONS

That the above considerations are no idle speculation is shown by the many available examples drawn from experimental studies. Some of these have already been noted in Chapter 2, and they may be summarized in the following terms.

(1) During the early stages in development, environmental conditions may be potent in bringing out, or suppressing, certain genetic tendencies. This is clearly seen in the case of the developing larvae of *Drosophila* in which both excessive temperature and humidity can bring out such features as reduplicated legs or striped belly respectively, in a genetically homogeneous breed which normally does not show these abnormalities.

(2) The example of suppressing the deposition of yellow fat in rabbits by the environmental inclusion of food lacking green-stuffs is an illustration of the environmental effects at a later stage of development.

(3) The development of patches of black hair in the Himalayan rabbit under conditions of low temperature illustrates the reversal of established process.

Experimental control of a genetic condition approaching a pathological state is seen in the rat. A skeletal malformation, "bent nose" (Heston), appears in some strains when the mother is deficient in vitamin D, and is on a diet with an unbalanced calcium–phosphorus ratio. Rats of the same strains on a normal diet produce normal young whilst the progeny of rats of other genetic constitution are uninfluenced by this nutritional deficiency.

Examples such as the last suggest that some genetic anomalies at any rate are likely to prove amenable to simple chemical treatment. Studies on colour in the Chinese primrose, in which the action of different genes in supplying a particular chemical component can be proved experimentally and the deficiency supplied, support that view.

CLINICAL PORTENTS

The assumption that genetic disease is not amenable to treatment, ill-founded as it is in the light of experimental and theoretical considerations, is moreover not borne out by results in human pathology. Admittedly the results as yet are meagre, but they do at any rate dispose of the prevalent fatalistic attitude.

The structural ravages of genetic disease are, of course, as amenable to surgical correction as those of other disturbances. Hereditary cataract presents no special problems. Likewise the physiological imbalances induced by genetic disease are not beyond control, as shown by the value of insulin in diabetes mellitus. The prevention of extensive, and even fatal, developments is illustrated by the recent understanding of the significance of the Rh factor in producing abortions or uterus gravis. The effect of splenectomy in familial acholuric jaundice is a yet further example of the control, though empirical, of a genetic affection. It is

likely that rickets is an example of a genetic affection controlled by simple chemical treatment. What evidence there is on the distribution of rickets suggests that a previous generation of clinicians did not err in regarding the affection as essentially hereditary; not all children exposed to the same environment developed rickets, and the distribution of affected to normal suggests that under suitable environmental conditions the affection was transmitted as a simple dominant. It would appear that vitamin D inhibits the expression of the pathogenic gene responsible for rickets.

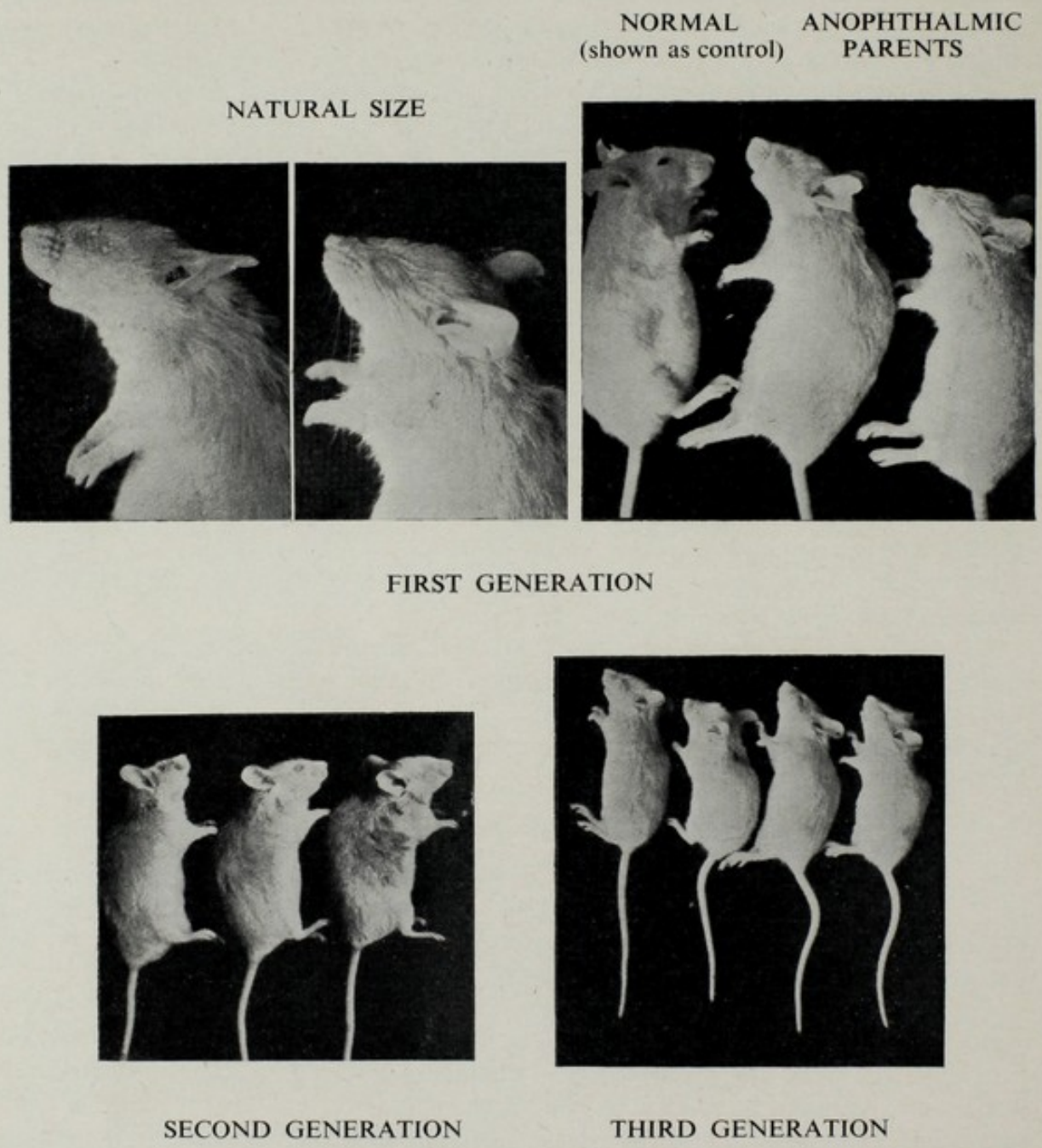


FIG. 44.—Anophthalmic mice. Anopthalmos in mice is inherited in a recessive manner. This photograph shows three successive generations in an inbred colony. (*Animals derived from stock kindly supplied by Dr. Herman B. Chase, Brown University, Providence, U.S.A.*)

The hazy demarcation clinically between genetic and environmental affections arises from the fact that genetic anomalies cannot be clearly separated from environmental disturbances except in extreme cases, and this in turn arises from the fact that genetic anomalies do not constitute rigid entities uninfluenced by other physiological mechanism. For practical purposes the significant thing is that some genetic anomalies arise from disturbance in intra-uterine life, producing congenital anomalies, whilst others, the abiotrophic group, occur in fully formed tissues which do not live out their normal span. The abiotrophic group presents at the moment the more hopeful line of approach, as the congenital anomalies are unlikely to be reversed to normalcy. The control of congenital anomalies requires a far fuller understanding of embryological physiology than is possessed today, while the control of abiotrophic anomalies raises complex problems of postnatal development.

These are all formidable issues, but the prevention of haemolytic jaundice of the newborn—now an accomplished fact—and the prevention of rickets (if rickets is indeed a genetically determined anomaly) are portents as hopeful as were the early results of bacteriology.

EXPERIMENTAL MEDICAL GENETICS

Although there is much yet to be done in establishing the modes of inheritance in the recognized genetic disturbances, and in establishing criteria for the clinical recognition of as yet ill-defined affections with a genetic basis, further progress lies essentially in the creation of a science of experimental medical genetics. The study of patients with genetic disease has difficulties considerably greater than the study of patients with disturbances of environmental origin, for the full investigation of a patient with a genetic anomaly involves an extensive study of many relatives. This is not always possible, nor does medicine allow the experimental situations obtainable in animal investigations. For this reason it is essential that the counterparts of human genetic disease, when met in animals, should be submitted to the controlled techniques of the laboratory. Both congenital hereditary defects and abiotrophic anomalies occur in animals no less frequently than in man, and planned breeding can give an unlimited supply of experimental material. Ophthalmology in particular is suitable for such developments. Hereditary anophthalmos is known in mice (Fig. 44), buphthalmos in rabbits (Fig. 45) aniridia in cats, a lesion similar to retinitis pigmentosa in the Irish setter, and choroideremia in the rabbit. And there are many more such affections, the intensive investigation of which is as yet only beginning. Evidence from animal observations of the existence of abiotrophic lesions, and of their histological basis, is available from the studies by Bourne, Campbell and Tansley, in a strain of rats with congenital cataract. The retina is normal at birth, as observed histologically, and subsequently there develop histological changes simulating retinitis pigmentosa (Fig. 46). Work on Irish setters brings the same conclusion, confirmed both ophthalmoscopically (Fig. 48) and histologically (Fig. 47). The ultimate synthesis of such histological studies with biochemical investigations presents a hopeful prospect.

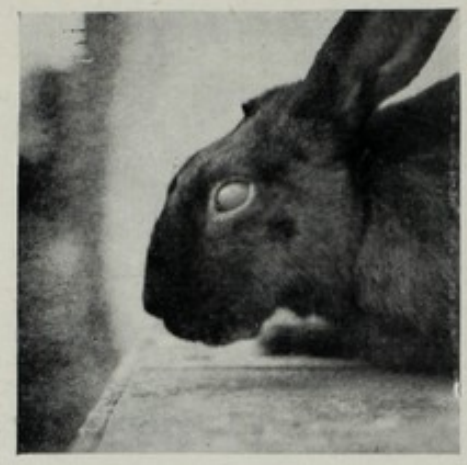


FIG. 45.—Buphthalmos in rabbits. This is also a recessive affection. The photograph shows a normal rabbit for contrast (left) and three successive generations in which the abnormality varied greatly in severity. In all animals the buphthalmos was obvious at birth and became intensified in growth. (*Animals derived from stock kindly supplied by Dr. R. Brückner of Basle.*)

INTERIM MEASURES

It is unlikely that the solution of genetic disease will come by one generally applicable procedure, any more than the control of infective disease was achieved by a single measure. For the present little can be done for most patients, beyond a human understanding of their difficulties and the giving of valid advice as to the prospects of transmitting the affection. No such advice is possible except in the light of the established Mendelian principles, and no such advice should be

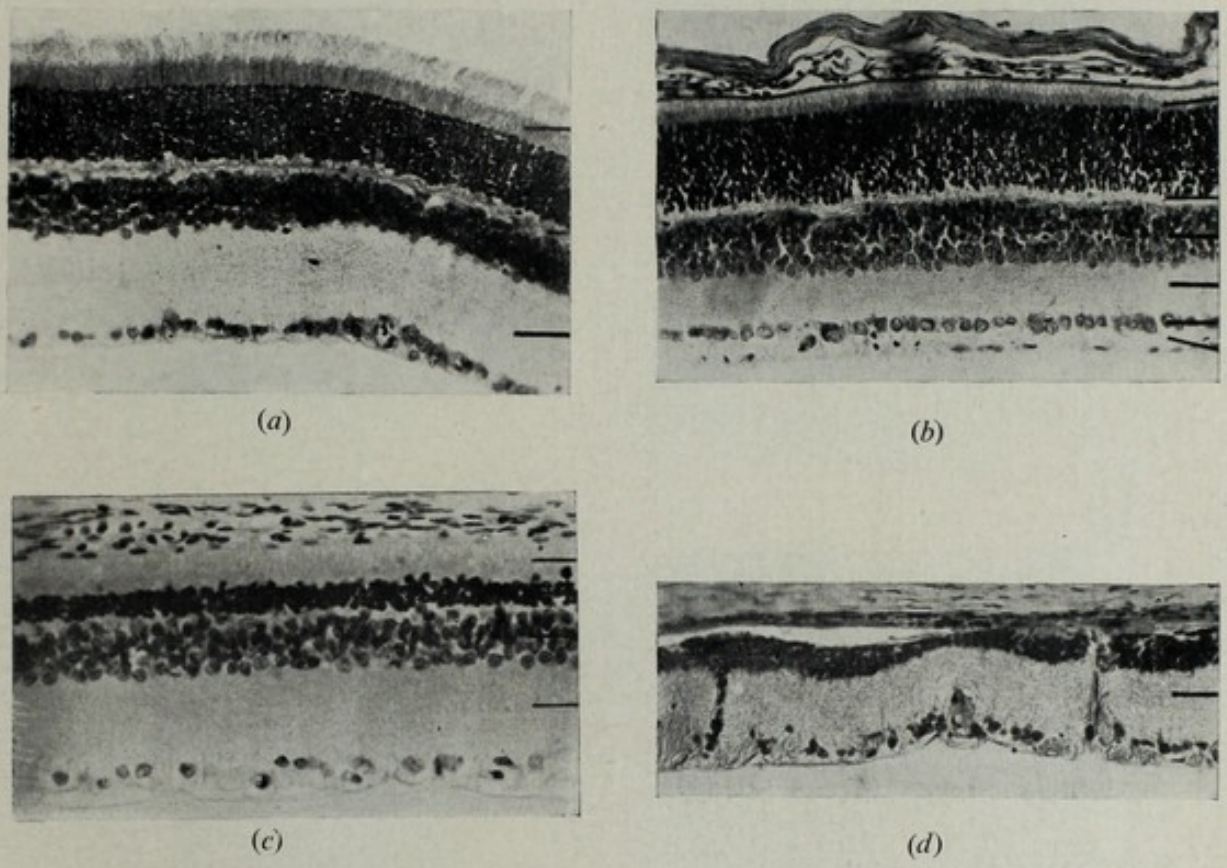
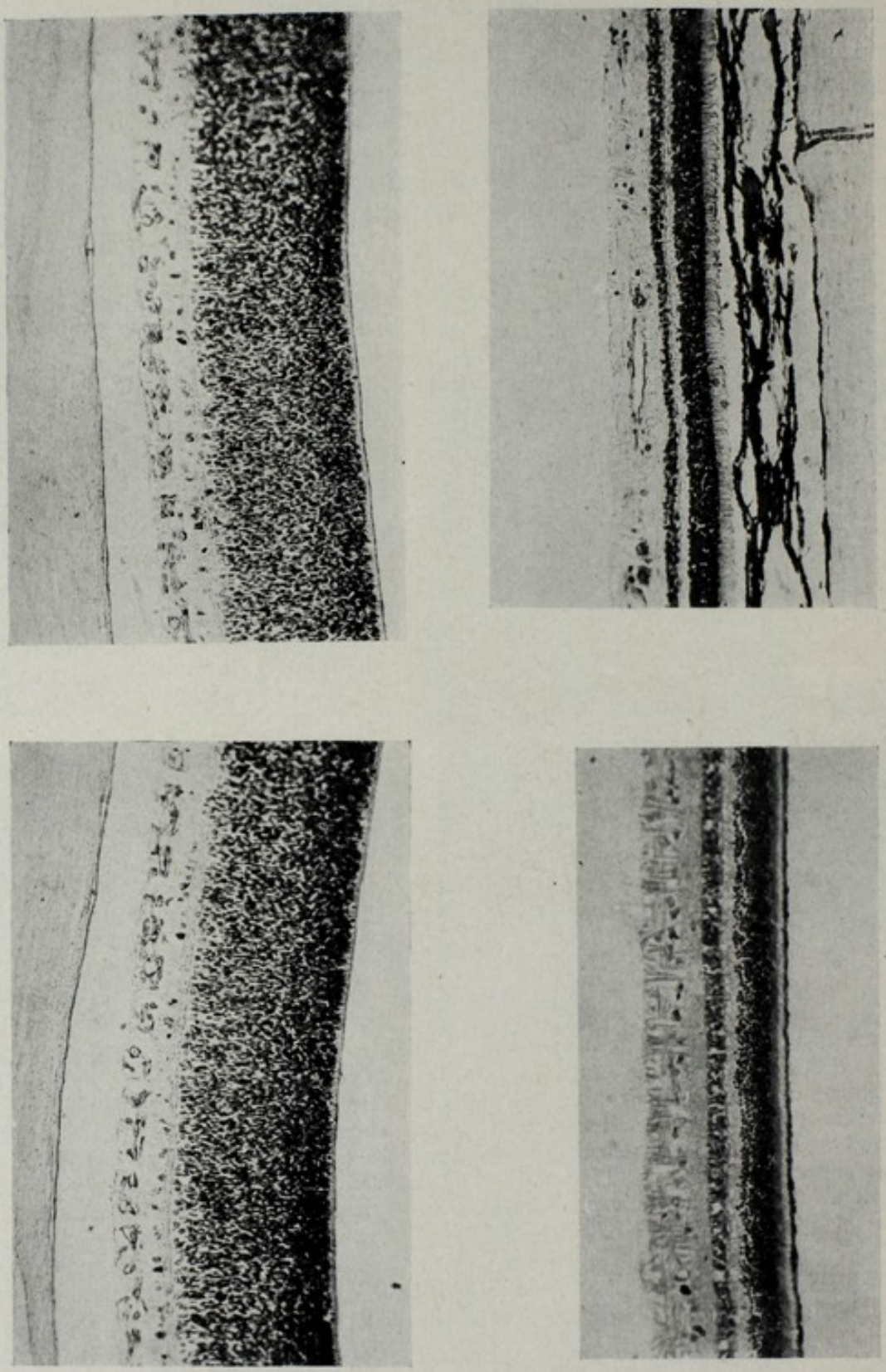


FIG. 46.—Histological sections of the retina in the rat. (*a*) Section through the normal adult retina. (*b*) Section of the retina of a rat aged 10 days from stock affected with a retinal dystrophy similar to retinitis pigmentosa. The retina had developed normally. (*c*) Section through the retina of a rat from affected stock aged 7 weeks. The outer nuclear layer is completely degenerate and the rods have lost their microscopic structure. (*d*) Section through the retina of a rat from the affected stock, aged 17 months. The degeneration is now very much advanced. (*After M. C. Bourne, D. A. Campbell and K. Tansley. Brit. J. Ophthal.*, 1938, 22, 613.)

given by anyone not fully conversant not only with modes of inheritance generally, but with the mode of inheritance in the patient's affection and particular family. This is a point of considerable importance. To advise a patient with retinitis pigmentosa as to the prospects of his transmitting the affection involves not only the recognition of the fact that in most instances retinitis pigmentosa is recessive, but also of the fact that there are other modes of inheritance which could only be disclosed by systematic study of the patient's family. The advice that would be


AFFECTED
NORMAL
1 day
4 weeks

11 weeks

Adult

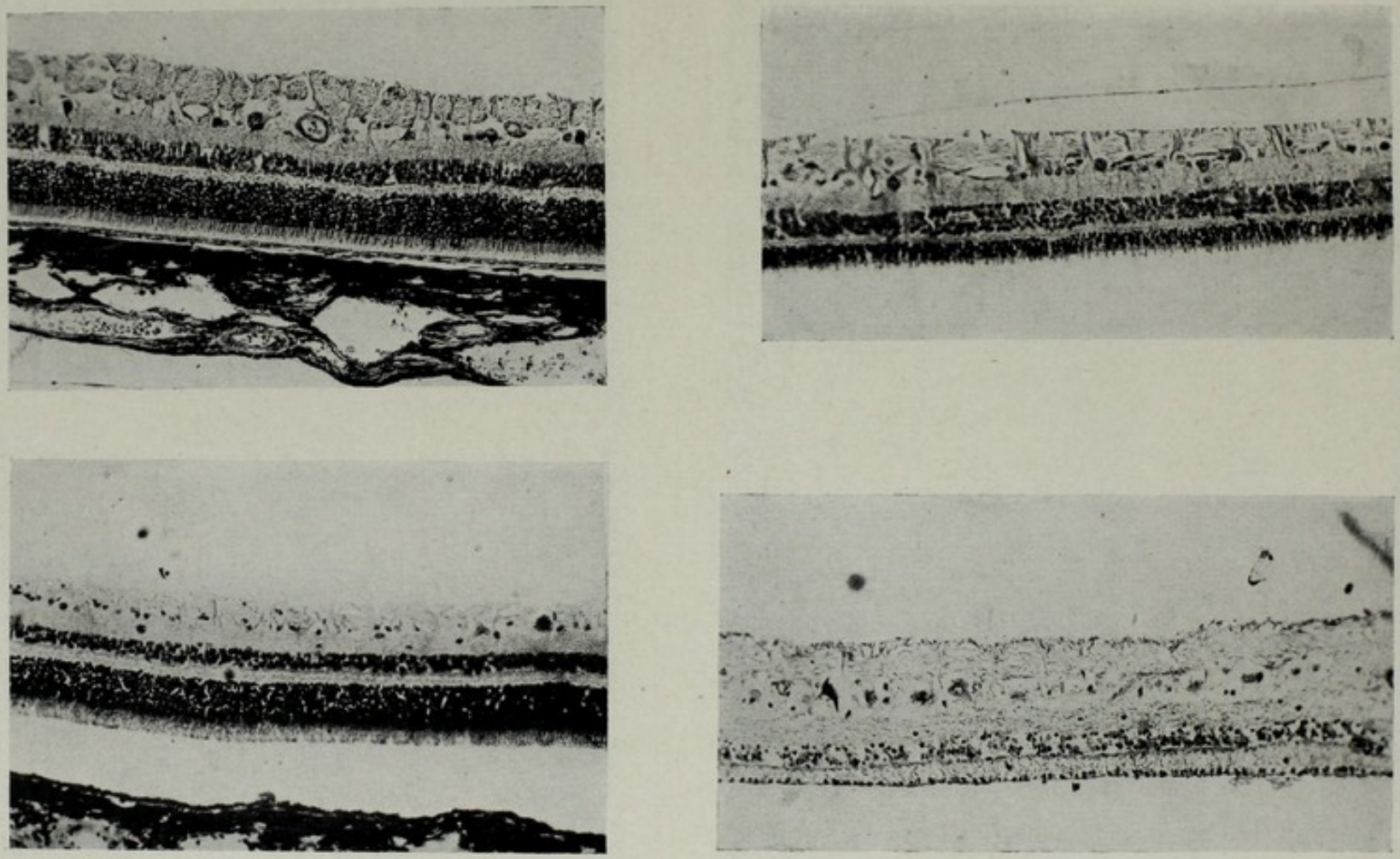
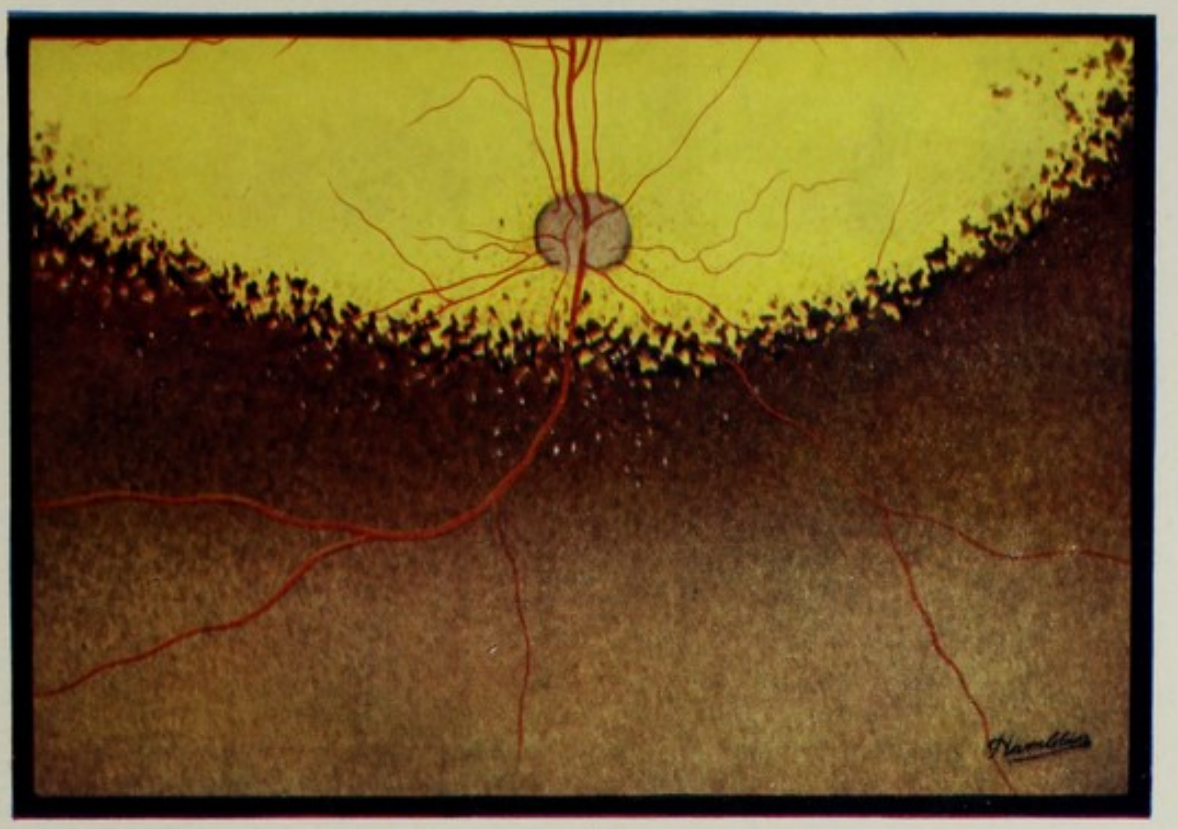


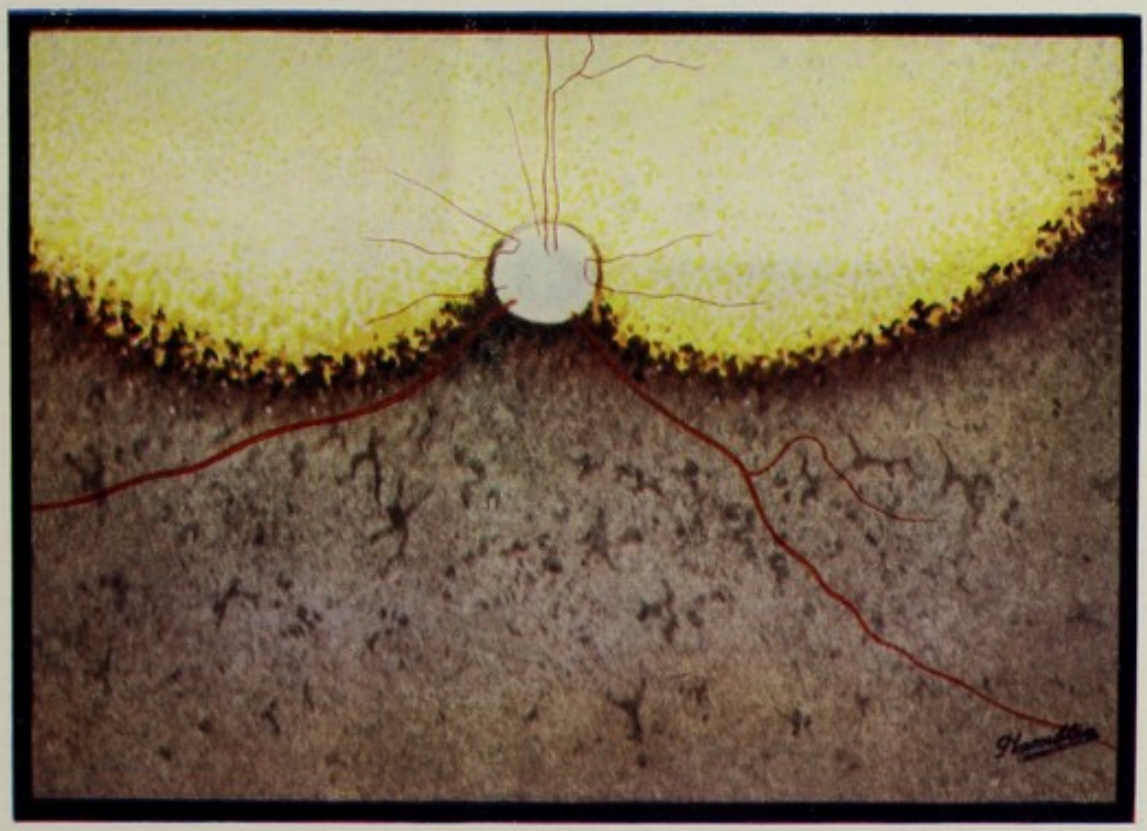
FIG. 47.—Retinal dystrophy in Irish setters. A comparative series of histological sections at different ages in normal and affected animals. Normal sections are shown in the left hand column, and sections from abnormal animals of the same age in the right hand column. In the affected animals pathological changes began to appear only after a normal and full post-natal development. (Personal observation).

given on the assumption that the patient suffers from the common form of recessive retinitis pigmentosa would be completely wrong, and disastrous, if it should prove that the patient's affection is transmitted in a dominant or a sex-linked manner.

The clinician has opportunities as well as responsibilities. Since each gene is pleiotropic in its action, it follows that a patient with a pathogenic gene is likely to manifest other features besides those represented by the clinical anomaly. The search for such features, which, of course, need not be significant pathologically, may lead to the possibility of establishing whether an apparently normal individual carries a pathogenic gene. Furthermore, studies on blood grouping, tasting, colour-blindness and such other "markers" of chromosomes and genes in both affected patients and their relatives are of potential clinical importance, since linkage may also be a clue to the presence of a pathogenic gene.



(*a*)



(*b*)

FIG. 48.—(*a*) Fundus of a normal adult Irish setter. (*b*) Fundus of an Irish setter a year old with a lesion simulating retinitis pigmentosa. (Personal observation.)

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SECTION II

ISOLATED OCULAR ANOMALIES

CHAPTER I

THE GLOBE AS A WHOLE

TYPICAL COLOBOMATOUS DEFECTS

THE INTENSIVE histological and embryological studies that have been carried out on congenital malformations of the globe have established that many of such defects originate from non-closure or faulty closure of the foetal choroidal cleft. Typical coloboma of the iris and choroid were obviously of such origin, and it was suspected that coloboma of the optic nerve might originate in the same manner.

Genetic studies of typical colobomatous defects in rabbits bred over many generations have brought out a wide range of anomalies previously not suspected to be variants of typical iris and choroidal coloboma. It would seem that such aberrations as persistent pupillary membrane, inferior conus, nasal conus, circumpapillary ectasia, coloboma of the lens, and possibly crater-like hole in the disc must all be regarded as fundamentally the same lesion. The conception has been extended to include a wide range of defects from minimal anomalies in the iris or choroid in the region of the primitive choroidal cleft at the one extreme, to microphthalmos with cyst formation, and even rudimentary formation of the globes (spurious anophthalmos) at the other extreme. This unifying conception is borne out by many isolated observations and a limited number of extensive pedigrees in man (Figs. 49 and 50).

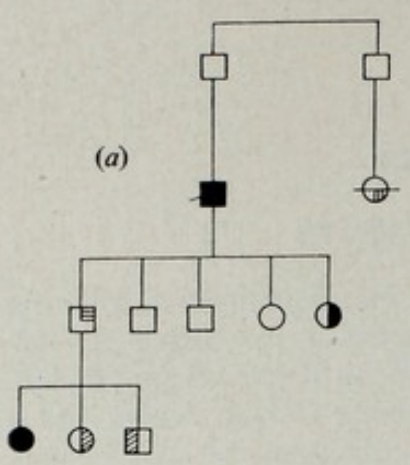
Several considerations emerge from pedigrees of this type, and many less extensive observations over one or two generations.

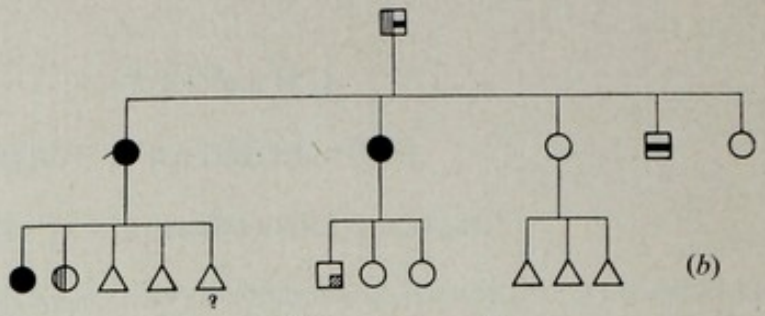
In the first place the whole group of these affections must be regarded as dominant. Secondly, assuming the affections to be monofactorial, the pathogenic gene has a wide range of expression extending from anomalies with little or no effect on vision to spurious bilateral anophthalmos. Thirdly, the available literature does not clearly establish whether modes of inheritance other than dominant may occur, nor is there adequate information on the penetrance of the dominant gene. It is likely that within given families considerable similarity in the expression of the gene may occur, so that in some families only coloboma of the iris, or iris and choroid, will be observed (Fig. 51), whilst in others the more serious variants may be seen frequently. What is not clear is whether constancy or variation in the manifestation of the gene is the more frequent.

GROSS MALDEVELOPMENT OF THE GLOBE

MICROPHTHALMOS

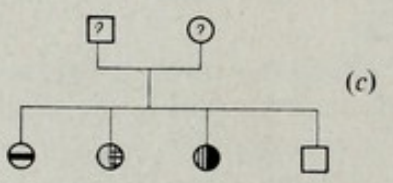
As distinct from microphthalmos which is a variant of colobomatous defects, there are two other varieties: (1) the so-called pure microphthalmos, in which the eye is normal apart from being small; and (2) microphthalmos with a variety of anomalies that have nothing to do with typical colobomas.

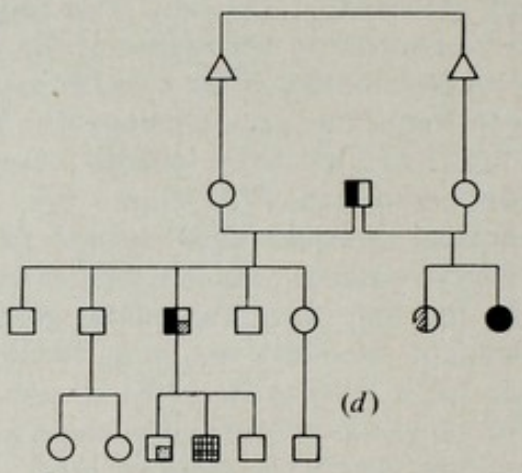




Left coloboma of iris, downwards.
Deep physiological excavation, right eye.
Partial coloboma of optic nerve, bilateral and left side respectively.
Total coloboma of both optic nerves.
Total coloboma of both optic nerves with changes at maculae.

Microphthalmos and coloboma of iris and choroid, bilateral.
Microphthalmos and coloboma of iris and choroid and coloboma of lens, right.
Microphthalmos and coloboma of iris and choroid, left.
Coloboma of iris and choroid, right.
Coloboma of iris and choroid, left.
Coloboma of choroid, left.
Coloboma of iris left ; fundus could not be seen.





Not known.
Coloboma of optic nerve, bilateral.
Right opaque nerve fibres, left microphthalmos and coloboma of iris.
Right microphthalmos and coloboma of iris and choroid, left rudimentary eye.
Normal.

Anophthalmos, bilateral.
Anophthalmos, right.
Microphthalmos.
Coloboma of iris and lens, left.
Coloboma of choroid, right.
Coloboma of iris, left.

FIG. 49.—Four pedigrees illustrating intrafamilial range of typical colobomatous defects.
(*a*) A family showing anomalies extending from coloboma of the iris and of the lens to microphthalmos. (*After E. Selz* (1900). *Eine Colobom-Familie. Jena: Thesis. Modified from B. Fleischer* (1938) *In Handbuch der Erbkrankheiten. Ed. by A. Gütt, Vol.* 5, *p.* 13. *Leipzig; Georg Thieme.*)
(*b*) A family, one member of which shows coloboma of the iris and the other members various degrees of coloboma of the optic nerve. (*After F. Weyert* (1890). *Klin. Mbl. Augenheilk.*, **28,** 325.)
(*c*) A sibship showing bilateral coloboma of the iris with microphthalmos in two members, and coloboma of the optic nerve in a third member. (*After F. Pfanmüller* (1894). *Beitr. Kolobomes Auges. Giessen: Thesis. Quoted by Julia Bell* (1933). *Treasury of Human Inheritance. Ed. by K. Pearson, Vol. II, p.* 537. *London; Cambridge University Press.*)
(*d*) A family showing a range of defects from unilateral coloboma of the iris to bilateral anophthalmos. (*After B. Fleischer* (1938). *In Handbuch der Erbkrankheiten. Ed. by A. Gütt, Vol.* 5, *p.* 14, *Leipzig; Georg Thieme.*)

Pure microphthalmos

Actual measurement of such eyes shows them to be about two-thirds of the normal adult measurements, and rather less than the average diameters observed in the newborn. The eyes are generally highly hypermetropic. The mode of

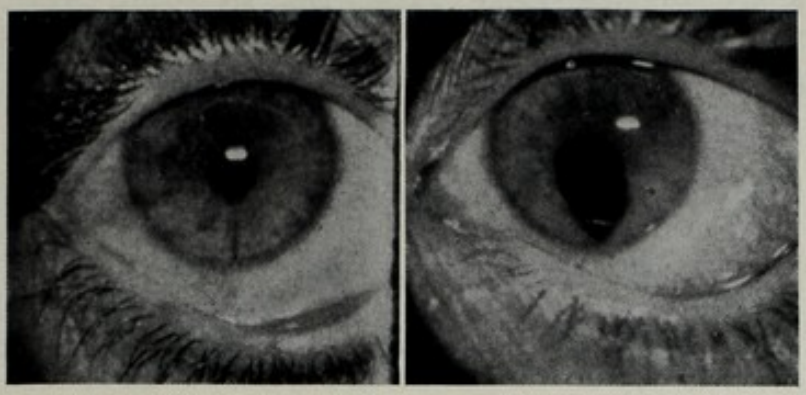


FIG. 50.—Rudimentary coloboma of iris in a woman and fully developed typical coloboma in her son. (*After B. Fleischer* (1938). *In Handbuch der Erbkrankheiten. Ed. by A. Gütt. Vol. 5, p. 12. Leipzig; Georg Thieme.*)

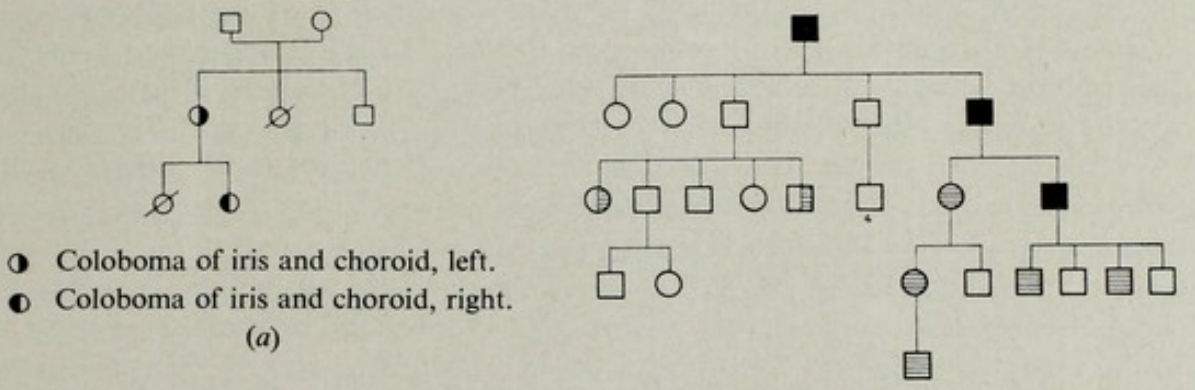


FIG. 51.—Pedigrees illustrative of similarity of colobomatous defects within the same family.

(*a*) Unilateral coloboma of iris and choroid in mother and daughter. Contralateral. (*Personal observation.*)

(*b*) Dominant inheritance of bilateral coloboma of iris, apparently with little variation. (*After C. J. Mollenbach* (1947). *Medføte defekter i øjects indre hinder, Fig. 24. Copenhagen; E. Munksgaard.*)

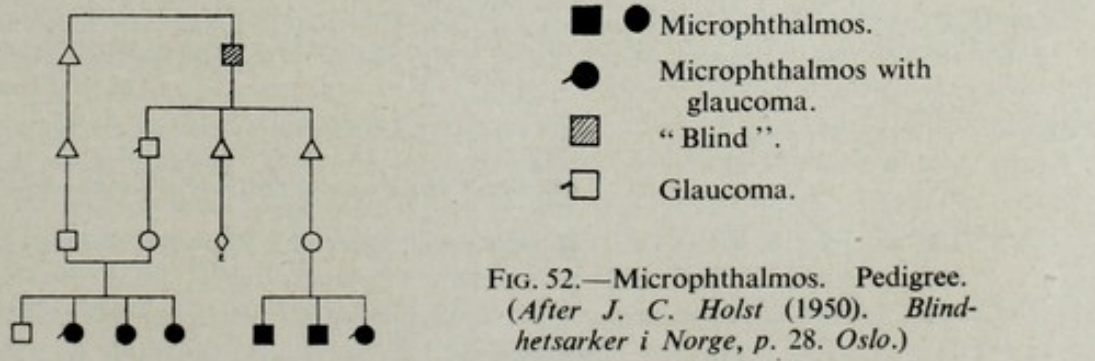


FIG. 52.—Microphthalmos. Pedigree. (*After J. C. Holst* (1950). *Blindhetsarker i Norge, p. 28. Oslo.*)

inheritance is not clearly established. Most of the recorded cases have been in sibs and consanguinity is generally not present. On the other hand there is no conclusive evidence that the affection is dominant (Fig. 52). (The oft-quoted pedigree of Martin would appear to refer to microcornea rather than to microphthalmos.)

In pure microphthalmos vision is generally grossly affected, possibly as a result of non-differentiation of the macula. Occasionally actual changes at the macula have been observed. Glaucoma is a not uncommon complication (Fig. 52). Dental anomalies in the form of small or absent incisors have also been observed.

Microphthalmos with other lesions

The variety of lesions seen in the complicated type of microphthalmos are such that there is considerable confusion in the literature as to whether a case is regarded as microphthalmos, or of some other lesion complicated by microphthalmos. Clinically, congenital cataract is frequently seen in small eyes, and successful operative procedures give disappointing results. It is almost a matter of personal taste whether such cases are recorded as congenital cataract with small eyes, or microphthalmos complicated by cataract. The non-genetic basis of some forms of microphthalmos is clear enough from the occurrence of microphthalmos in retrolental fibroplasia seen in premature babies. On the other hand, hereditary microphthalmos is well established by such pedigrees as that of Usher, in which microphthalmos was associated with ectopic pupils and myopia (Fig. 53 *a*). In other pedigrees cataract has been observed (Fig. 53 *b*), and in yet others various anomalies in the cornea, lens and fundus.

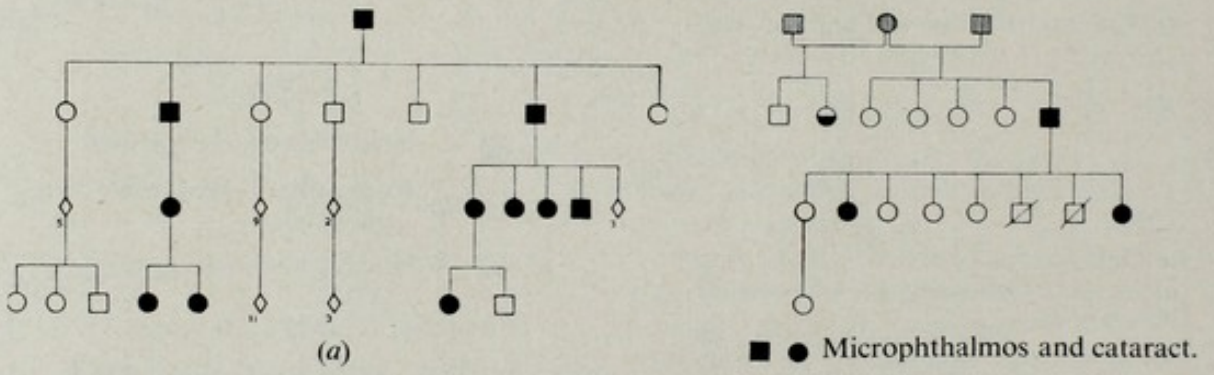


FIG. 53.—Microphthalmos with other ocular lesions. Pedigrees. (*a*) Pedigree showing dominant inheritance of microphthalmos with myopia and ectopic pupils. (*After C. H. Usher* (1921). *Brit. J. Ophthal.*, **5**, 298.) (*b*) Pedigree showing presumed dominant inheritance of microphthalmos and cataract. (*After N. B. Harman* (1910). *In Treasury of Human Inheritance, Ed. by K. Pearson, Vol.* 1, *Fig.* 339. *London; Cambridge University Press.*)

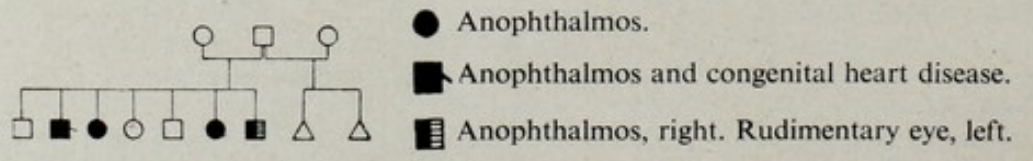


FIG. 54.—Anophthalmos. An early pedigree. (*After J. Briggs* (1813). *In A. Sorsby* (1934). *Brit. J. Ophthal.*, **18**, 469.)

Cryptophthalmos

In cryptophthalmos the eyes are barely developed, and, apart from the lids being closed, there are generally various systemic malformations such as syndactyly, and frequently anomalies that are inconsistent with a viable foetus. Apart from a number of sibships, the condition has been recorded over two generations.

Anophthalmos

In true anophthalmos there is no rudiment of an eye, and this anomaly can arise only if there is failure in the development of the primitive optic vesicle, or degeneration of a vesicle that has formed. Abnormal development at that stage inevitably involves the brain. That viable children should result is surprising. Such pedigrees as are available suggest that true anophthalmos is a recessive condition. Records are available in only one generation and consanguinity is frequent (Fig. 54).

GLAUCOMA AFFECTIONS

Buphthalmos

As with adult glaucoma there is a primary and a secondary type. A genetic factor hardly comes into the question in secondary buphthalmos such as that due to expansion of the eye in an infant with a massive retinal glioma, or the occasional buphthalmos seen after an injury. Primary buphthalmos, like primary glaucoma, is probably a composite entity.

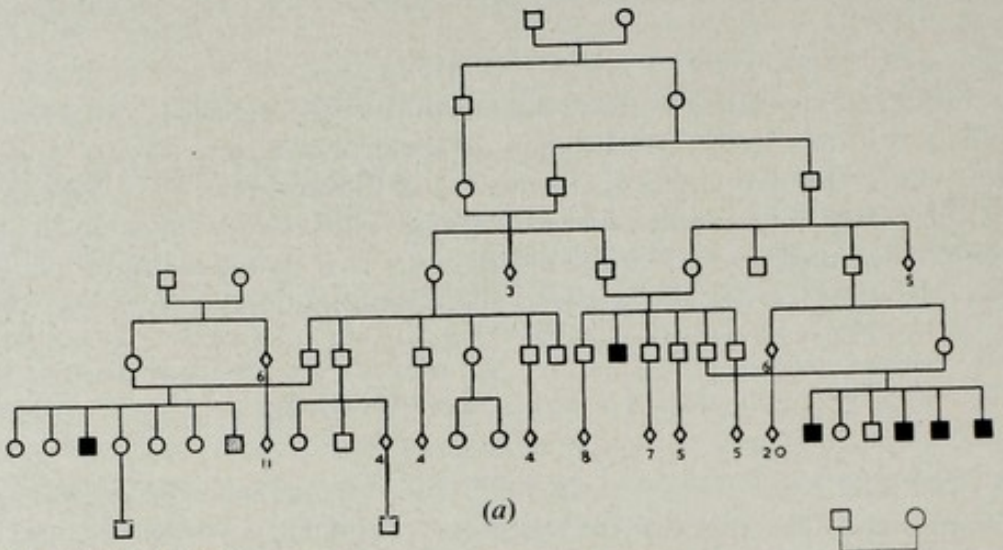
Clinically two different types of primary buphthalmos can be differentiated fairly clearly. Commonly buphthalmos shows a regularly enlarged cornea, a deep anterior chamber, and ruptures in Descemet's membrane, whilst the cornea as a whole may be hazy from the increased tension. In contrast there is a type of buphthalmos with a shallow anterior chamber and marked corneal changes—haziness, opacification and even staphyloma; the iris may be adherent to the cornea. There is the possibility that these two types merely represent different degrees of severity, but this is not established. Genetic analysis should help to clarify this issue.

The older view that buphthalmcs was the result of an intra-uterine infection is no longer held. Anatomical evidence clearly implicates a malformation of the angle, though this may be overshadowed in individual cases by secondary inflammatory reactions.

Evidence of the genetic basis of buphthalmos is derived from the fact that the condition has been observed several times in uniovular twins, and repeatedly in a number of sibs. In the two pedigrees shown in Fig. 55, the affected children were the offspring of first or second cousins, and the rather sparse literature suggests that consanguinity is probably present in about 10–15 per cent of cases. On the other hand, there are a number of pedigrees in which the affection occurred over two generations in direct descent (Fig. 56 *a*) and one in which a boy and his paternal aunt were affected (Fig. 56 *b*). There is no record of the affection over three generations. There is little information on the progeny of patients with hereditary buphthalmos. In the one observation on record, the two sons of an affected man and the only son of his affected sister were normal (Fig. 57).

The affection is usually sporadic. Brons investigated the family history of 172 cases seen at Tübingen between 1875 and 1935; 153 were isolated cases and 19

were familial, distributed over seven families. Westerlund followed up 122 cases seen in Denmark and found 91 to be isolated cases, and 31 familial distributed over eleven families. He holds that the gene is recessive and has a penetrance of about 40 per cent.



■ Buphthalmos.
□ "Congenital corneal degeneration."

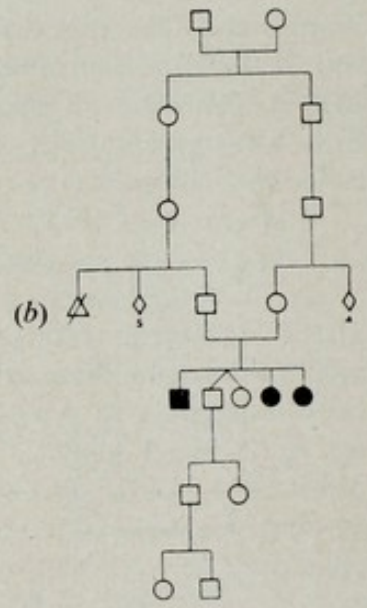
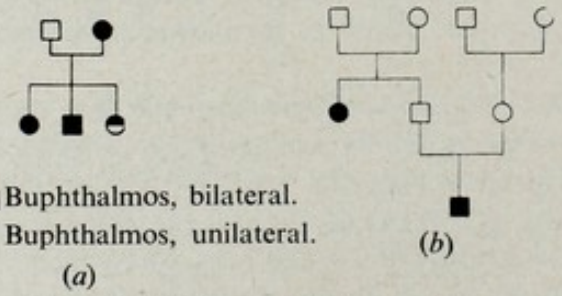


FIG. 55.—Buphthalmos. Pedigrees illustrative of recessive inheritance. (*After E. Westerlund* (1947). *Clinical and Genetic Studies on the Primary Glaucoma Diseases, Figs.* 4 *and* 5. *Copenhagen: Munksgaard.*)
(*a*) Buphthalmos in three collateral branches of a family heavily intermarried.
(*b*) Buphthalmos in the offspring of parents who were second cousins.



● ■ Buphthalmos, bilateral.
◓ Buphthalmos, unilateral.

(*a*)

FIG. 56.—Buphthalmos. Pedigrees illustrative of a possibly dominant mode of inheritance of buphthalmos.
(*a*) Buphthalmos over two generations. (*After Argyll Robertson* (1891). *Trans. Ophthal. Soc. U.K.*, **11**, 239.)
(*b*) Buphthalmos in an aunt and nephew. (*After M. E. Sourdille* (1925). *Bull. Mém. Soc. franc. d'ophtal.*, **38**, 229).

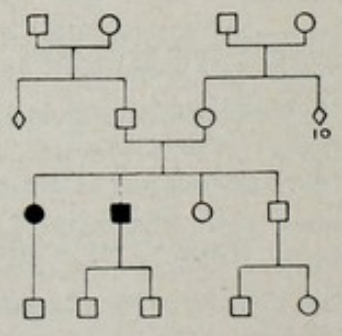


FIG. 57.—Pedigree showing normal offspring of an affected woman and also of her affected brother. (*After A. D. Griffith and L. H. Savin. Hitherto unpublished. Royal Eye Hospital No.* 0/6210.)

Buphthalmos is more common in boys than in girls. Most large series show a proportion of 6 : 4. It is only exceptionally unilateral in hereditary cases. Buphthalmos is occasionally seen in patients with typical coloboma of the eye. Only exceptionally has glaucoma been observed in the antecedents.

Glaucoma

As with buphthalmos, a genetic analysis of glaucoma is complicated by the fact that there are probably a great variety of different pathological states grouped under one clinical designation. It is not established whether intermittent glaucoma with its subacute attacks and glaucoma simplex are different entities.

Juvenile glaucoma

The conception of juvenile glaucoma as a distinct clinical entity, elaborated by Löhlein, is based on a statistical fallacy consequent on the use of selected material. Drawing mainly on cases recorded in the literature, Löhlein held that juvenile glaucoma was a clinical entity because in the group as a whole—extending from the artificial limits of the ages of 5–35 years—something like 40 per cent occurred between the ages of 16 and 20; in addition, some 50 per cent were myopic, and there was a familial occurrence in some 20 per cent. He also held that unlike senile glaucoma this type of affection occurs most often in men. These are hardly valid criteria. The concentration of cases within the age-group of 16–20 years in material collected from the literature obviously carries an element of selection; in patients over 20 years of age, the condition is less likely to be recorded. The sex difference noted in Löhlein's series was not statistically significant. Any excess in the incidence of myopia is easily explained by the fact that the eye was still expansile at the ages under consideration. A familial occurrence in 20 per cent of cases is not strikingly different from the percentage obtained for other forms of glaucoma. What is true in Löhlein's conception is the fact, already observed by the older ophthalmologists, that glaucoma is not exclusively a disease of the aged, though its frequency increases with age. Reports abound on these early cases because of the exceptional interest they have aroused. Furthermore, as in many other affections, the "familial stamp" applies: within given families glaucoma tends to have the same onset and to run the same course.

Inheritance in glaucoma

Most of the records on the inheritance of glaucoma deal with families in which the affection had an early onset—the so-called juvenile glaucoma. In many such families no history of early onset could be obtained for the antecedents. The early onset was in most cases the reason for an intensive investigation of the family —an investigation made possible by the fact that frequently many members of antecedent generations would still be alive. Pedigrees on inheritance of glaucoma are therefore largely selected. Amongst the unsatisfactory features of such material is the hearsay evidence that glaucoma had not affected some of the antecedents at the same early age—doubtful justification for the conception of "anticipation".

Many pedigrees illustrate the occurrence of glaucoma in several sibs. Pedigrees extending over two generations are not uncommon, and several pedigrees over

three generations are available (Fig. 58). Irregular dominance is suggested by some pedigrees in which the members were affected at a relatively early age (Fig. 59). On the other hand, a high degree of penetrance and expression over 5 generations is suggested by the pedigrees recorded in Fig. 60 *a* and *b*; in these families, too, glaucoma occurred rather early in life. Consanguinity is recorded only exceptionally. A pedigree of this type is shown in Fig. 60 *c*.

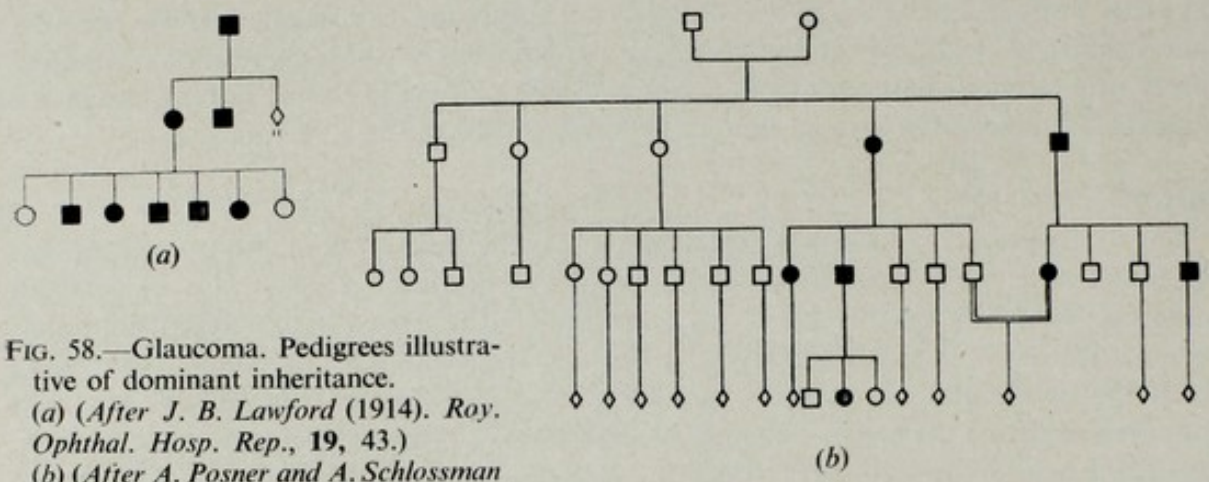


FIG. 58.—Glaucoma. Pedigrees illustrative of dominant inheritance.
(*a*) (*After J. B. Lawford* (1914). *Roy. Ophthal. Hosp. Rep.*, **19**, 43.)
(*b*) (*After A. Posner and A. Schlossman* (1949). *Arch. Ophthal.*, **41**, 125).

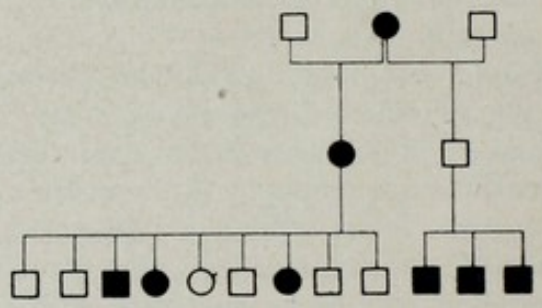
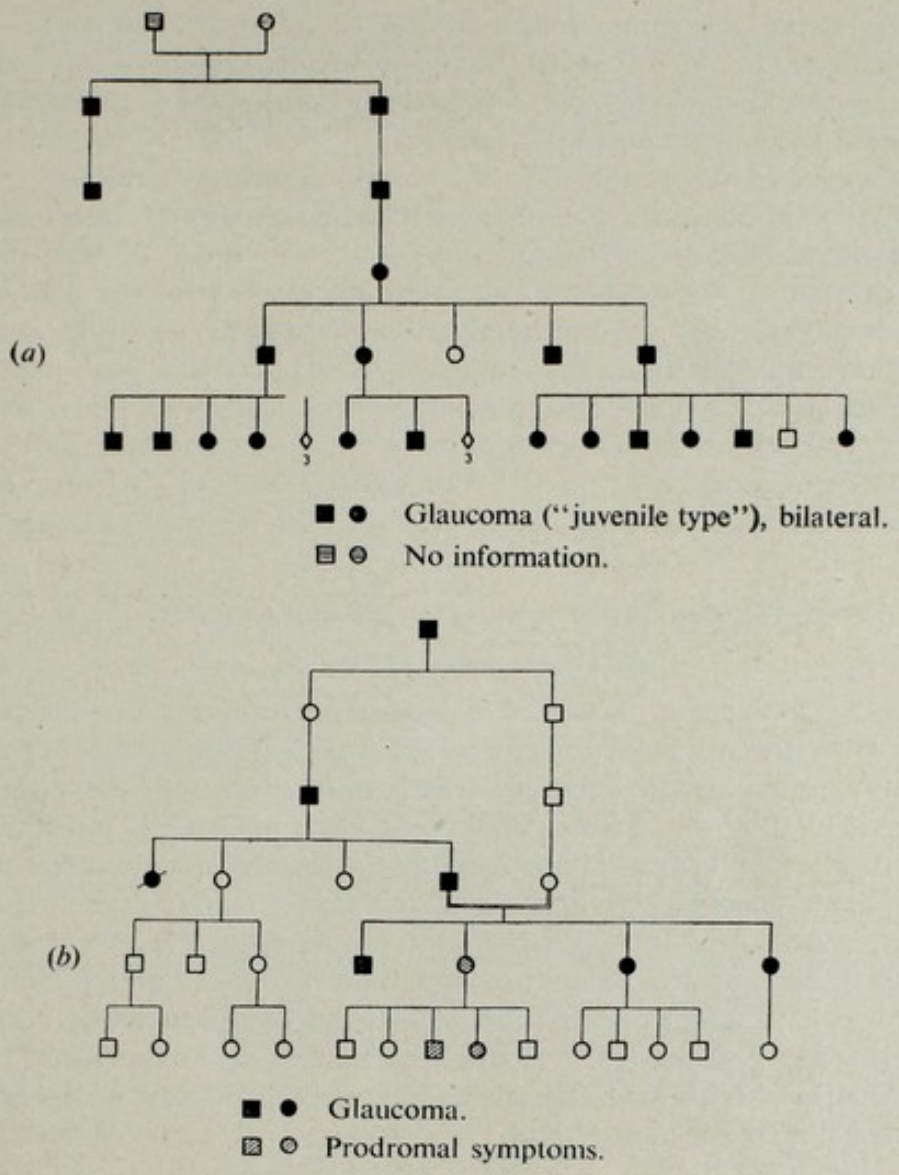


FIG. 59.—Glaucoma. A pedigree suggestive of irregular dominance. (*After I. Biro* (1939). *Ophthalmologica*, **98**, 43.)

Westerlund has stressed environmental precipitating causes. He recorded the case of two brothers, uniovular twins, one of whom developed intermittent glaucoma at the age of 42 years, and the other at the age of 56 years. The first patient led a strenuous life as an editor; the second, the quiet regular life of a schoolmaster. On the basis of his material he sought to establish a distinction between intermittent glaucoma and glaucoma simplex, holding that it is intermittent glaucoma which is hereditary. It is unlikely that this view is valid.

To what extent the many pedigrees of glaucoma present a common, or an exceptional situation, is not known. Because of its relatively late onset, little information is available on the genetic background of the affection. There are only two studies of unselected material. In one series, 43 cases out of a total of 761 (5·6 per cent) had a family history of glaucoma. In the second series—possibly more exhaustively investigated—there were 51 such cases in a total of 373 (13·7 per cent).



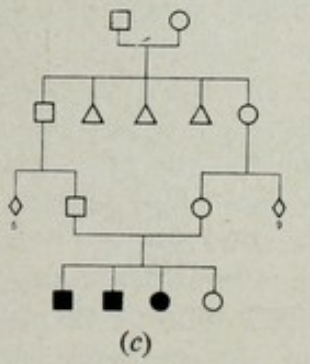


FIG. 60.—Glaucoma observed at a relatively early age ("juvenile glaucoma"). (*a*) and (*b*) Pedigrees extending over five generations.
(*a*) *After F. Berg* (1932). *Acta Ophthal.*, **10,** 568.
(*b*) *After R. Plocher* (1918). *Klin. Mbl. Augenheilk.*, **60,** 592.
(*c*) Pedigree suggestive of recessive inheritance. (*After J. C. Holst* (1950). *Blindhetsarker i Norge, p.* 36. *Oslo.*)

Relationship between buphthalmos and glaucoma

Genetically there would appear to be little support for regarding glaucoma and buphthalmos as one entity. The available evidence suggests that buphthalmos is recessive, though this cannot be accepted as proved. The evidence for glaucoma is conclusively in favour of dominance. Were one gene with a variable rate of expression responsible for the two affections, the association of buphthalmos

and glaucoma within the same family should occur more frequently than has actually been observed. In a detailed analysis, Westerlund concludes that there is nothing to suggest that buphthalmos represents the dominant gene of glaucoma on its downward route towards recessiveness.

There is, of course, no compelling reason for equating hereditary glaucoma with hereditary buphthalmos. The markedly different age at onset suggests a different genetic mechanism. Theoretically, however, there is this possibility: glaucoma is not a true dominant but an intermediate, and in the duplex state—most readily brought about by consanguineous marriages—it would produce the severe affection of buphthalmos. This supposition requires that both parents carry the intermediate gene for glaucoma. Generally the parents are seen whilst they are still young, and there is little information on the ocular condition of the parents at the usual glaucoma age, nor on the sibs of buphthalmos patients, when such sibs—possible carriers of one gene—have also reached the glaucoma age.

REFRACTION AND ITS ABERRATIONS

Emmetropia and Ametropia

A sharp antithesis between myopia and hypermetropia and the various mechanical explanations as to the origin of myopia—viewpoints of the nineteenth century—have given way to biological concepts which originated with the pioneer work of Steiger in 1913. Steiger stressed that there were no optical constants in the components of total refraction. He showed that there was a wide range of corneal refraction in the emmetropic eye and assumed a similar wide range in axial length (as opposed to the schematic 24·5 millimetres). In Steiger's view, emmetropia was a point in a normal range extending from high myopia to high hypermetropia, and that the whole range of ocular refraction could be produced by combination of the two variables represented by corneal refraction and axial length. Steiger's concepts—a radical break with the past—are now generally accepted, though with considerable modification.

The individual components of total refraction

The two other main components of total refraction, the depth of the anterior chamber and the refractive power of the lens (as distinct from corneal refraction and axial length stressed by Steiger) are also not constants, but have a considerable range, so that the total refraction of the eye is made up of at least four distinct and variable components. Fig. 61 shows the range in corneal refraction as determined by Steiger. It is seen to extend from $>$39·5 D to $<$47 D. Figs. 62 *a* and *b* show the ranges observed by Tron for depth of anterior chamber (2·2–5·0 millimetres) and of refractive power of the lens (14·9–28·9 D). The range of axial length of eyes as computed by Tron in a series of eyes excluding those with a myopia of over 6 D, is shown in Fig. 62 *c* ($>$20 to $<$28 millimetres).

With the normal ranges in the components observed in emmetropia, the same axial length can produce a refraction extending from +6 D to −9 D. Tron has shown that most cases of ametropia are due not to abnormal components, but to the way in which normal components are combined: "combination ametropia". In only 30·2 per cent of his cases of ametropia was the axial length outside the

limits of distribution for emmetropia, and this percentage was greatly reduced if hypermetropia over 4 D and myopia over 6 D are excluded. The main feature of Steiger's hypothesis may therefore be taken as proved.

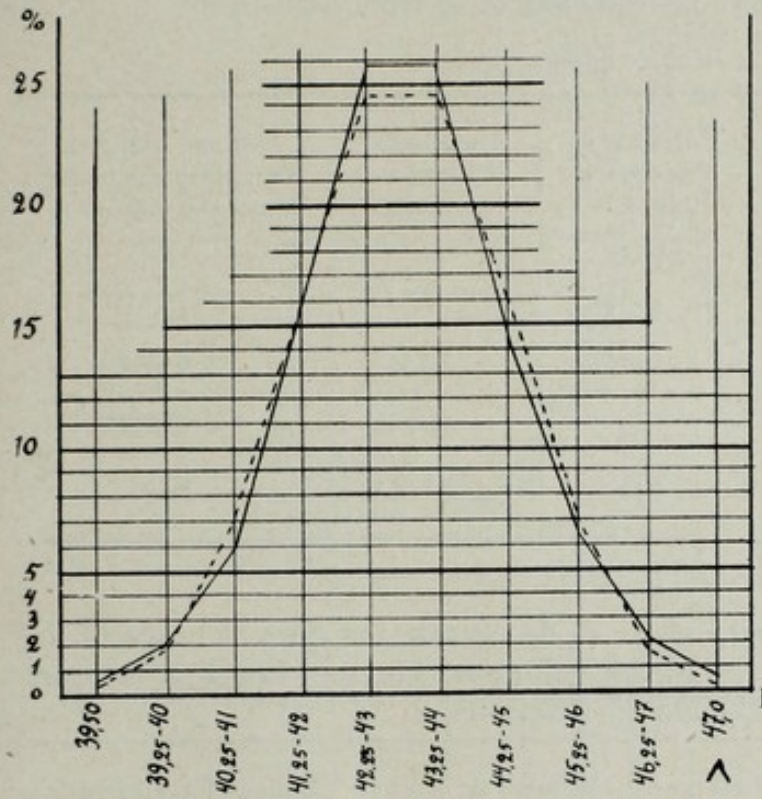


FIG. 61.—Variability of the refractive power of the cornea (Steiger): .....=curve of actual distribution;————=binomial curve. (*After A. Steiger* (1913). *Die Entstehung der sphärischen Refraktionen des menschlichen Auges. Berlin; Springer.*)

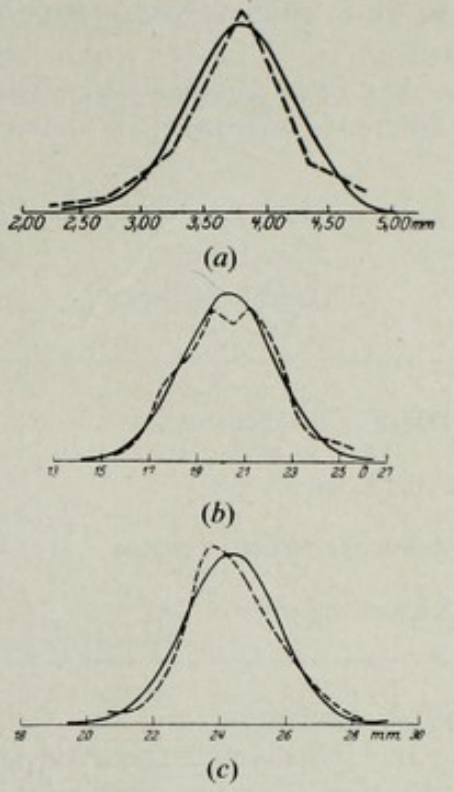


FIG. 62.—Variability of some of the components of refraction. The full lines show the theoretical binomial curve; the broken lines the actual distribution. (*After E. Tron* (1940). *In Modern Trends in Ophthalmology. Vol. I. Ed. by F. Ridley and A. Sorsby. Fig.* 102. *London; Butterworth.*)
(*a*) Anterior chamber.
(*b*) Lens.
(*c*) Axial length (myopic eyes of more than 6 D excluded).

Axial length.—Tron's work on axial length was based on computations. Now that a simple radiological technique is available for measuring axial length, it has been possible to confirm the concept of combination ametropia by actual observation. In a series of 1,000 actual measurements, Stenström obtained the following data:

	Axial length	
	Range	Modal value
Emmetropia to + 1·0 D – – –	21·5–26·5 mm.	23·5–24·0 mm.
Hypermetropia: +1·0 + to 6·0 D – –	20·0–26·5 mm.	
Myopia: up to – 6·0 D – – – –	22.0–28·0 mm.	

The wide and not markedly dissimilar range in axial length for eyes with the different types of refraction is therefore objectively established, and whilst myopic eyes tend to have the longer axial length, in individual cases the longer axis may be in an emmetropic or hypermetropic eye.

The other components.—The range of possible and actual variations with the different components is shown by the following table from Stenström:

CHANGES IN REFRACTION

Optical component	Variation in the optical element	Theoretical change in refraction	Average change in refraction calculated from the regression
Depth of the chamber – – –	± 1 mm.	± 1·35 D	± 2·58 D
Axial length – – – –	± 1 mm.	± 2·5 D	± 0·83 D
Refractive power of cornea – –	± 1 D	± 0·99 D	± 0·28 D
Refractive power of lens – –	± 1 D	± 0·77 D	± 0 D

High ametropia

In high myopia the axial length tends to lie outside the normal range of distribution. This was shown by Tron for his computed axes and in actual measurement by Stenström and by Sorsby and his associates.

	Degree of myopia	Number of cases	Range of axial length
Stenström – – –	6–14 D	23	25·5–26·0 in 2 cases
			26·0–29·0 in 21 cases
Sorsby – – –	7·5–16 D	5	25·0–28·5 mm.

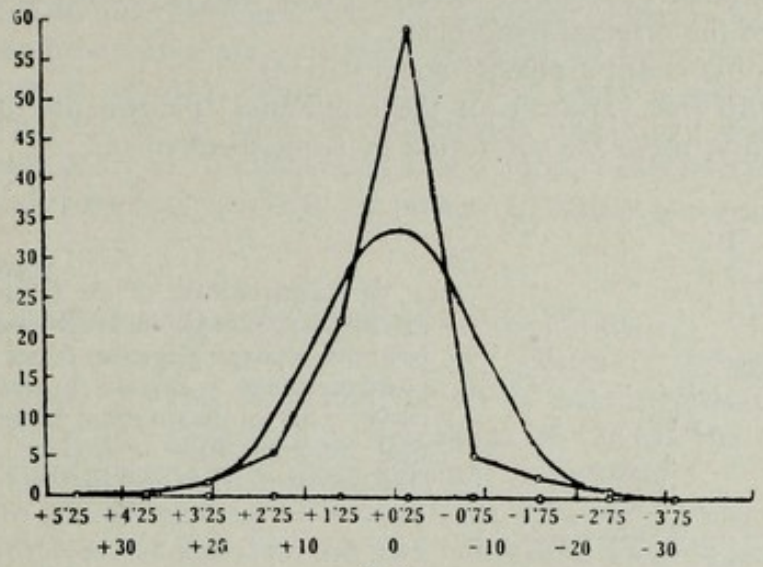
Though high myopia is determined by excessive axial length there is no definite relationship between axial length and the degree of myopia. In Stenström's series, a case of myopia 7–8 D had an axial length of 29·0–29·5 millimetres, whilst a case of −13 to −14 D had an axis 2 millimetres shorter. In Sorsby's series a case of −14·5 D had an axial length of 25·5 millimetres, whilst an eye with −10 D had an axis 3 millimetres longer.

In high hypermetropia too, the computations of Tron and the measurements by Stenström show that the axial length falls outside the normal range.

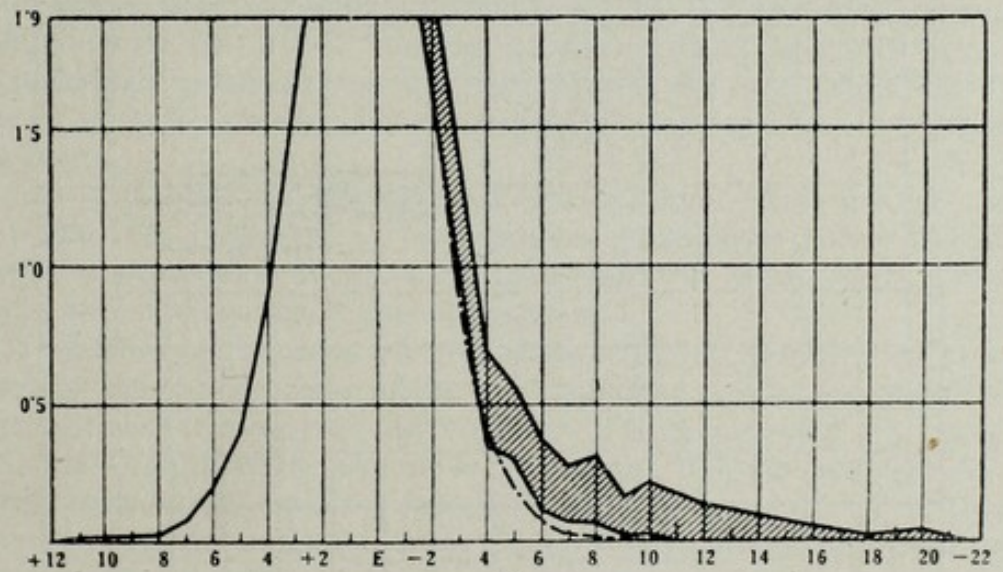
Emmetropization and excess of myopia

On optical grounds, Steiger's hypothesis in its original form is therefore untenable, since the axial length of eyes with extreme ametropia fall outside the range of normal values. These normal values, as can be seen from Figs. 61 and 62,

plot out as binomial curves—regular, somewhat bell-shaped curves with a high model point and symmetrical limbs tapering off to the extreme values on either side. A curve of refractive errors, as seen in an unselected population, would be a binomial curve, if the individual components, freely variable, were to produce the whole range of refractive errors. Actually, such curves as are available show two departures from the theoretical binomial curve. There is in the first place a great excess of refractions towards emmetropia and also an excess of



(*a*)



(*b*)

FIG. 63.—Actual distribution of refraction against binomial curves.
(*a*) Comparison of the refraction curve established by Scheerer and Betsch with the theoretically derived binomial curve. (*After A. Franceschetti* (1930). *In Kurzes Handbuch der Ophthalmologie. Ed. by F. Schieck and A. Brückner. Vol.* I., *p.* 720. *Berlin: Springer.*)
(*b*) Curve showing departure from the binomial curve for myopia over 6 D. (*After R. Scheerer* (1928). *Ber. dtsch. oph. Ges.*, **47**, 118.)

refractions at the extreme of the myopia component of the curve (Fig. 63). The second of these deviations emphasizes that high myopia falls outside the range of normal refractions—as already seen from the study of axial lengths. The excess of refractions towards emmetropia must be taken to show that the individual components of total refraction are not freely variable, as held by Steiger, but correlated towards the production of an excess of emmetropes. The nature of this correlating mechanism towards emmetropization is unknown.

Any study of ametropia must, therefore, take into account these two significant departures from the original hypothesis:

(1) High myopia is not a physiological variant.

(2) There is no free variation of the individual components of refraction. On the contrary, these are correlated by some mechanism.

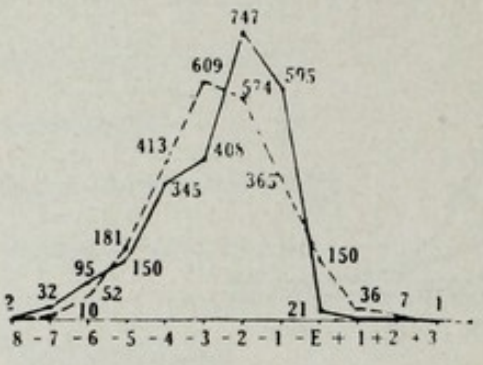


FIG. 64.—Distribution of the refractive errors under atropine cycloplegia in a composite series of 2,398 newborn infants. Negative values = hypermetropia; positive values = myopia in diopters. Continuous curve = actual distribution; broken curve = theoretical binomial curve (Wibaut). (*After F. Wibaut* (1925) *Arch. f. Ophthal.* **116,** 596.)

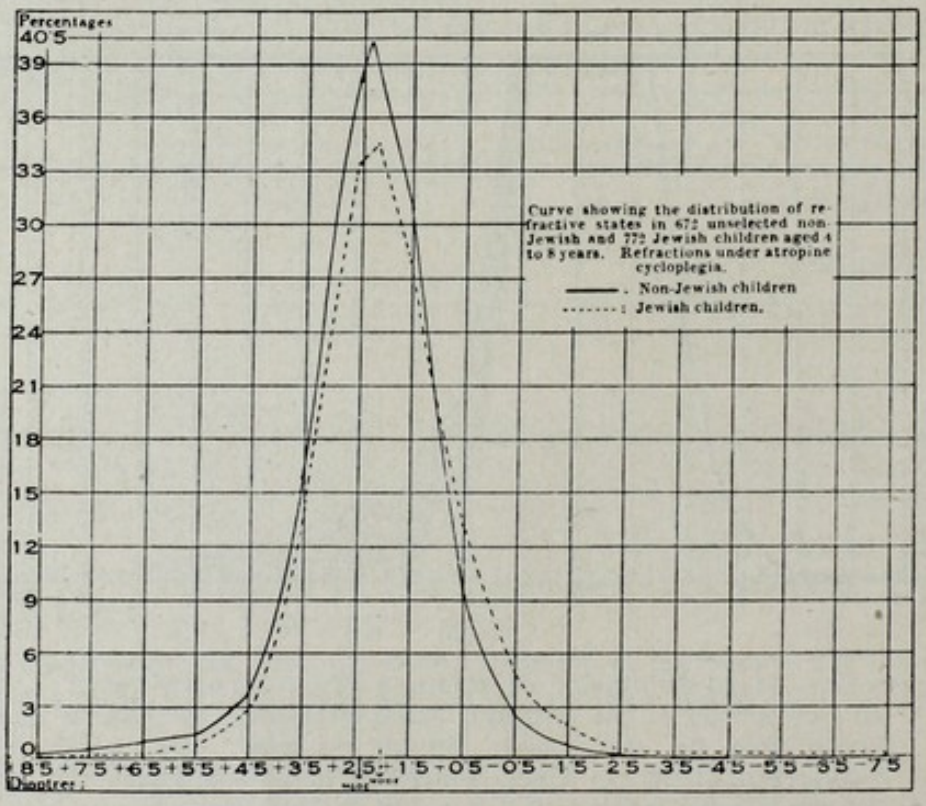


FIG. 65.
(*After A. Sorsby* (1938). *Trans. Ophthal. Soc. U.K.*, **57,** 394.)

The correlating mechanism is of further significance in studying the actual course of events in the developing eye. The eye at birth is about two-thirds of its normal diameters and its refraction would appear to conform to binomial distribution (Fig. 64). During the process of growth, probably completed by about the age of 8 years, the eye therefore lengthens by about 8 millimetres. As there is general enlargement of the globe, myopia does not result. Myopia normally develops late in school-life when the growth of the eye is presumably complete. The assumption that this myopia is axial in character is hardly tenable now that it is known that these cases are generally examples of combination ametropia. The development of myopia could readily arise from a disturbance in the correlating mechanism which aims at emmetropia and racial differences in the refraction of adults conform to differences already observable in children (Fig. 65). Studies on the individual components are needed to clarify this issue.

The present position

The following crucial points may be taken as established:

(1) There are no optical constants in the eye. There are instead at least four variable components—corneal refraction, depth of anterior chamber, refraction of lens, and axial length—each with a wide range of values. The total refraction is the result of the combination of these different components.

(2) Neither the emmetropic nor the ametropic eye has specific values for the individual components, except that on the whole the axial length tends to be onger for myopic eyes than for hypermetropic eyes. In individual cases this does not necessarily apply.

(3) Most ametropias are of the combination type: the ametropia results from the combination of the variable "normal" components of total refraction.

(4) In both high hypermetropia and high myopia, the axial length falls outside the range of normal variation, but the degree of ametropia is not dependent on the axial length.

On the basis of these findings, the ametropias, excluding high myopia and high hypermetropia, are physiological variants in a continuous curve of refraction in which refractions approaching emmetropia are the most frequent and considerably in excess of the theoretical expectation.

Further evidence of the unity of the different types of combination ametropia is supplied by the relative value of the axial length to the transverse and vertical diameters of the eye, measured radiologically. The emmetropic eye tends to be spherical, the hypermetropic eye rather flattened, and the myopic eye rather lengthened. Here again, however, individual cases do not conform to type. The axial length may be the longest diameter in both emmetropic and hypermetropic eyes. Furthermore, in anisometropia it is the myopic eye which may show the more "normal" values; in two such pairs of eyes, it was the emmetropic eye which showed marked flattening and the myopic eye was almost spherical.

Genetic implications

These considerations emphasize two points:

(i) It is fallacious to seek genetic interpretation of refraction and its anomalies by taking into account only the total refraction of the eye or the clinical refraction.

(ii) A genetic analysis is only possible if the mode of inheritance and the course of the postnatal development of each of the variable components are known.

In genetic terms, total refraction presents a problem of continuous variation with its polygenic basis, as opposed to discontinuous variation typically shown by a sharply defined pathological lesion, and usually monofactorial.

With these considerable complexities it is hardly surprising that little is known of the inheritance of refractive errors. It is not unlikely that the different components of refraction are inherited not only independently but possibly also in different modes of inheritance and that the resultant total refraction will show the complexities seen with characters of known polygenic inheritance. Such pedigrees as are available are largely selected because a clear mode of inheritance could be seen. They do not necessarily apply to the general run of cases, though there is little doubt that refraction, like stature, is largely genetically determined.

Inheritance of Individual Components of Refraction

Little is known as to the inheritance of the individual components of refraction.

Corneal refraction

There is little direct evidence as to the inheritance of total corneal refraction. Steiger did indeed show that the offspring of individuals with the extremes in corneal refraction tend themselves also to show these extremes. There are a number of pedigrees which show the transmission of astigmatism over several generations, not only as to the amount but also as to the direction of the axis. Whilst it would appear that astigmatism is generally dominant, other modes of inheritance may also occur—recessive, sex-linked—and possibly intermediate inheritance. So little is clearly known that even polygenic inheritance has been suggested.

Depth of anterior chamber: refractive power of the lens and axial length

Nothing definite is known. Clinical measurement of the depth of the anterior chamber presents some difficulties as regards accurate results, whilst measurement of the refraction of the lens is even more difficult. The development of relatively simple radiological techniques for measuring the axial length and the other diameters of the eye, and also the total refraction of the eye, opens the possibility of obtaining valid data on the inheritance of these components.

Inheritance of Total Spherical Refraction

Evidence from studies in twins

Evidence as to the inheritance of spherical refraction is provided by the extensive studies that have been carried out on twins. In uniovular twins, the range of variation, as calculated by Waardenburg, is 2·75 D. In his own material 119 out of 132 observations (90 per cent) showed differences of 1 D or less, and 98 out of 132 (74 per cent), a difference of 0·5 D or less. (High degrees of myopia were

excluded from these computations; in uniovular twins with high myopia, whilst both showed high myopia, differences were more marked, and in one case with extreme myopia the difference was as much as 11 D.) In binovular twins, on the other hand, the differences are always very much greater. With increasing age, such differences as are present in uniovular twins tend to become less marked, whilst differences in binovular twins become more marked. The lack of any support for the view that environmental factors are responsible for myopia is well shown by the fact that uniovular twins developed similar refractive states even when one was doing close work and the other was not, whilst binovular twins differed in their refractions in spite of similar environmental conditions.

Hypermetropia

Such pedigrees as are available show a great tendency for the hypermetropia to be of approximately the same degree, and they suggest a dominant mode of inheritance for the milder degrees of hypermetropia (Fig. 66). It is possible that for high degrees of hypermetropia there is a recessive mode of inheritance. That hypermetropia can be inherited independently from astigmatism is suggested by some limited studies (Fig. 67).

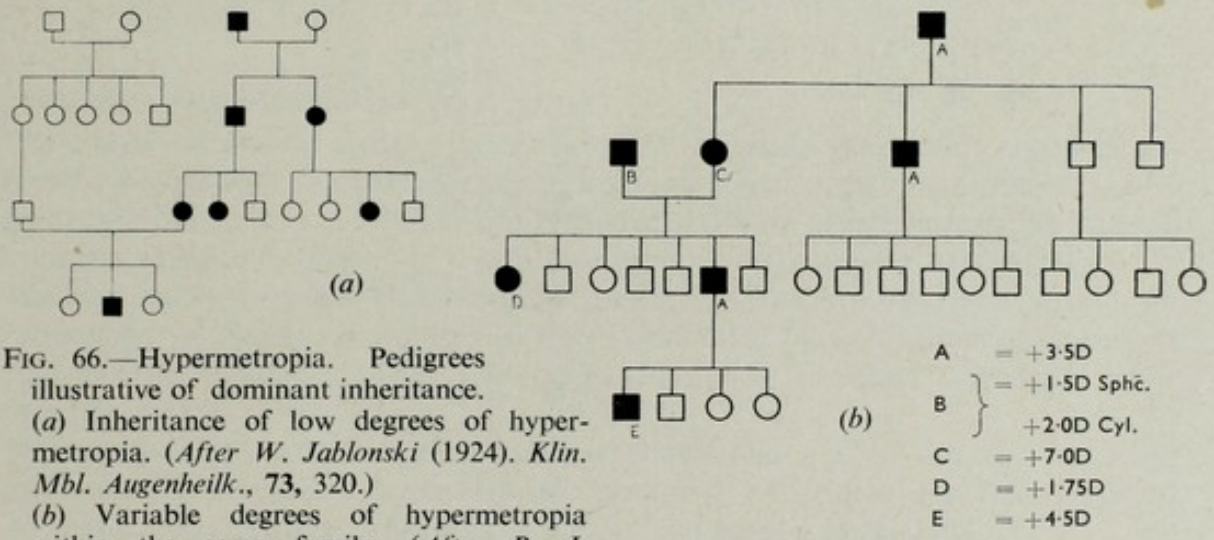


FIG. 66.—Hypermetropia. Pedigrees illustrative of dominant inheritance.
(*a*) Inheritance of low degrees of hypermetropia. (*After W. Jablonski* (1924). *Klin. Mbl. Augenheilk.*, **73**, 320.)
(*b*) Variable degrees of hypermetropia within the same family. (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 493. *The Hague; Nijhoff.*)

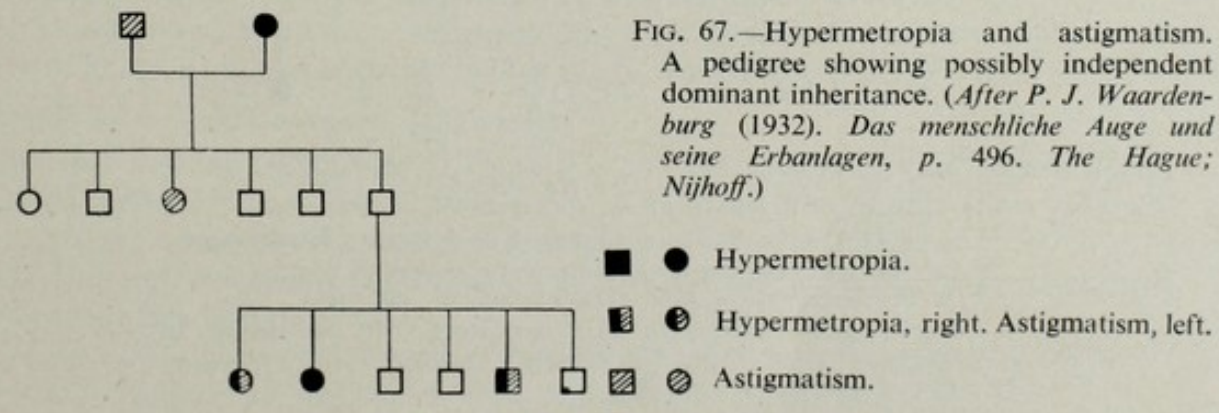


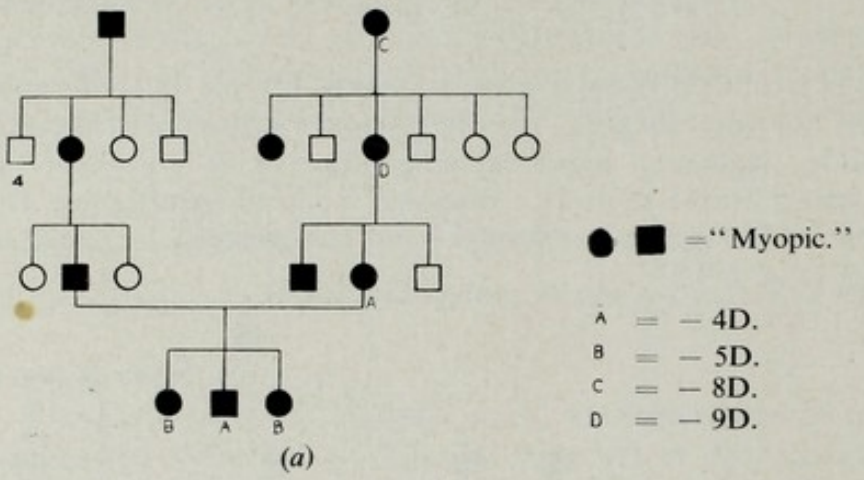
FIG. 67.—Hypermetropia and astigmatism. A pedigree showing possibly independent dominant inheritance. (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 496. *The Hague; Nijhoff.*)

Physiological myopia

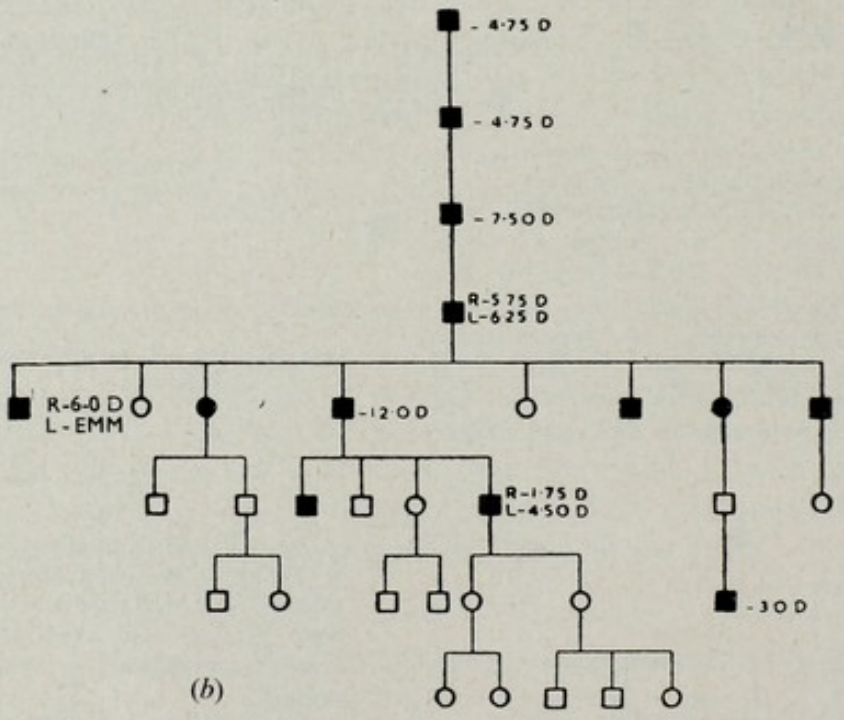
There are a number of pedigrees showing dominant inheritance (Fig. 68). Some pedigrees suggest intermediate inheritance (Fig. 69).

Pathological myopia

The separation of pathological myopia from physiological myopia is well founded, and it would appear that pathological myopia is a composite entity embracing a number of distinct clinical and probably genetic types. For the present, only a schematic classification is possible.



(*a*)



(*b*)

FIG. 68.—Myopia. Pedigree suggestive of dominant inheritance.
(*a*) Pedigree showing some range in the degree of myopia. (*After W. Jablonski* (1922). *Klin. Mbl. Augenheilk.*, **68,** 560.)
(*b*) Pedigree showing a fair consistency in the degree of myopia. (*After E. Wolfflin* (1949). *Z. menschl. Vererb.-Konstit.*, **129,** 243.)

Uncomplicated myopia

Congenital myopia.—This is occasionally non-progressive. It has been observed in uniovular twins.

Myopia developing at adolescence.—Many high myopes have full vision and go through life without any complications of any type. Nothing definite is known of the genetic behaviour. Most cases are probably recessive. (The oft-quoted pedigree of Worth showing sex-linkage belongs in all probability to the group of night-blindness with myopia.)

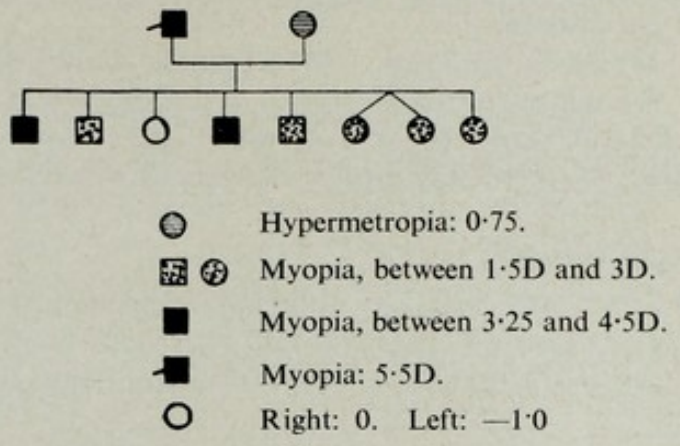


FIG. 69.—Myopia. Pedigree suggestive of intermediate inheritance, (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 502. *The Hague; Nijhoff.*)

Myopia with late complications

The complications of myopia generally come on many years after any increase in myopia has ceased. Mechanical explanations, such as "stretching of the choroid" can hardly apply. To what extent the different types of complications are genetic entities is not known. Clinically the following varieties have been recognized.

Medium and high myopia with choroidal atrophy.—This is a common type and not infrequently the degree of myopia is only moderate. Nothing definite is known of the genetic behaviour. The abiotrophic character of these lesions has been stressed by Vogt.

Medium and high myopia with macular haemorrhages.—This, too, is a common clinical type. The macular haemorrhages generally set in at about the age of 40 years. Here, too, nothing definite is known of the genetic behaviour.

Medium myopia with retinal detachment.—A number of pedigrees suggest that bilateral detachment at various periods in life occurs as a familial disturbance generally in myopes with a not particularly high degree of myopia. It is probably dominant, though recessive inheritance is also suggested (*see* Fig. 165).

High myopia with cataract.—Many high myopes develop hazy lenses and cataract in middle life. It is not known whether this is a genetic type.

Myopia in eyes with congenital anomalies

Myopia with night-blindness.—There are two clearly established genetic types, with ill-defined, if any, clinical differences. A number of pedigrees show recessive sex-linkage; others show autosomal recessiveness (*see* Fig. 142).

Myopia with nystagmus.—This, too, is a fairly well defined genetic type. Dominant inheritance has been observed.

Myopia with microphthalmos.—A dominant pedigree is shown in Fig. 53 *a*.

Myopia with microphakia.—A recessive pedigree is shown in Fig. 111.

Myopia in eyes with abiotrophic anomalies

Myopia in choroideremia.—The correlation between myopia and choroideremia seems fairly definite. It would also appear that the myopia develops during the progressive course of this sex-linked affection.

Myopia in gyrate atrophy.—This would appear to be recessive.

Myopia in generalized affections

Myopia in mongolism.—A considerable incidence of high myopia in mongolism has been observed repeatedly. Whether the myopia is inherited independently is not known.

Myopia in albinism.—Most albinos show a moderate degree of myopia.

Myopia in arachnodactyly.—Axial myopia is frequent.

Clarification of some of these types requires intensive studies of the optical structure of the eye and of the genetic behaviour of the associated lesions.

Anisometropia

There are pedigrees showing transmission over two generations (Fig. 70 *a*). Fig. 70 *b* shows anisometropia in a large family with emmetropes and myopes of varying degree, the parents themselves being emmetropic and not related.

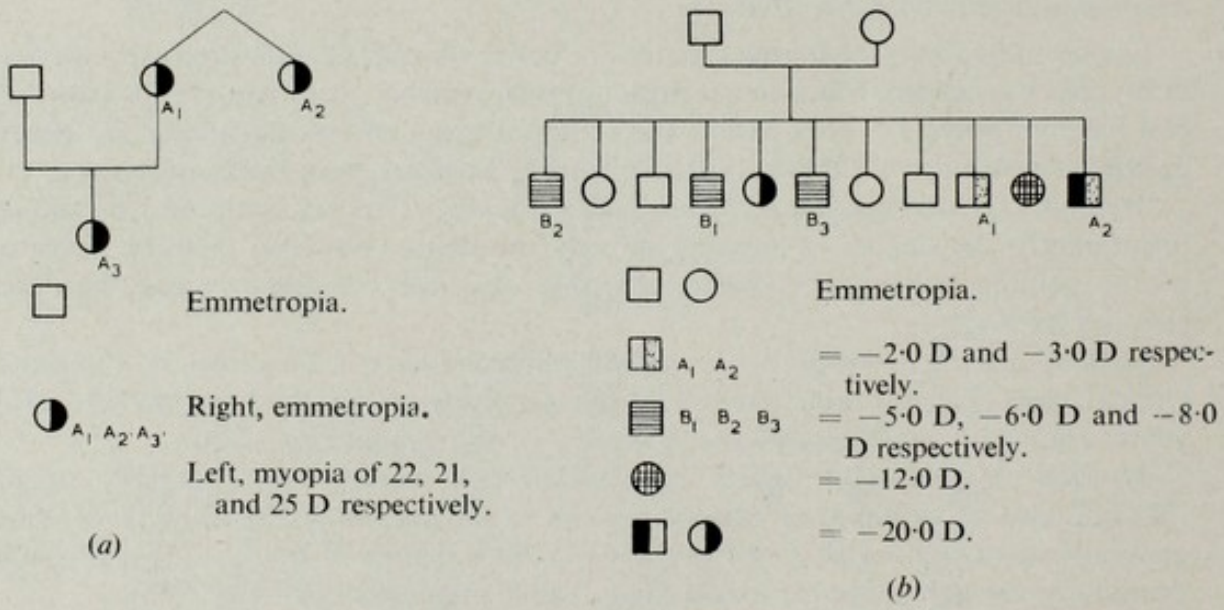


FIG. 70.—Anisometropia. Pedigrees.
(*a*) Pedigree suggestive of dominant inheritance. (*After N. Blatt* (1924). *Arch. Ophthal.*, **114**, 604.)
(*b*) Pedigree suggestive of recessive inheritance. (*Personal observation.*)

It would seem that while in many ocular conditions the need is to study consecutive unselected cases, in the refractive errors the primary need is to study the inheritance of the individual components of total refraction. The congenital and abiotrophic manifestations seen in some varieties of myopia and of the congenital anomalies in high hypermetropia are likewise separate problems.

ANOMALIES OF OCULAR MOVEMENT

The Extra-ocular Muscles

Ptosis, isolated ocular palsies, partial or total external ophthalmoplegia, and retraction of the globe all present considerable anatomical problems. In a given case or a family it is often difficult to establish whether the anomaly arises from a central or peripheral defect, for either a failure in innervation or an abnormality in muscle development, or both, could be incriminated equally plausibly. For this reason the available classifications are still largely clinical, and represent broad groups rather than clear individual entities.

The syndrome of embryonic fixation (*Waardenburg*) (*ptosis with epicanthus*)

Many cases recorded in the literature as examples of congenital ptosis, hereditary ptosis, ptosis with epicanthus, blepharophimosis, abnormal lengthening of canaliculi with ankyloblepharon and other designations have been shown by Waardenburg to constitute a distinct clinical entity. There is blepharophimosis rather than ptosis, though this itself is present. In addition a number of other anomalies are observed: hypoplasia of the caruncle, and the plica semilunaris; displacement of the puncta, especially the lower, laterally towards the cornea; and broadening of the nasal bridge with consequent wide interpupillary distance.

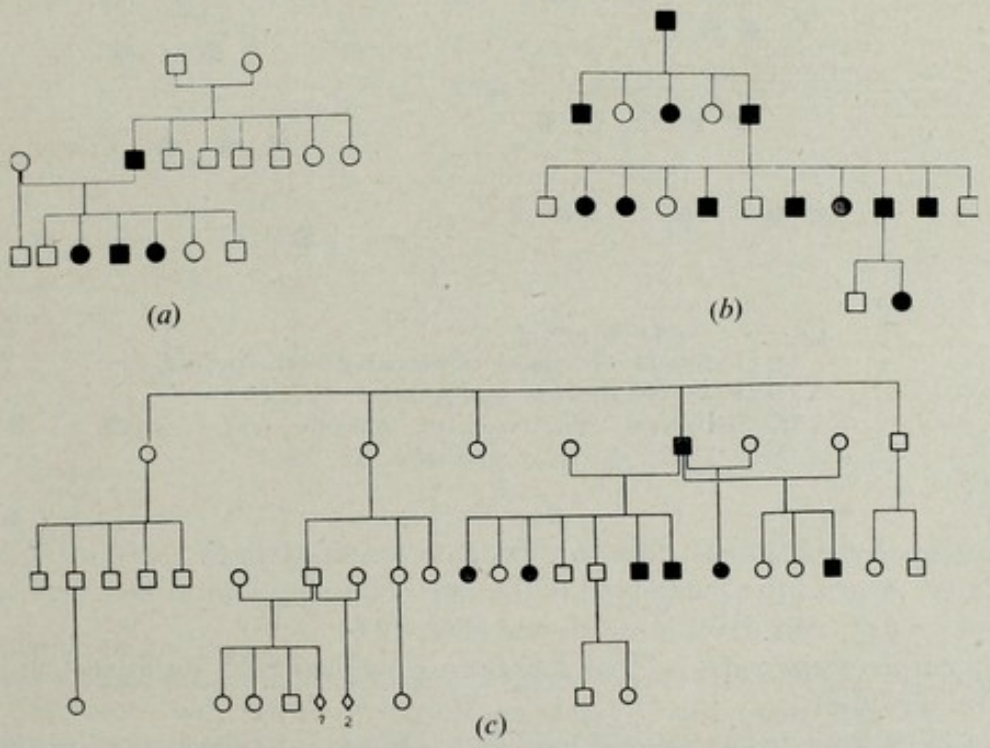


Fig. 71.—Ptosis with epicanthus. Pedigrees showing dominant inheritance.
(*a*) In this family the full syndrome of embryonic fixation (Waardenburg) was present. (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 90. *The Hague; Nijhoff.*)
(*b*) Pedigree showing direct transmission over four generations. (*After J. H. McIlroy* (1930). *Proc. R. Soc. Med.*, **23**, 285.)
(*c*) Pedigree showing transmission by an affected man to his children by three marriages. (*After C. H. Usher* (1935). *Trans. Ophthal. Soc. U.K.*, **55**, 164.)

Yet other anomalies that may be present are limitation of ocular movement (which like the ptosis is probably due to hypoplasia of the muscles), underdevelopment of the orbit, thickening of the tarsus, epicanthus, and such generalized defects as brachycephaly. Waardenburg regards these appearances as persistence of the normal relationships in the embryo at 8–10 weeks, so that the syndrome is parallel in nature to the persistence of the embryonic choroidal cleft.

Regular dominant inheritance is the rule (Fig. 71).

Simple epicanthus.—This is discussed under Lids.

External ophthalmoplegia

This is a large and possibly composite group. Within given families, a particular type of defect tends to occur, but the possible unity of the different clinical types is suggested by the fact that in large families transitional forms occur frequently.

The following classification is therefore largely schematic:

Isolated ptosis.—Ptosis has been observed repeatedly as a congenital bilateral—and rarely as a unilateral—anomaly with dominant inheritance, but only exceptionally without some palsy of the extra-ocular muscles (72 *a*).

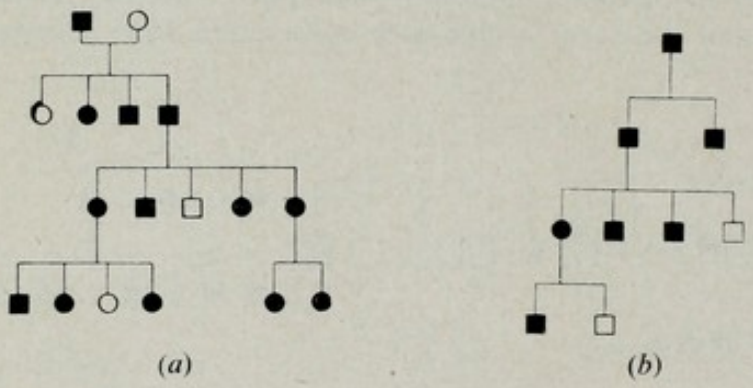


FIG. 72.—Isolated ptosis.
(*a*) Dominant inheritance of the congenital type. (*After G. Tirelli* (1935). *Rass. ital. Ottalm.*, **4**, 224.)
(*b*) Dominant inheritance of the late type. (*After Dutil* (1892). *Rev. gen. Ophtalm.*, **11**, 564.)

Occasionally the ptosis does not become manifest until early in childhood or even later. A not infrequent type is the one occurring late in life, between 40 and 60 years of age, and developing slowly (Fig. 72 *b*).

Isolated abducens palsy.—This has been observed as a dominant unilateral or bilateral affection.

Isolated palsies of the vertical muscles.—Dominant inheritance is suggested by two case reports. It is possible that the condition is not uncommon and that some cases of concomitant squint with vertical deviation are primarily isolated vertical palsies with secondary squint.

Total and incomplete external ophthalmoplegia.—In some families, ptosis is a marked feature (Fig. 73), whilst in others it is lacking. The degree of involvement of the other extra-ocular muscles also varies with different families.

As with isolated ptosis there is a congenital and an abiotrophic type, generally with dominant inheritance (Figs. 73 *a* and *b*). Dominant inheritance associated with nystagmus is shown in Fig. 73 *c*.

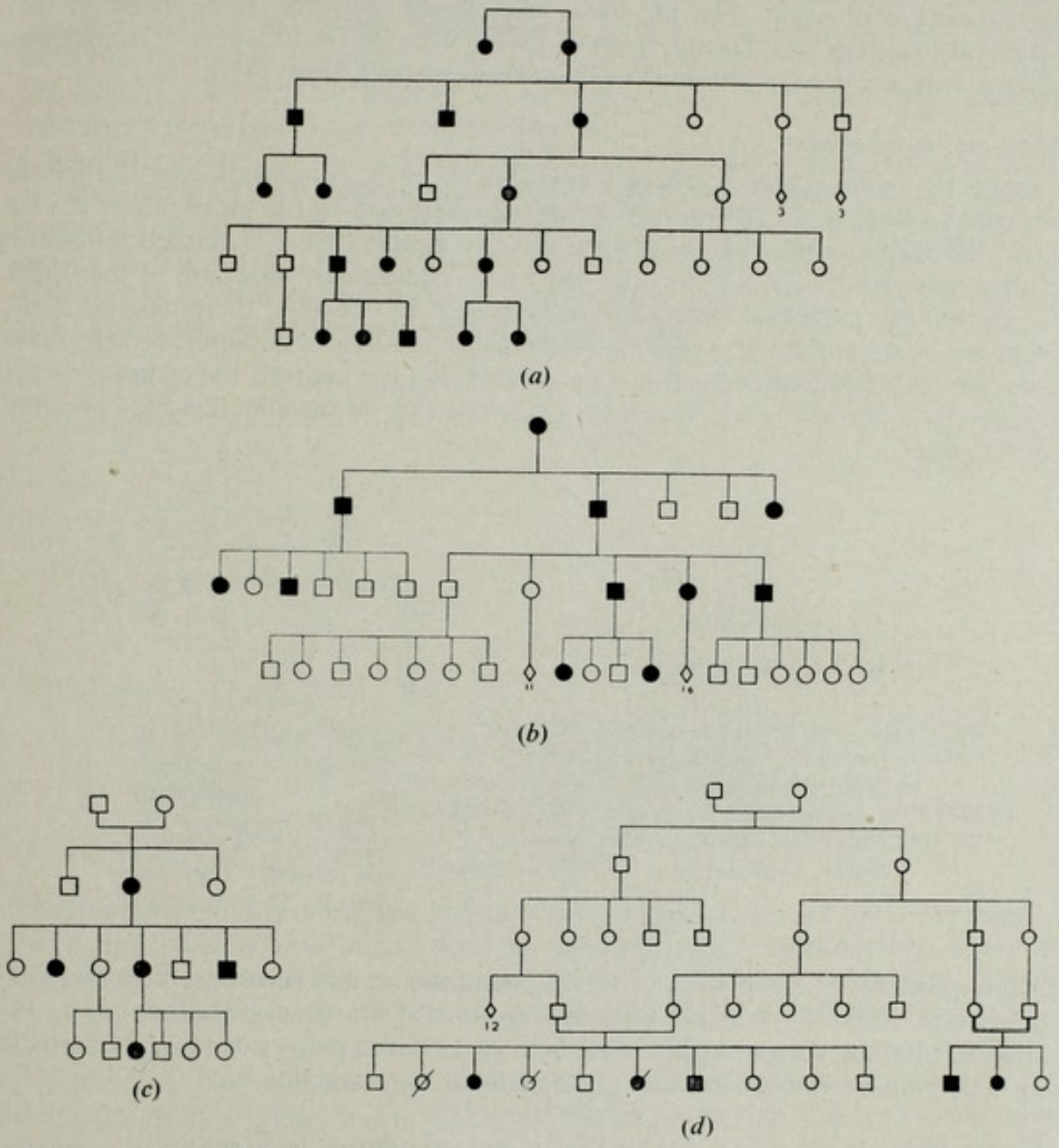


FIG. 73.—External ophthalmoplegia.

(*a*) Pedigree showing dominant inheritance in a family in which the affection was present at birth. Ptosis was marked. (*After A. A. Bradburne* (1912). *Trans. Ophthal. Soc. U.K.*, **32**, 142.)

(*b*) Pedigree showing dominant inheritance in a family in which the affection appeared in adult life. Here too ptosis was marked. (*After W. M. Beaumont* (1900). *Trans. Ophthal. Soc. U.K.*, **20**, 258.)

(*c*) Pedigree showing dominant inheritance in a family in which ptosis and nystagmus were marked additional features. (*After O. Crouzon and P. Béhague* (1920). *Bull. Mém. Soc. méd. Hôp. Paris*, **44**, 372.)

(*d*) Pedigree showing the exceptional occurrence of recessive inheritance. In this family ptosis and miosis were associated lesions. (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 96. *The Hague; Nijhoff.*)

A number of records are available showing ophthalmoplegia in one generation only and consanguinity has occasionally been recorded. In a family studied by Waardenburg, there was complete external ophthalmoplegia and in addition the pupils were contracted. The affection was clearly recessive: it occurred in two collateral branches of a family, both of which were derived from consanguineous parents with a common ancestry four generations back (Fig. 73 *d*).

Abnormal movements

Retractio bulbi (*Duane's phenomenon*).—This is a congenital and frequently unilateral anomaly. In addition to impaired abduction of the globe, there is also some difficulty in adduction, and when this is attempted there is marked retraction of the corresponding globe into the orbit with consequent drooping of the upper lid, so that the palpebral fissure becomes closed. In contrast, there may be slight proptosis of the globe and widening of the palpebral fissure on abduction. In these cases the underlying abnormality is peripheral and not central; the external rectus is generally a fibrous band. As can be seen from Fig. 74 the affection may possibly be dominant.

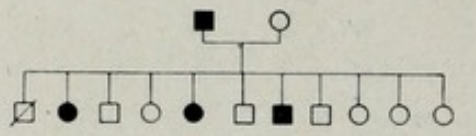


FIG. 74.—Duane's retraction syndrome (Retractio bulbi). (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 100. *The Hague: Nijhoff.*)

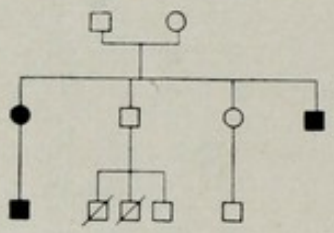


FIG. 75.—Marcus Gunn syndrome. Inheritance over two generations. (*After H. F. Falls, W. T. Kruse and C. W. Cotterman* (1949). *Amer. J. Ophthal.*, **32** 6, (ii), 53.)

Other anomalies.—The Marcus Gunn phenomenon has been observed over two generations (Fig. 75). It is possible that there is also a genetic basis for the condition of bilateral congenital abducens and facial nerve palsy with its characteristic Bell's phenomenon when an attempt is made to close the lids.

CONCOMITANT SQUINT

Convergent squint

According to Waardenburg, secondary squint has to be distinguished from primary squint, the essential characteristic of secondary squint being that there is an underlying cause, sometimes acquired, sometimes hereditary. An example of a non-hereditary secondary squint is the squint seen in a child with a corneal scar following ophthalmia neonatorum, whilst examples of secondary squint of genetic origin are squint in inherited hypermetropia, and the squint in inherited extensive remains of persistent pupillary membrane.

The evidence for the inheritance of primary squint comes from two sources. In the first place, if one of a pair of uniovular twins shows a squint, a similar squint is generally also seen in the other twin. In contrast there is no such concordance in binovular twins. Waardenburg gives a concordance of 81·2 per cent for uniovular twins as against a concordance of 8·9 per cent of binovular twins. The squint need not necessarily be ipsilateral in a uniovular twin; "crossed similarity" or mirror image is not infrequent.

Secondly, there are the pedigrees of squint which show dominant inheritance of the affection. This becomes all the more apparent if heterophoria, which is merely latent squint, is regarded as part of the picture. A typical pedigree is shown in Fig. 76*a*. Fig. 76*b* illustrates the fact that the presence of hypermetropia is in itself not necessarily a precipitating factor for squint, since squint and hypermetropia can be inherited independently.

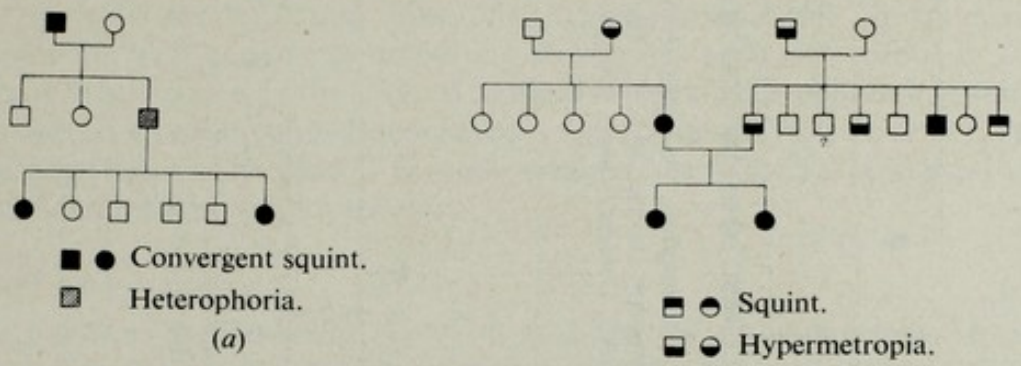


FIG. 76.—Convergent squint.
(*a*) Dominant inheritance in a family showing heterophoria as an incomplete form of squint. (*After P. J. Waardenburg* (1948). *In Modern Trends in Ophthalmology, Vol. II, Ed. by A. Sorsby, p.* 169. *London; Butterworth.*)
(*b*) A pedigree showing the dominant inheritance of squint and hypermetropia independently. (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 108. *The Hague; Nijhoff.*)

In earlier analyses of inheritance of squint, Czellitzer found that only some 15 per cent of members of squint families showed squint—considerably below the expected 50 per cent for a dominant affection. He sought to explain this discrepancy on the basis of two recessive genes being responsible. This possibility was further supported by the fact that in his families there was a consanguinity rate of 6 per cent. This explanation is unlikely to be valid. It is more likely that a single dominant gene is responsible, and that the expression of this gene may range from a low degree of esophoria and weakness of fusion to manifest squint—constant or intermittent.

Amblyopia.—Amblyopia is a secondary feature and not genetically determined. This is shown by the fact that the frequency of amblyopia in uniovular twins is not different from the general average of amblyopia in squint. If amblyopia were genetically determined the partner of a uniovular twin with amblyopia should also have amblyopia, and this is not always the case.

Divergent squint

Secondary divergent squint occurs in a series of hereditary and non-hereditary corneal abnormalities, as also occasionally in congenital ocular anomalies.

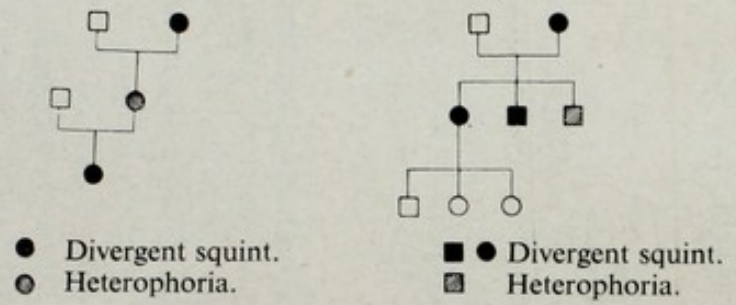


FIG. 77.—Divergent squint. Two pedigrees suggestive of dominant inheritance and showing heterophoria as the incomplete form of divergent squint. (*After P. J. Waardenburg* (1948). *In Modern Trends in Ophthalmology, Vol. II, Ed. by A. Sorsby, Figs.* 68 (1) and (3). *p.* 174. *London; Butterworth.*)

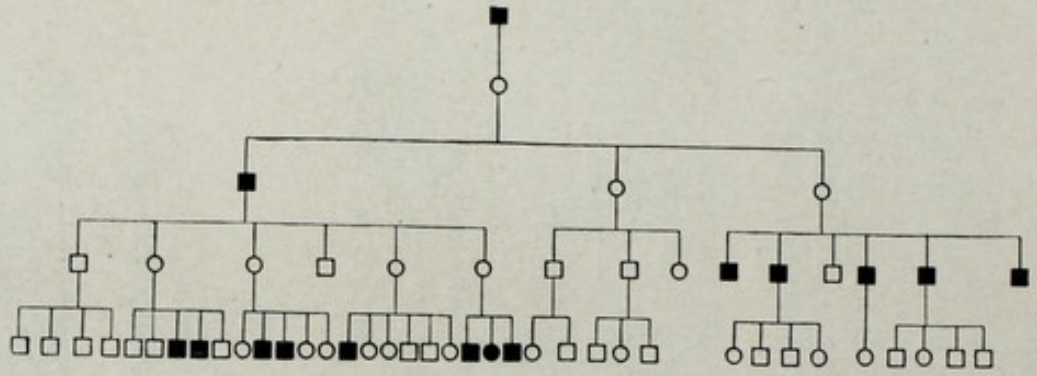


FIG. 78.—Nystagmus. Pedigree showing recessive sex-linked inheritance with manifestation in one woman. (*After G. D. Hemmes* (1924). *Over hereditairen nystagmus. Utrecht; Thesis. Pedigree LL.*)

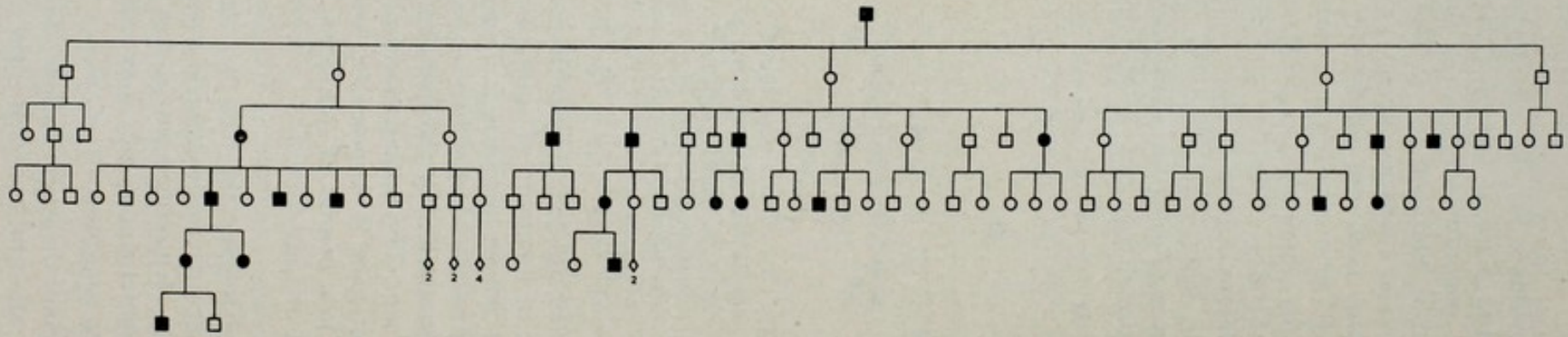


FIG. 79.—Nystagmus. A pedigree suggestive of dominant sex-linked inheritance with suppression of the manifestation in some one-third to one-half of the women carrying the gene. (*After W. Niccol* (1915). *Ophthalmoscope*, **13,** 224.)

Factors which tend to produce a simple hereditary exophoria can readily precipitate a manifest divergent squint.

As for primary divergent squint, such few pedigrees as are available suggest a dominant inheritance, and that heterophoria represents a partial expression (Fig. 77). Evidence from twins also supports the view that divergent squint is genetic in origin.

Nystagmus

Nystagmus occurs as a symptom of many hereditary ocular affections, such as albinism and total colour-blindness, apart from being a symptom of many hereditary affections of the central nervous system.

Congenital hereditary nystagmus may, however, occur in eyes that are apparently normal. In some cases there may be hypoplasia of the macula, and this is not easy to determine in the nystagmic eye. This explanation cannot always apply, for many patients with congenital hereditary nystagmus have full vision. In all cases a characteristic feature is the lack of subjective sensations of moving objects, so trying in acquired nystagmus. It would seem that the underlying cause of nystagmus may be anywhere in the central nervous system—the macula, the central connexions, and the labyrinthine apparatus.

Modes of inheritance

Recessive sex-linked inheritance.—This is shown by many pedigrees. Associated head nodding is uncommon. Occasionally, though apparently far less frequently than in dichromatism, a heterozygous woman shows the affection (Fig. 78).

Irregular dominance.—This is fairly frequent, and head nodding is commonly, but not always, present. The irregular dominance was regarded as autosomal for many years, but many pedigrees are best explained on the assumption of X chromosomal dominance with suppression of the manifestation in some one-third to one-half of the women carrying the gene. This assumption explains the frequently observed fact that affected men do not pass the affection on to their sons (Fig. 79). The view that the dominant gene is X-chromosomal and not autosomal has been extended to include the possibility that both the recessive and the dominant sex-linked genes for nystagmus, as also the sex-linked gene for ocular albinism with nystagmus, are alleles with different phenotypical manifestations.

CHAPTER 2

THE CORNEA

NORMAL MEASUREMENTS AND THEIR VARIATION

Diameters

THE ACTUAL distribution of measurements of the horizontal diameter of the cornea —as determined by Peter in 1,024 eyes of children aged from 5 to 16 years—is shown in Fig. 80. These observations agree with the classical findings of Priestley Smith, and do not differ markedly from much similar material. It would, therefore, appear that a cornea with a horizontal diameter of less than 10 millimetres or more than 13·5 millimetres must be regarded as falling outside the range of normal,

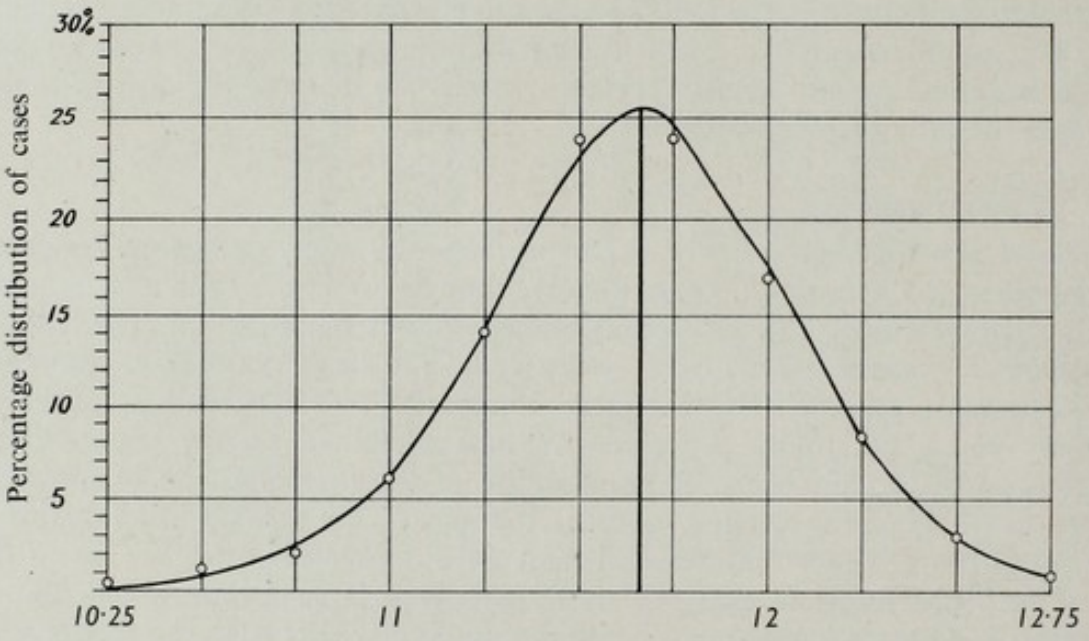


FIG. 80.—The frequency of distribution of the horizontal diameter of the cornea (in mm.). (*After Rosa Peter* (1925). *Arch. f. Ophthal.*, **115,** 29.)

o = Actual mean values. — = Theoretical binomial curve.

and that the most frequent value is 11–12 millimetres. The most frequent value for the vertical diameter is rather less: from 10·5 to 11 millimetres.

Refraction

The significance of corneal refraction and of its normal variation in total refraction has been discussed in the section on refractive errors. Corneae with a refraction of less than 35 D and more than 50 D are outside physiological limits.

Radius of curvature

The normal range of the radius of curvature appears to lie between 6·75 millimetres and 9·25 millimetres.

ABNORMALITY IN SIZE

Microcornea

The smaller the diameter of the cornea, the greater is the corneal refraction. As most eyes with small corneae are not markedly ametropic it must be assumed that the axial length is probably small, and that the line of demarcation between microcornea and pure microphthalmos is fine. Most eyes with microcornea have good vision. The pedigree recorded by Martin (Fig. 81) as an instance of microphthalmos is probably an example of microcornea.

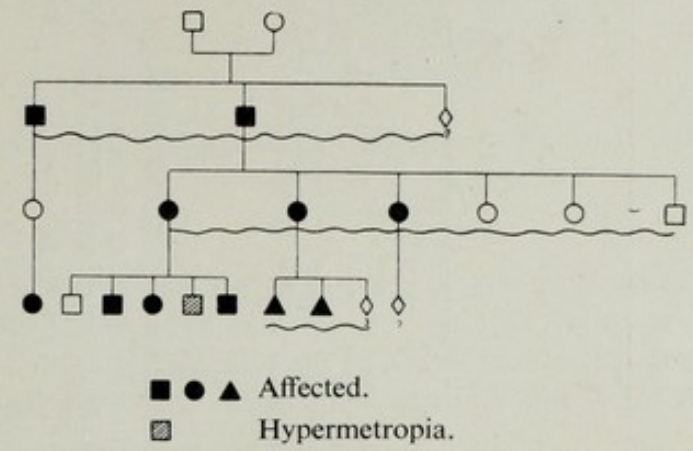


FIG. 81.—Microcornea. Inheritance over three generations. Recorded originally in 1888 as cases of microphthalmos. Vision appears to have been unaffected, and it is likely that this was a family with microcornea rather than microphthalmos. (*After F. Martin* (1888). *Uber Mikrophthalmus. Erlangen: Thesis. Quoted by A. Franceschetti* (1930). *In Kurzes Handbuch der Ophthalmologie. Ed. by F. Schieck and A. Brückner. Vol.* 1, *p.* 702. *Berlin; Springer.*)

Megalocornea

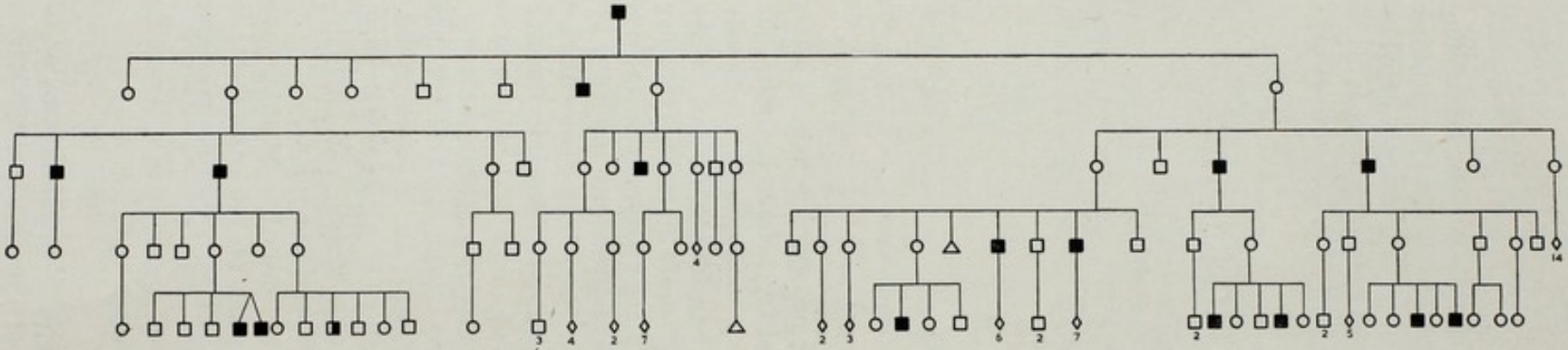
The same difficulty as in demarcating microcornea from microphthalmos arises in distinguishing between megalocornea and buphthalmos. Here, however, the line of demarcation is more definite. Megalocornea is seen almost exclusively in males, is always bilateral, vision is generally good and demarcation from the sclera is as well defined as in the normal eye. With the slit-lamp increased relucency is seen at the limbus. Occasionally, changes in the anterior segment of the eye may be present, making differential diagnosis from buphthalmos difficult. In buphthalmos the cornea is generally abnormal in other ways than mere enlargement, for opacities and rupture of Descemet's membrane are frequent. The line of demarcation from the sclera is not always well defined, and a thin bluish sclera is generally evident. When changes are present in the anterior segment in megalocornea, the anterior chamber is deep, the iris may be tremulous, and the lens though normal in early life frequently becomes opaque later on. In buphthalmos the anterior chamber is either normal or shallow, and only occasionally deep, iridodonesis is rare, and secondary cataract is common in severe cases. Megalocornea is a non-progressive anomaly, buphthalmos a progressive affection.

In modes of inheritance the two conditions are sharply contrasted. Buphthalmos is in all probability an autosomal recessive, megalocornea on the other hand is clearly a sex-linked recessive in most cases (Fig. 82 *a* and *b*). A rather puzzling case is shown in Fig. 83.

ABNORMALITY IN CURVATURE

Cornea plana

The cornea may be small with a horizontal diameter of 8–10 millimetres or of normal dimensions. The abnormal flatness may produce a low corneal refraction,



■ Bilateral.
◧ Unilateral.

FIG. 82.—Megalocornea. Recessive sex-linked inheritance. (*a*) A pedigree over five generations showing recessive sex-linkage. (*After B. Kayser* (1914 *and* 1919). *Klin. Mbl. Augenheilk.*, **52,** 226, *and* **60,** 349).

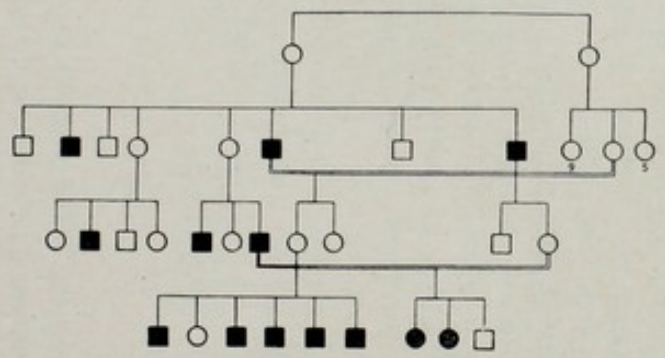


Fig. 82.—(*b*) A pedigree showing two affected women in the last generation. It may be assumed that they received an X chromosome with a pathogenic gene from each of their parents. (*After V. Grönholm* (1921). *Klin. Mbl. Augenheilk.*, **67,** 1.)

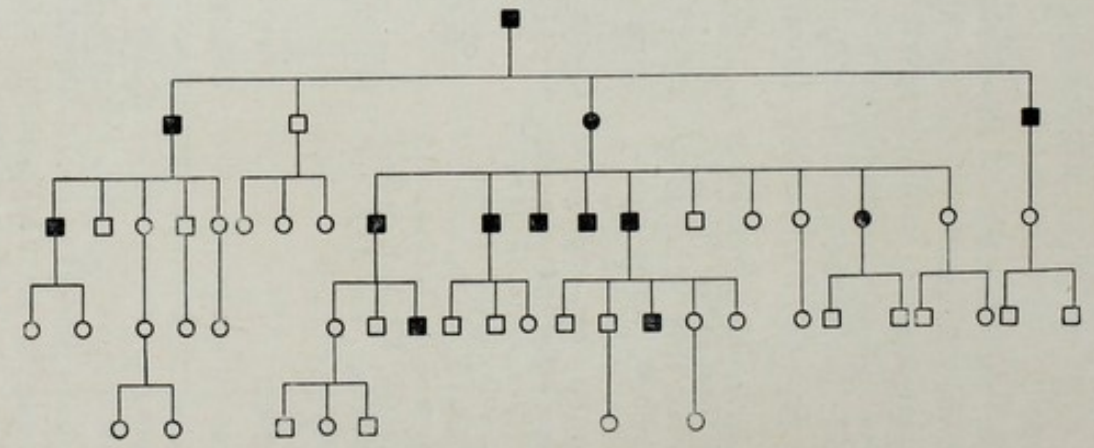


FIG. 83.—Megalocornea. A unique pedigree suggestive of autosomal dominance. (*After C. Gredig* (1926). *Arch. Klaus-Stift. Vererbr.-Forsch.* **2,** 79. *Quoted by A. Franceschetti* (1930). *In Kurzes Handbuch der Ophthalmologie. Ed. by F. Schieck and A. Brückner, Vol.* 1, *p.* 730. *Berlin; Springer.*)

though still within normal limits. The line of demarcation with the sclera is ill-defined, and the transparent part of the cornea tends to be horizontally oval. Frequently there are associated ocular anomalies, so that vision is poor. Cornea plana is probably inherited in a dominant manner (Fig. 84), though some pedigrees suggest a recessive mode of inheritance. Cornea plana together with bluish

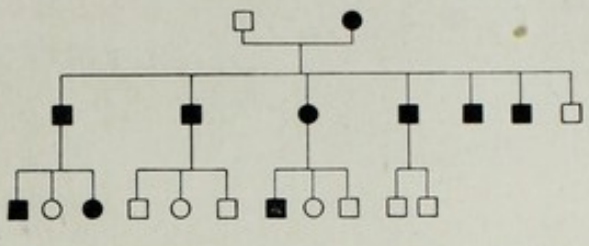


FIG. 84.—Cornea plana. Pedigree showing dominant inheritance. (*After V. Larsen and A. Eriksen* (1949). *Acta Ophthal.*, **27**, 275.)

coloration of the sclera and xerosis of the conjunctiva has been observed once over two generations.

Keratoconus

In some pedigrees (Fig. 85 *a*) keratoconus and severe corneal astigmatism appear as alternative forms within the same family. Frequently, too, when there is keratoconus in one eye there is a high degree of astigmatism in the other. This would suggest that high degrees of astigmatism are abortive forms of keratoconus,

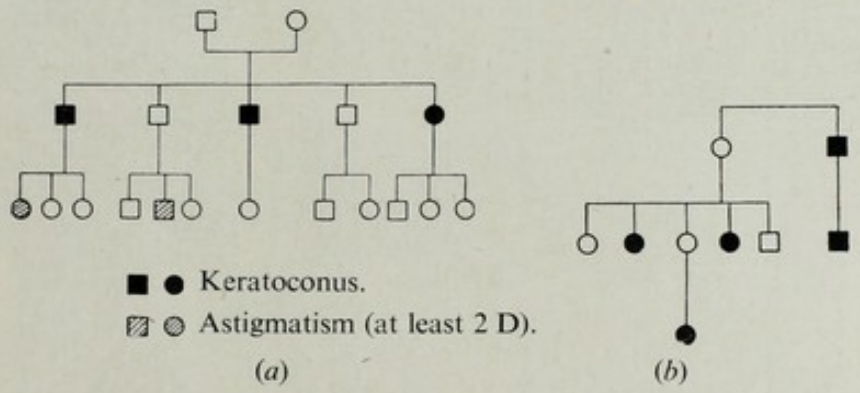


FIG. 85.—Keratoconus. (*a*) Pedigree over two generations showing keratoconus and severe astigmatism as alternative forms. (*After J. Rumpf* (1937). *Contribution à l'étude de l'hérédité du Keratocône, p.* 65, *Lausanne: Thesis.*) (*b*) Pedigree suggestive of dominant inheritance. (*After J. Stähli* (1925). *Klin. Mbl. Augenheilk.*, **75**, 465.)

and there is evidence that some, at any rate, tend to evolve into the fully developed type. The majority of records concern sibships only and would suggest recessiveness, but there are a substantial number of cases observed over two generations, and even three (Fig. 85 *b*). The interpretation of these pedigrees depends largely upon the significance attached to astigmatism as an abortive form of keratoconus.

ABNORMALITIES IN TRANSPARENCY

Congenital opacification of the cornea and corneal staphyloma

Congenital opacification of the cornea presents considerable clinical complexities. It is not unlikely that many of the early records in the literature were partial observations on a variety of genetic affections ranging from embryotoxon to

gargoylism, and it is also likely that ill-defined inflammatory conditions, and possibly ill-recognized cases of severe buphthalmos, have figured in the reports. Corneal staphyloma has been observed in infants in whom the other eye showed corneal opacification only.

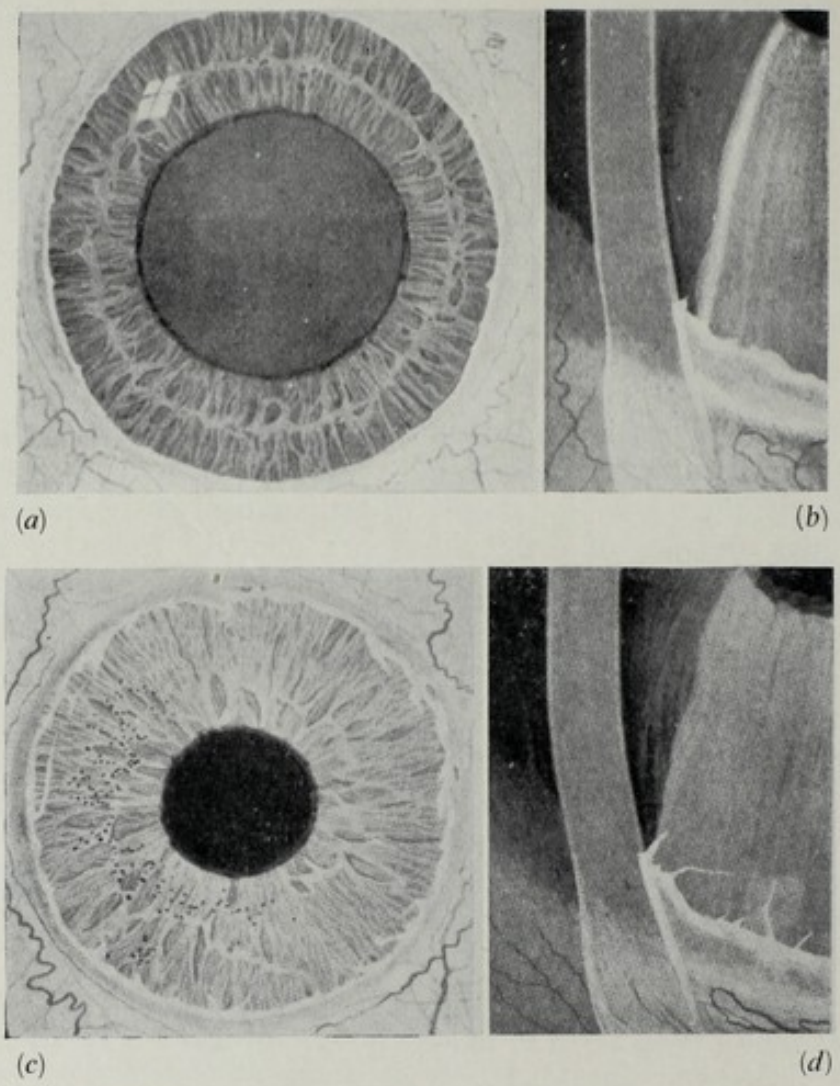
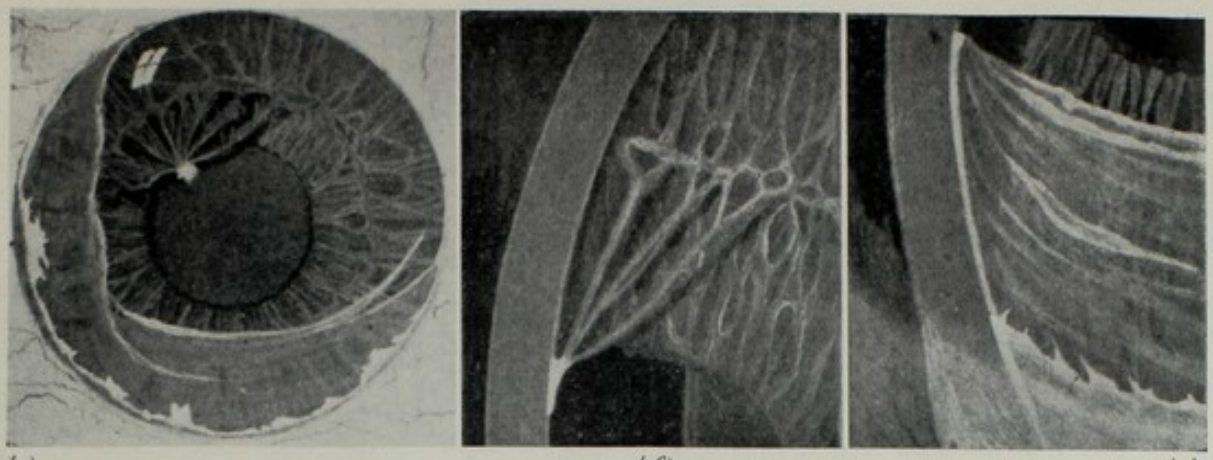


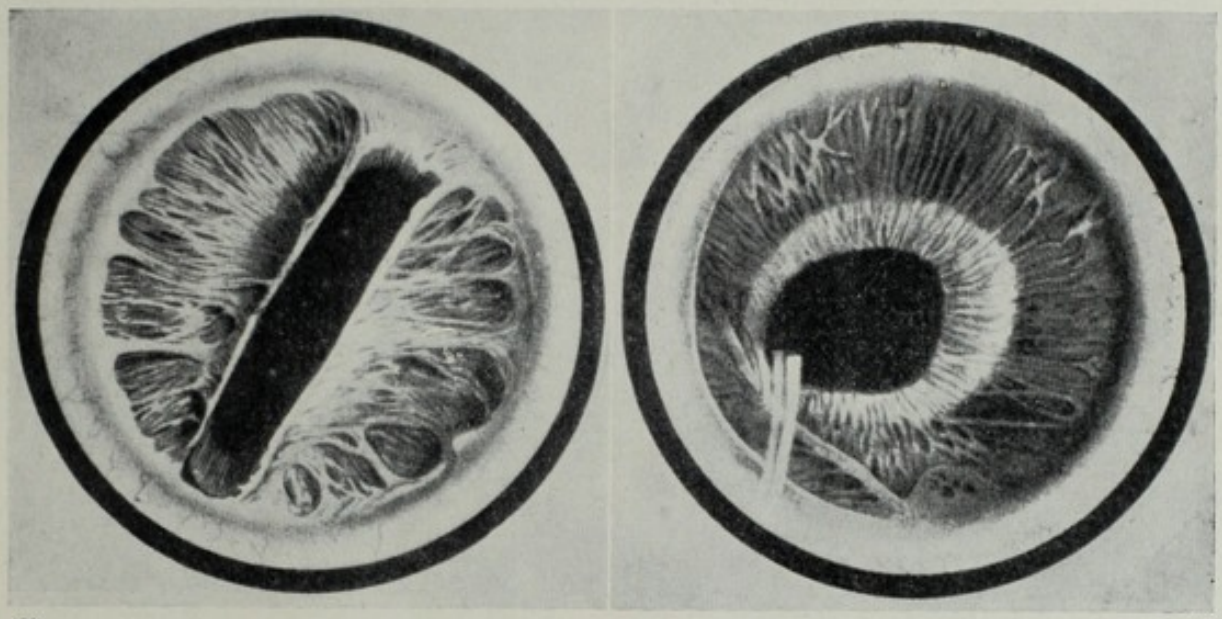
FIG. 86.—Range of appearances in posterior embryotoxon (posterior marginal dysplasia of the cornea). (*After E. B. Streiff* (1949). *Ophthalmologica*, **118,** 815.)
(*a*) and (*b*) Face view and slit-lamp view respectively in a mild case.
(*c*) and (*d*) Similar views in a case with floating hyaline filaments in the anterior chamber.

Embryotoxon

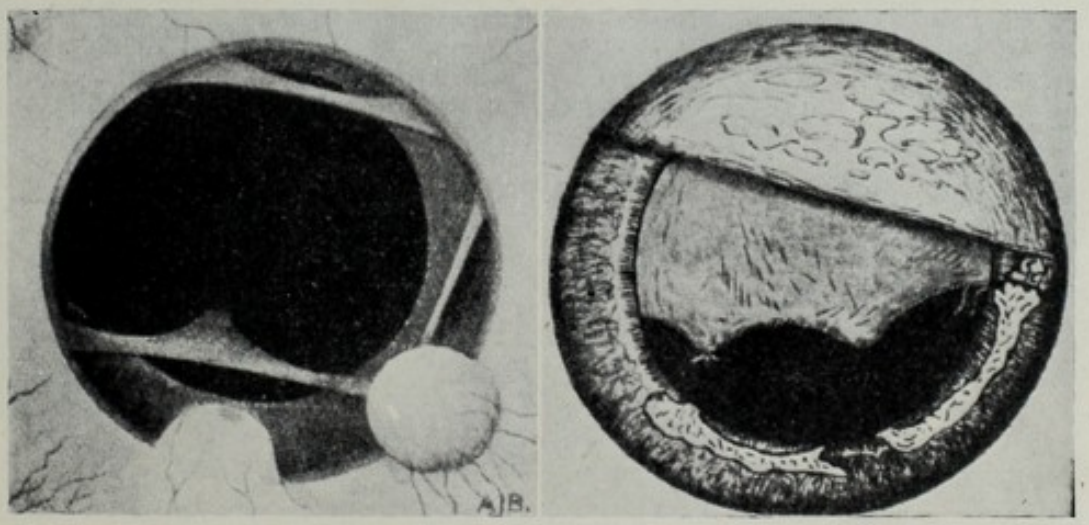
This, too, is probably a clinically complex entity. Embryotoxon occurs frequently in megalocornea, and in the syndrome of blue sclerotics with fragilitas ossium. The range of anomalies seen in embryotoxon are illustrated in Fig. 86. *Arcus juvenilis* would appear to be the mildest form and is probably dominant. Extensive defects giving the appearances of congenital corneal opacities have been observed in two sisters (Fig. 87).



(e) (f) (g)

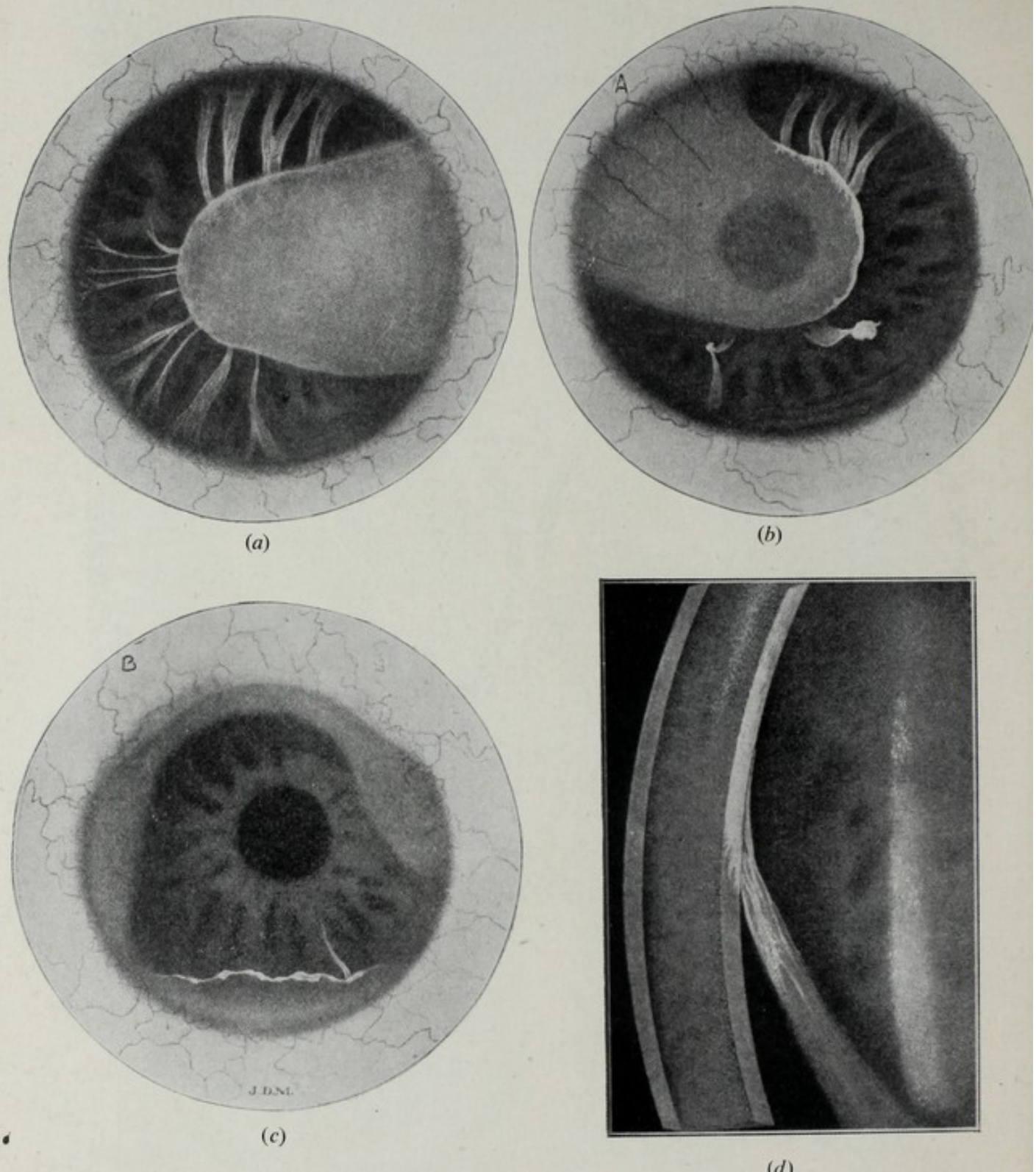


(h) (i)



(j) (k)

FIG. 86 (*cont.*).—(*e, f and g*) Face view and slit-lamp views in a marked case in which the corneal opacity is well developed, and numerous filaments stretch from the collarette of the iris. There was microphthalmos.
(*h* and *i*) Two cases with marked anomalies of the iris.
(*j* and *k*) Two cases with still more marked anomalies.



(*a*) (*b*) (*c*) (*d*)

FIG. 87.—Embryotoxon. Appearances in two sisters. (*After F. H. Theodore* (1944). *Arch. Ophthal.*, **31**, 138.)
(*a*) Right eye of a girl aged 6 years. There was some ptosis owing to slight microphthalmos. The left eye was normal.
(*b*) and (*c*) The left and right eyes of her sister five years older.
(*d*) Slit-lamp view of lower part of the cornea shown in (*c*).

Vortex-like veil ("vortex dystrophy", cornea verticillata)

Vortex-like veil is a non-progressive lesion without effect on vision (Fig. 88). It is probably inherited in a dominant manner (Fig. 89).

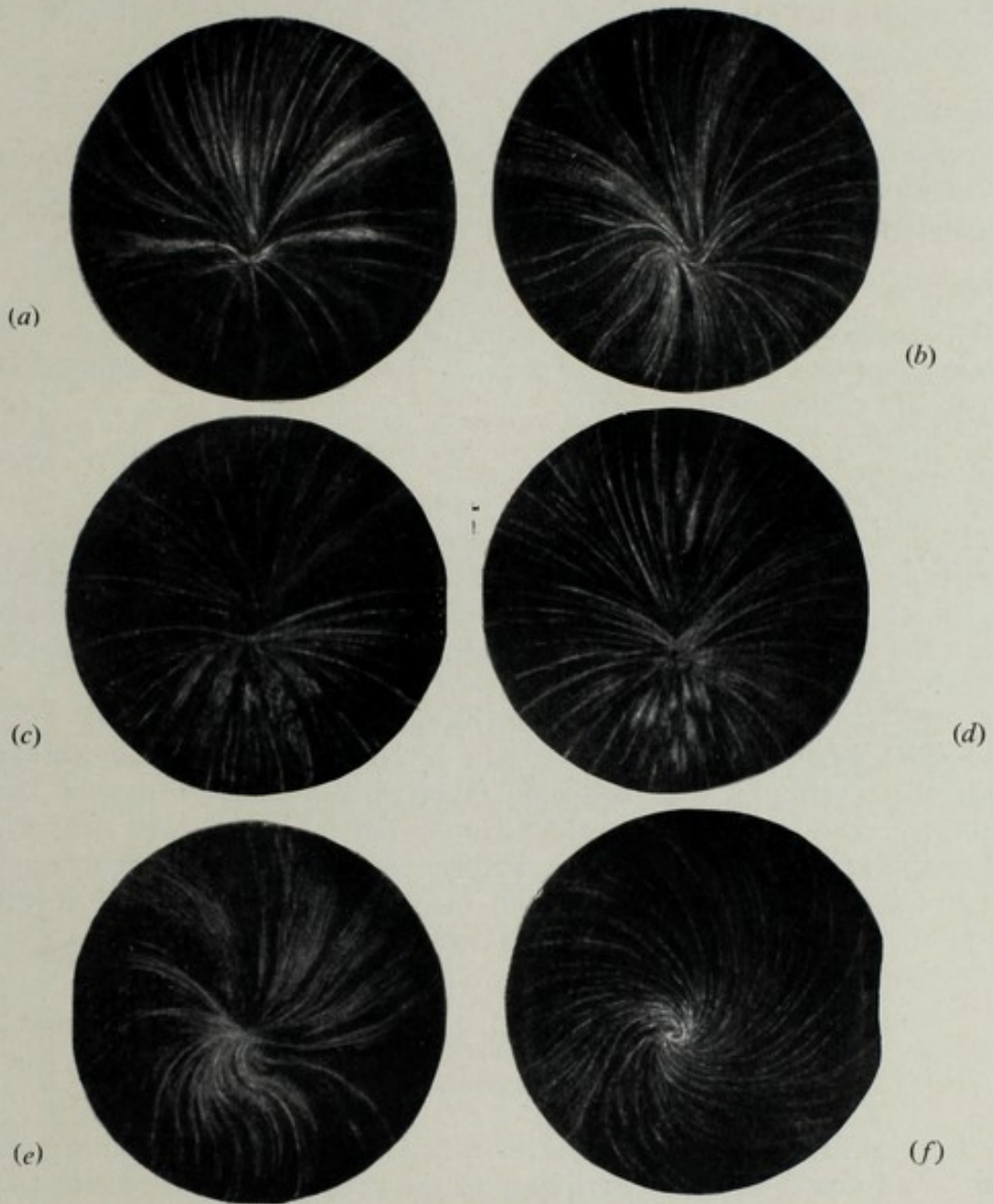


FIG. 88.—Vortex-like veil. (*After M. Gruber* (1946). *Ophthalmologica*, **112,** 88.)
(*a*) and (*b*) The right and left corneae of a woman aged 56 years.
(*c*) and (*d*) The right and left corneae of a daughter, aged 30 years.
(*e*) and (*f*) The right and left corneae of a son, aged 28 years.

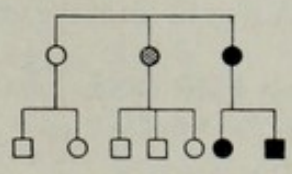


FIG. 89.—Vortex-like veil. Pedigree suggestive of dominant inheritance. (*After M. Gruber* (1946). *Ophthalmologica*, **112,** 88.)

ABNORMALITIES IN PIGMENTATION

Limbal pigment ring

This abnormality is a normal feature in some of the dark-coloured races. Waardenburg has observed it over three generations in the offspring of marriages between Caucasians and Malays.

Krukenberg's spindle

Krukenberg's spindle has been observed in megalocornea with its recessive sex-linkage, and also apparently as a dominant feature in women over two generations. In uncomplicated cases the female excess is striking.

Kayser-Fleischer ring

This ocular sign of hepatolenticular degeneration—occasionally a pointing sign in this recessive affection—is generally observed in all the affected sibs of a family, and has been seen in twins.

CORNEAL DYSTROPHIES

Considerable clarification has been achieved as a result of the stress laid by Kraupa on the different reactions shown by the different layers of the cornea, and of the work of Bücklers on the mode of inheritance of the classical forms of corneal dystrophy.

Kraupa stressed the secondary involvement of the epithelium in primary endothelial dystrophies, and isolated a juvenile form of presumably primary endothelial dystrophy with epithelial involvement. Bücklers showed that most of the recorded cases of corneal dystrophy fell into three well defined clinical and genetic entities. It has, however, become clear that there are many more forms of corneal dystrophy. A combination of anatomical and genetic investigation has produced rapid advances in the recognition of these affections.

Dystrophies Involving all the Layers of the Cornea (Total Corneal Dystrophies)

The total corneal dystrophies all show a striking lack of inflammatory reactions. Even in advanced cases the periphery of the cornea tends to remain clear, and vascularization is exceptional and generally occurs as a secondary feature to erosions of the epithelial surface which may develop. Whilst the reactions are essentially parenchymatous, both the epithelium and endothelium become involved, though the deeper layers of the cornea remain relatively uninvolved. "Acute attacks" with severe symptoms but without any tangible structural changes are fairly frequent in both the recessive macular type and the dominant lattice-like type.

The total, corneal dystrophies are the classical forms. Their clinical and genetic features are brought out in the following classification by Bücklers (*see* Table V and Figs. 90–92).

TABLE V

TOTAL CORNEAL DYSTROPHIES

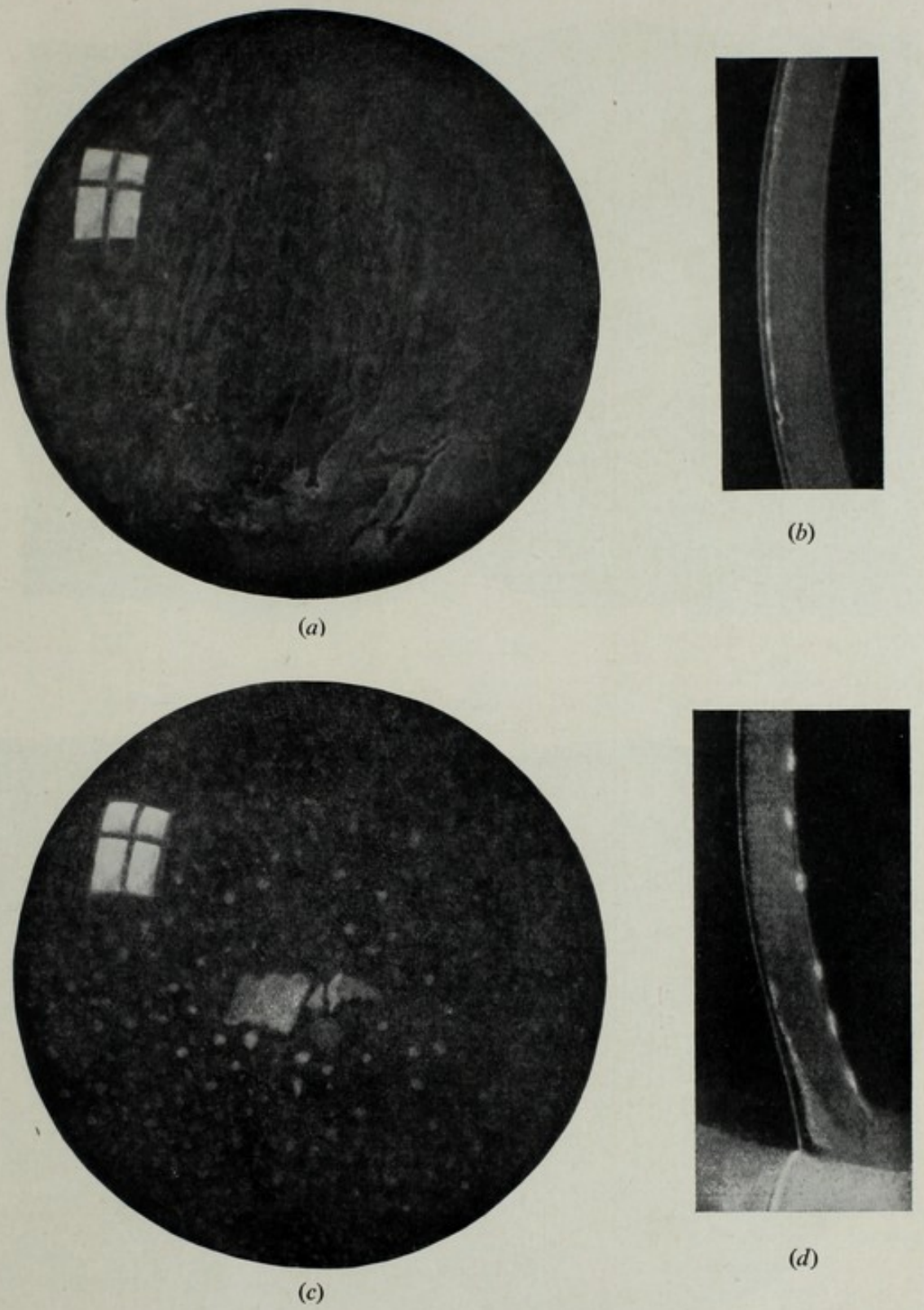
Tabulation of the Significant Characteristics

Features	Dominant granular dystrophy	Recessive macular dystrophy	Dominant lattice-like dystrophy
Age of onset – –	At about 5 years	The first decade of life	Occasionally in infancy. More frequently in the second decade of life
Earliest signs – –	Small white dots in centre of cornea, some superficial, some fairly deep May take the form of radiating lines from the centre	A thin superficial corneal veil seen with the loupe or slit-lamp. In this fine diffuse haze, isolated ill-defined subepithelial opacities occur	A cobweb of delicate lines which frequently ramify and produce a lattice-like pattern when the lines cross each other. Here and there the crossings produce the illusion of a nodular reaction. The lines in the superficial layers of the parenchyma tend to raise the epithelium. The corneal tissue tends to be diffusely clouded. Though most marked at the centre of the cornea, the periphery is also involved
Course – – –	The dots increase in size and number, and lose the radial arrangement sometimes seen in the early stages The centre of the cornea is now studded with patterned figures of irregular shape and size	Increasing haziness of the central part of the cornea with an increasing number of isolated opacities which tend to become larger. At about puberty the corneal surface may be uneven and the fundus no longer clearly seen ophthalmoscopically. These changes become more intense so that the picture is one of largish, ill-defined opacities against a hazy background. The changes are most marked centrally but spread towards the periphery. By about the age of 30 years vision is grossly damaged. The further course is one of increasing opacification of the cornea, especially centrally	Increase in the number and thickness of line, "nodules" and general diffuseness of the affected cornea. Sometimes at 20 years of age, and sometimes not until 40 years or so, the centre of the cornea has become an irregular ill-defined opacity with raised epithelium

(*continued overleaf*)

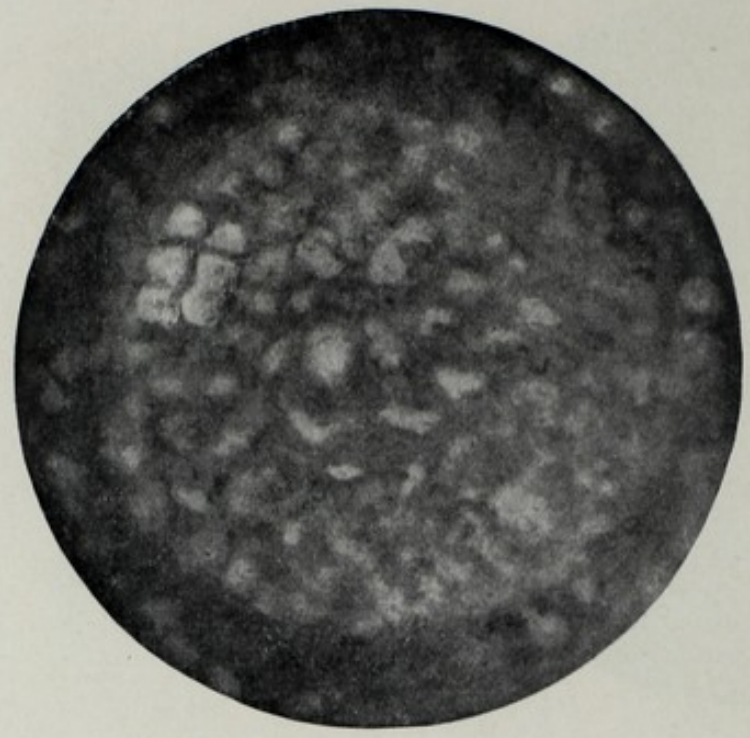
TABLE V (*cont.*)

Features	Dominant granular dystrophy	Recessive macular dystrophy	Dominant latttice-like dystrophy
End-stage	By about the age of 50 years the opacities are sufficiently well marked to be visible with the naked eye. Until then the presence of this anomaly is frequently an incidental finding. At this stage the cornea loses some of its superficial lustre, and subsequently small localized elevations of the epithelium may occur	Late in life, corneal opacification is such that it may not be possible to see the pupil. The corneal epithelium remains intact until almost the end, though small localized epithelial projections may occur relatively early	Towards the end all evidence of the lattice-like appearance disappears in the diffuse opacification. At the extreme periphery of the cornea the lattice-like lines may still be seen
Corneal sensitivity	Only slightly, or not affected until late in life	This is diminished early and there is increasing loss of sensitivity	Affected early and diminishes progressively
"Acute attacks"	Absent, or possibly rare	Frequent. The symptoms are out of proportion to the physical signs. There is much photophobia and lacrimation. Vascularization is absent. These attacks are of short duration	Frequent. Epithelial erosions may occur
Slit-lamp appearance	Essentially an interstitial reaction Most marked in the intermediate and deepest layers	The earliest opacities are at the level of Bowman's membrane. Later there may be epithelial projections over these opacities and considerable diffuse opacification throughout the parenchyma	The lines are seen to be obliquely running spaces, doubly contoured The intervening parenchyma is hazy The whole depth of the parenchyma is involved
Symptoms	Largely asymptomatic. Many patients remain unaware of the existence of the lesion	Declining vision, "acute attacks" and relatively early onset of blindness	As for recessive macular dystrophy, though perhaps not so severe
Effect on vision	Frequently none, and generally not severe, even late in life	Severe	Some cases run a mild course. In most, severe visual disturbances are present by the age of 30 years or earlier. The end-result is not infrequently only less severe than with recessive macular dystrophy



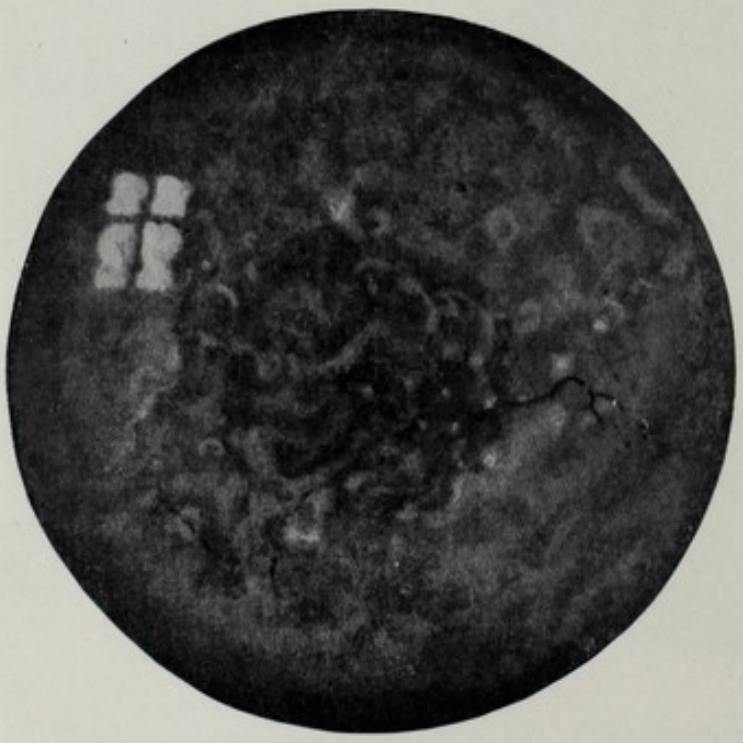
(*a*) (*b*) (*c*) (*d*)

FIG. 90.—Recessive macular dystrophy of the cornea. The range of appearances as seen at different ages (in individuals not all of the same family). Face views and optical sections respectively are shown in each case. (*After M. Bücklers* (1938). *Die erblichen Hornhautdystrophien. Stuttgart; Ferdinand Enke.*)
(*a*) and (*b*) Appearances in a girl aged 11 years.
(*c*) and (*d*) Appearances in a man aged 28 years.



(*e*)

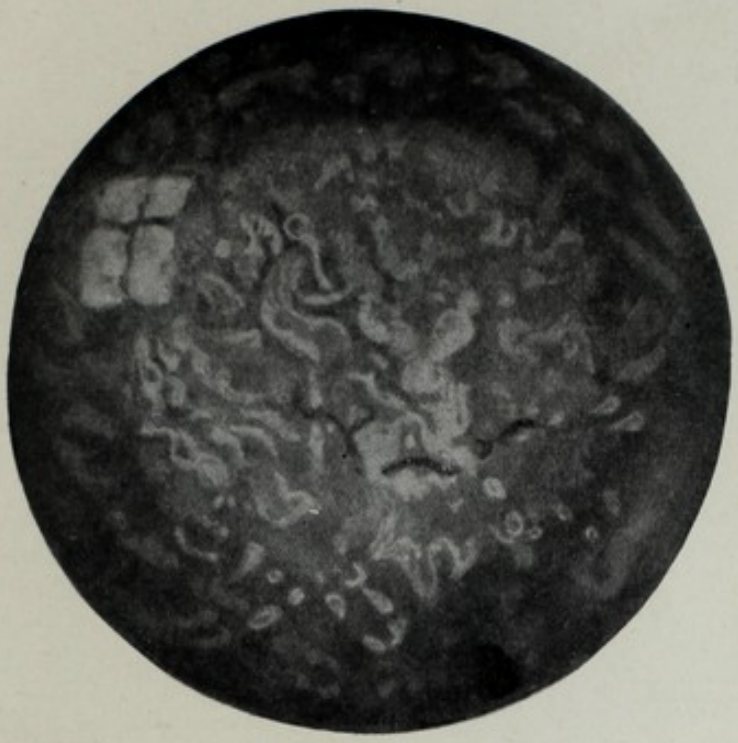
(*f*)



(*g*)

(*h*)

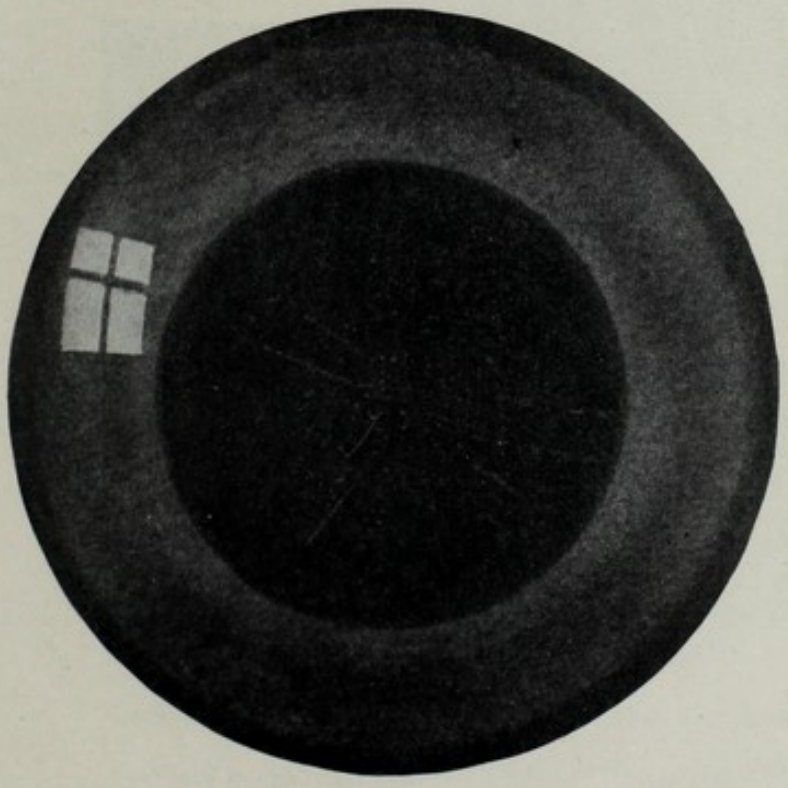
FIG. 90 (*cont.*)—(*e*) and (*f*) Appearances in a man aged 38 years.
(*g*) and (*h*) Appearances in a woman aged 63 years.



(*i*)

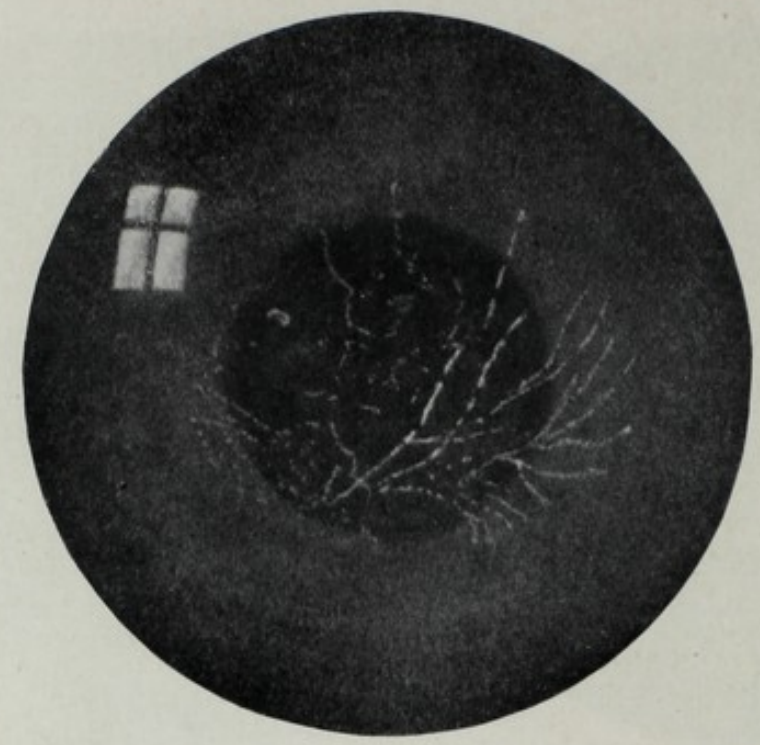
(*j*)

FIG. 90 (*cont.*).—(*i*) and (*j*) Appearances in a woman aged 69 years.

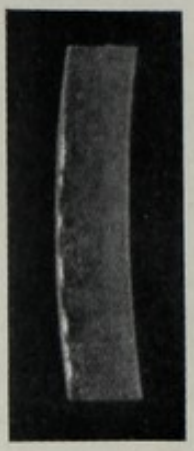


(*a*)

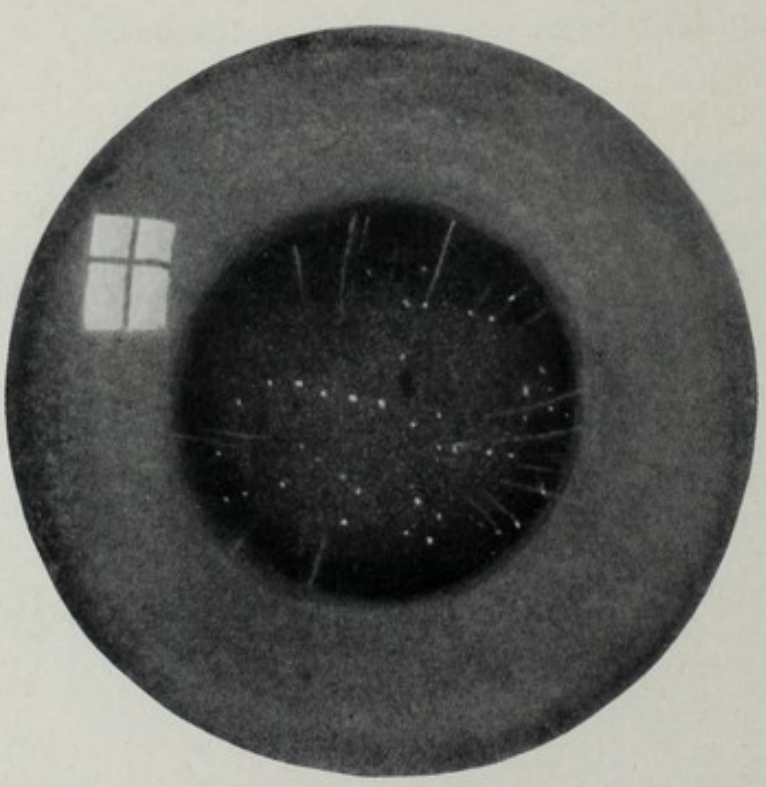
FIG. 91.—Dominant granular dystrophy of the cornea. Range of appearances as seen at different ages in members of an extensive family with many collateral branches. (*After M. Bücklers* (1938). *Die erblichen Hornhautdystrophien. Stuttgart; Ferdinand Enke.*)
(*a*) Appearance in a boy aged 4 years. Face view.



(*b*)



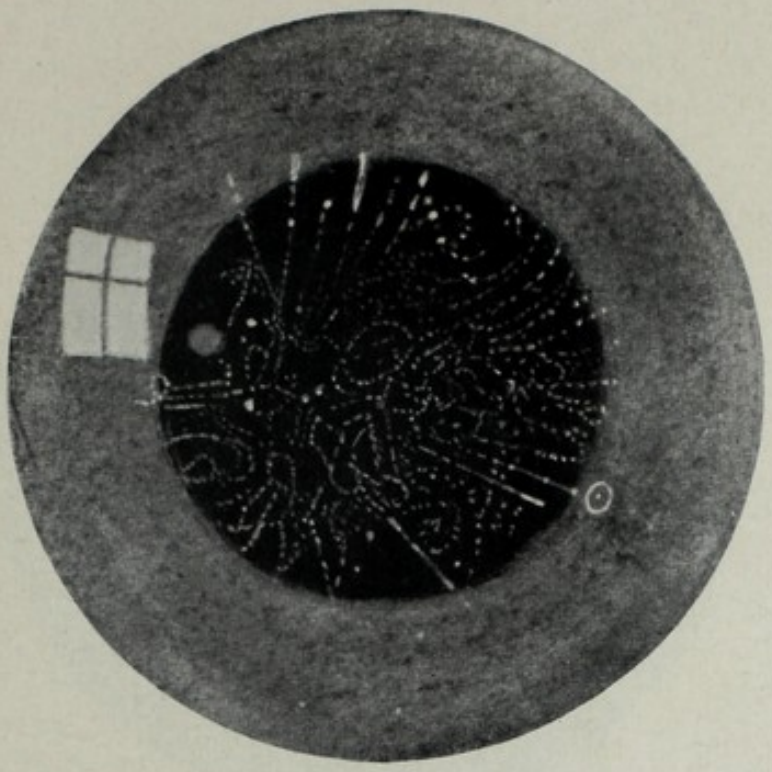
(*c*)



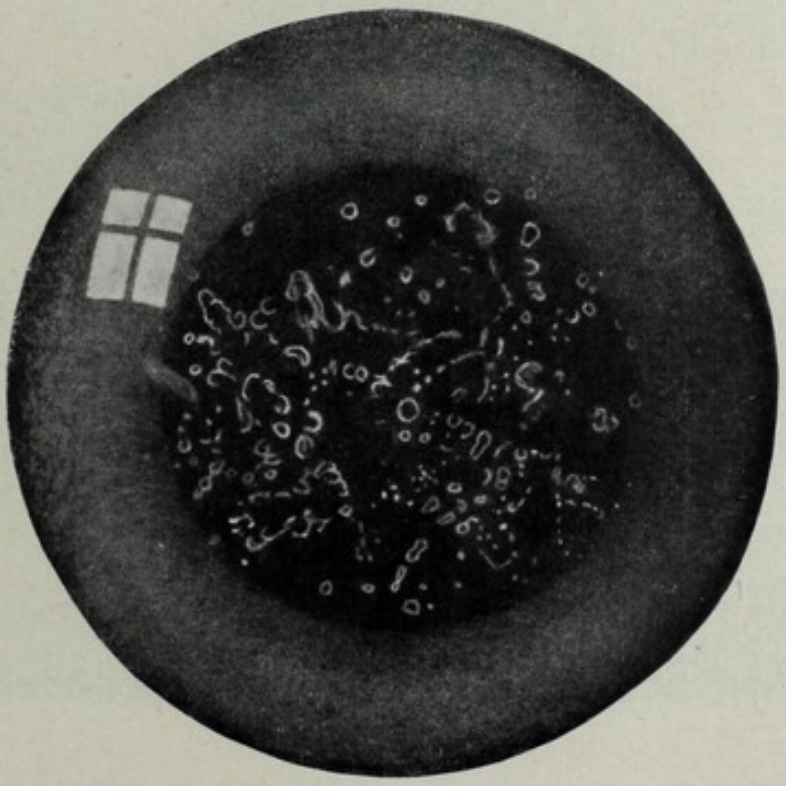
(*d*)

(*e*)

FIG. 91 (*cont.*).—(*b*) and (*c*) Appearances in a girl aged 8 years. Face view and optical section respectively.
(*d*) and (*e*) Appearances in a boy aged 12 years. Face view and optical section respectively.

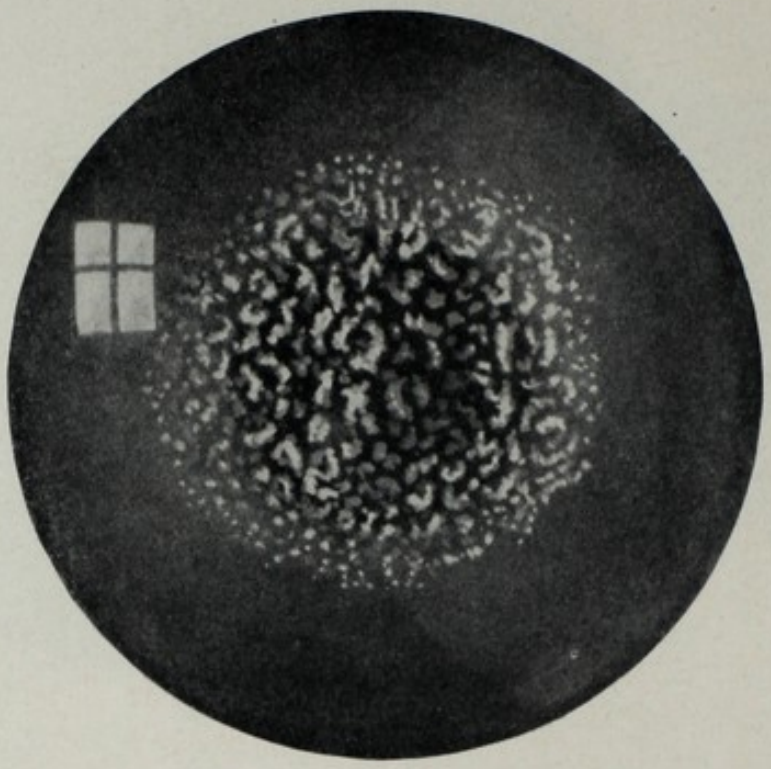


(*f*)

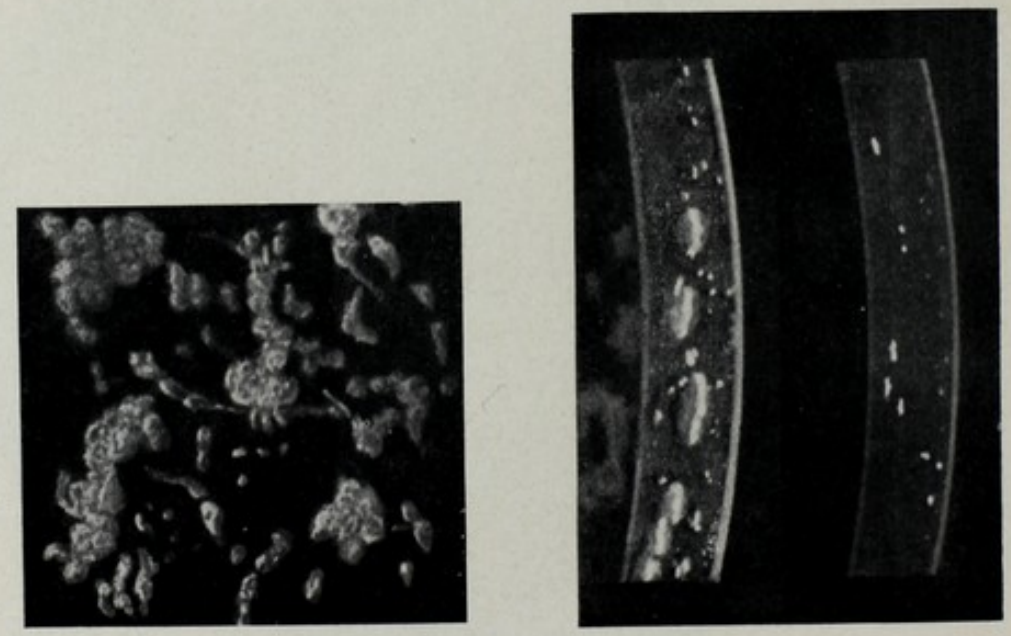


(*g*)

FIG. 91 (*cont.*).—(*f*) Appearances in a man aged 19 years. Face view.
(*g*) Appearances in a man aged 32 years. Face view.

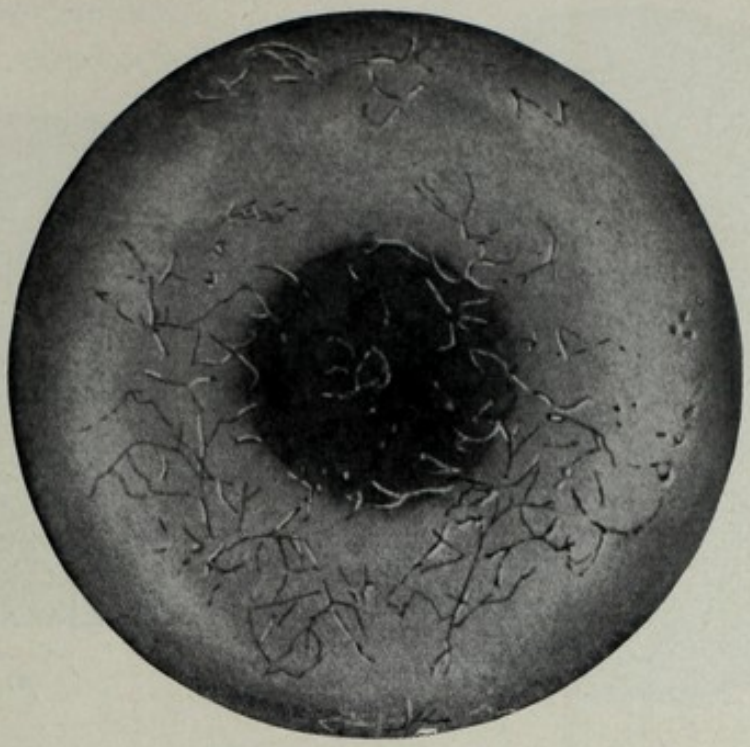


(*h*)

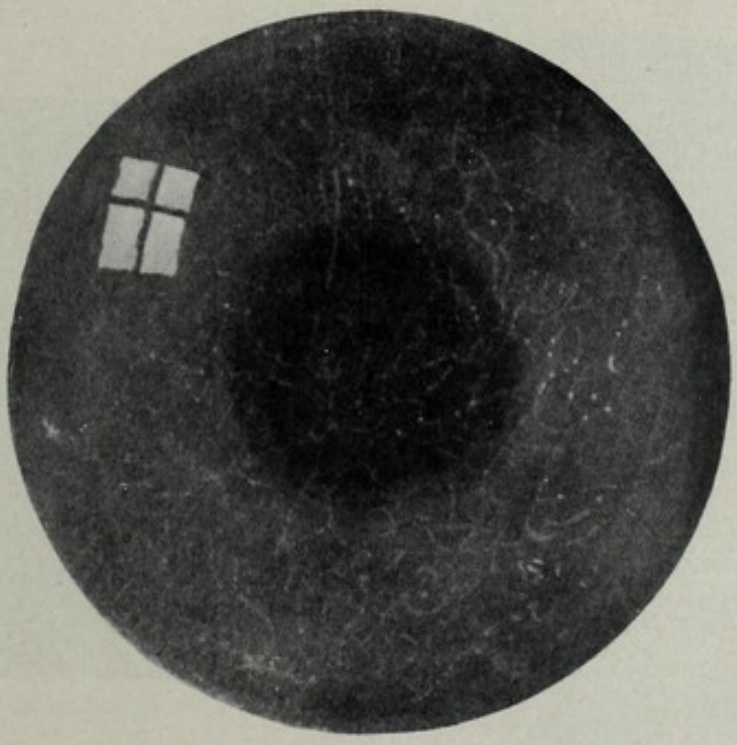


(*i*) (*j*)

FIG. 91 (*cont.*).—(*h*, *i*, *j*) Appearances in a woman aged 52 years; face view; section of face view (× 24); and optical section, respectively.

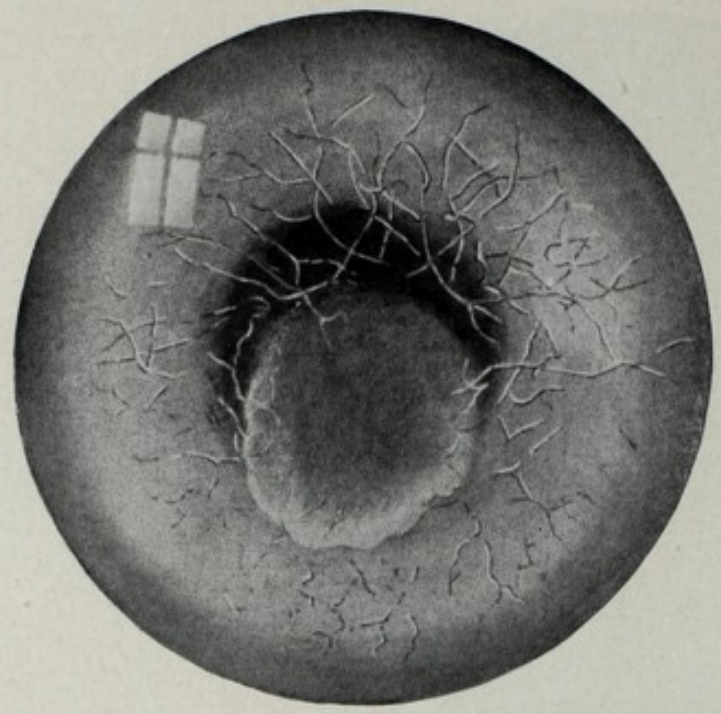


(*a*)



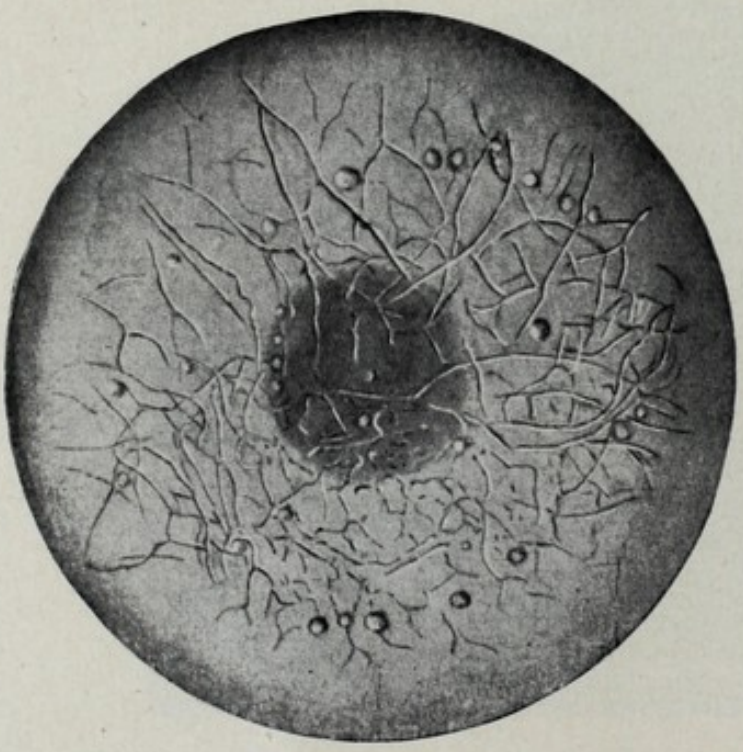
(*b*)

FIG. 92.—Lattice-like corneal dystrophy. The range of clinical appearances as seen at different ages in different members of one family. (*After M. Bücklers* (1938). *Die erblichen Hornhautdystrophien. Stuttgart; Ferdinand Enke.*)
(*a*) Appearance in a man aged 18 years. Face view (retro-illumination).
(*b*) Appearance in a man aged 23 years. Face view (direct illumination).



(*c*)

(*d*)



(*e*)

(*f*)

FIG. 92 (*cont.*).—(*c*) and (*d*) Appearances in a woman aged 44 years. Face view and optical section respectively.
(*e*) and (*f*) Appearances in a man aged 50 years. Face view and optical sections —paracentral and more peripheral, respectively.

Recessive macular dystrophy

The earliest changes appear in the first decade of life as a delicate diffuse opacity of the whole corneal surface with thicker patches here and there. In the second decade the opacities become more marked, so that at puberty vision is already affected and the fundus is not easily seen. Increasing changes ultimately produce a characteristic corneal picture in which ill-defined opacities stand out in a diffusely cloudy cornea. There is no actual loss of epithelial substance, but there is an increasing loss of corneal sensation. By the age of 30 years, most patients are practically blind. The mode of inheritance is clearly recessive (Fig. 93).

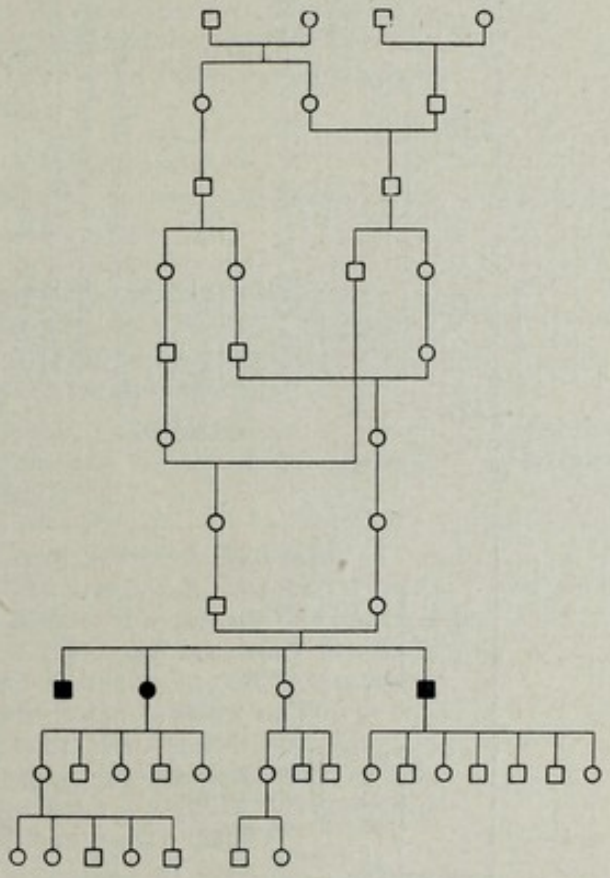


FIG. 93.—Macular dystrophy of cornea. Pedigree showing recessive inheritance. (*After M. Bücklers and T. Gilch* (1938). *In Handbuch der Erbkrankheiten. Ed. by A. Gütt. Vol.* 5, *p.* 82. *Leipzig; Georg Thieme.*)

Dominant granular dystrophy

This affection begins at about the age of 5 years as a disturbance in the centre of the cornea, and progresses very slowly. From initial fine interstitial dots fine lines radiate out in all directions, and ultimately the greater part of the cornea is studded with white chalky interstitial opacities. Vision is not severely affected, and sometimes not at all. Frequently the finding is incidental in the course of a routine examination.

As can be seen from the pedigree shown in Fig. 94, the condition is clearly dominant.

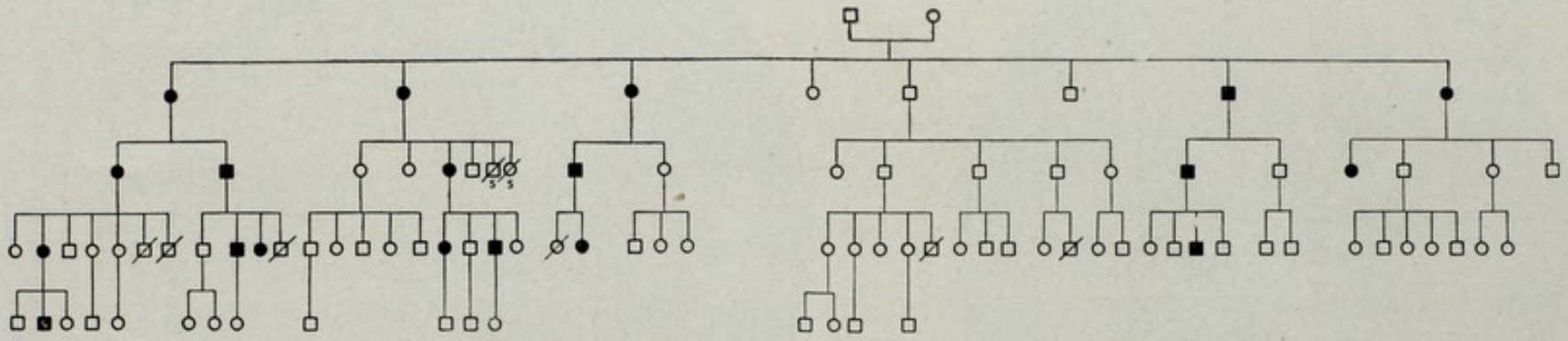


FIG. 94.—Granular dystrophy of cornea. Pedigree over four generations showing dominant inheritance. Cases observed over four generations. (*After T. Gilch* (1937). *Z. menschl. Vererb.-u. Konstit.*, **21,** 1.)

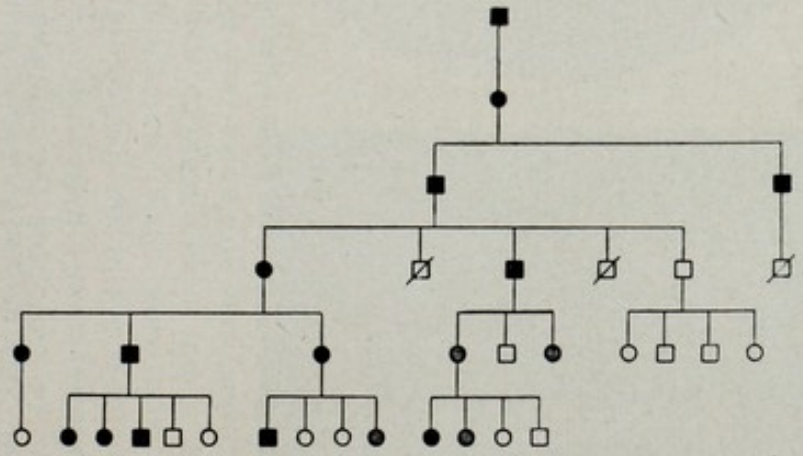


FIG. 95.—Lattice-like corneal dystrophy. Pedigree over six generations showing dominant inheritance. Cases observed over three generations. (*After R. Frykholm* (1935). *Klin. Mbl. Augenheilk.*, **94,** 76.)

TABLE VI

DYSTROPHIES OF INDIVIDUAL LAYERS OF THE CORNEA

TABULATION OF THE SIGNIFICANT CHARACTERISTICS

Condition	Clinical features	Mode of inheritance
	Epithelial	
Recurrent corneal erosion	Onset early in life. Reduced corneal sensation. Frequent relapses. Tendency to quiescence after 50 years of age	Dominant
Diffuse epithelial dystrophy	Onset in infancy. Repeated "acute attacks". Appearances of superficial punctate keratitis or herpes corneae. In late stages Bowman's membrane is involved. Ultimately there develops scar formation especially in the exposed interpalpebral area of the cornea	Dominant
	Endothelial	
Endothelial dystrophy –	Onset early in life. ? Congenital. In late stages overlying parenchyma involved	Dominant
	Compound Endothelial and Epithelial	
Senile epithelial dystrophy (Fuchs')	Develops after the age of 50 years. Endothelial changes develop first. Subsequently there are progressive changes in the epithelium	?
Juvenile epithelial dystrophy (Kraupa's)	Onset early in life. ? Congenital Parenchyma as well as epithelium tends to become involved	? Dominant ? Recessive
	Dystrophies of Bowman's Membrane	
Ring-like dystrophy –	Onset in childhood with frequent "acute attacks". The earliest changes are in Bowman's membrane, but there are secondary epithelial defects. Corneal sensation is reduced, recovery from acute attacks is slow recalling neuro-paralytic keratitis (except that the lesion is bilateral). The confluence of many ring-like epithelial and sub-epithelial lesions gives a map-like appearance in late stages. Vision is grossly affected	Dominant
Calcareous band shaped dystrophy	Bowman's membrane is probably involved primarily. Sibships with a lesion in childhood, or late in life are recorded	?
	Parenchymatous	
Disciform crystalline dystrophy	Onset early in life. Progress is slow and asymptomatic with steadily declining vision. Needle like crystals are deposited axially in the superficial layers of the parenchyma. There are white dots in the adjacent stroma	Dominant
Circular peripheral opacity	A band-shaped, deeply contoured, greyish white opacity in the posterior layers of the cornea, resembling folds in Descemet's membrane	? Dominant

Dominant lattice-like (or reticular) dystrophy

This is a rare form of corneal dystrophy. It begins at puberty or earlier and may present difficulty in diagnosis owing to a spurious appearance of nodules where two of the characteristic lattice lines cross. The condition is generally steadily progressive and vision becomes severely affected. With the slit-lamp the linear opacities show double-contoured outlines, and are seen to be delicate clefts of the anterior layers of the parenchyma. As can be seen from Fig. 95, the condition shows characteristic dominant transmission.

Dystrophies Largely Confined to One Layer of the Cornea

This group of dystrophies still requires considerable clarification, both as to clinical features and modes of inheritance (Table VI.)

Epithelial dystrophies

Recurrent corneal erosion.—In a well-worked-out pedigree Franceschetti has recorded this affection as a dominant over six generations. In the affected members there was always reduced corneal sensitivity, which he regarded as the underlying condition. Recurrences were frequent, and tended to subside at about the age of 50 years (Fig. 96).

Diffuse epithelial dystrophy.—Diffuse corneal dystrophy limited to the epithelium and involving Bowman's membrane in the late stages, is a progressive affection beginning in infancy. Repeated "acute attacks" lead to scar formation with reduction in vision. The interpalpebral exposed cornea is most severely affected. In the early stages the appearance of superficial punctate keratitis, or of herpes cornea is seen. The scarring in the late stages may take on a striking yellow colour (Fig. 97). The affection is dominant (Fig. 98).

Endothelial dystrophies

Endothelial dystrophy, or cornea guttata, is generally regarded as a non-pathological senile change. It would appear that there is a variety with dominant inheritance, in which the changes are present possibly at birth, or come on early in life. Some involvement of the parenchyma may occur, but the epithelium is not involved. Vision may be severely affected owing to the diffuse cloudiness produced (Figs. 99 and 100).

Compound endothelial and epithelial dystrophies

Two types of compound endothelial and epithelial dystrophies may be distinguished (Fig. 102). It is not known whether they are not in fact different aspects of one and the same entity.

Senile epithelial dystrophy (Fuchs').—This is the best known, and the compound nature of this affection is well established. It is generally accepted that the endothelial changes are primary. The possibility that this affection is genetically determined is supported by case records of the affection in sibships. The fact that the affection is one noted late in life may account for the difficulty in obtaining adequate pedigrees.

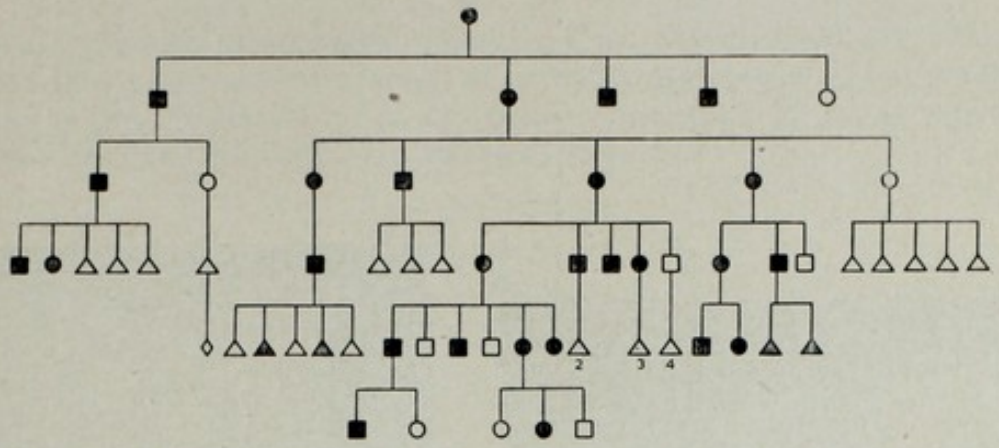
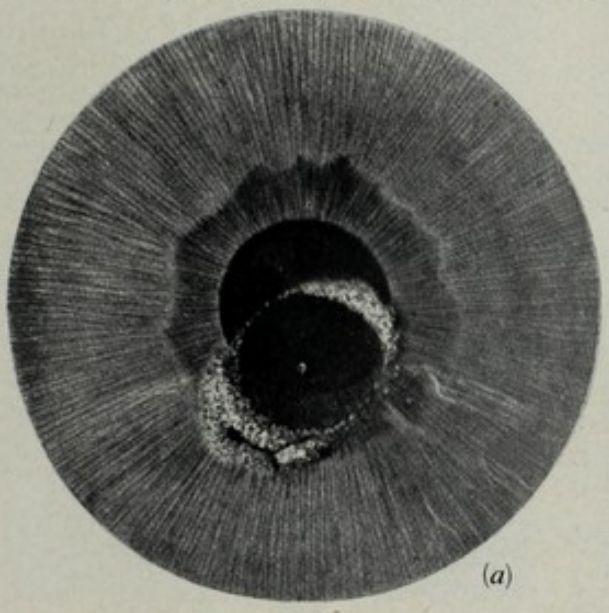


FIG. 96.—Recurrent corneal erosion. Pedigree over six generations. (*After A. Franceschetti* (1930). *In Kurzes Handbuch der Ophthalmologie. Ed. by F. Schieck and A. Brückner. Vol.* 1, *p.* 668. *Berlin; Springer.*)



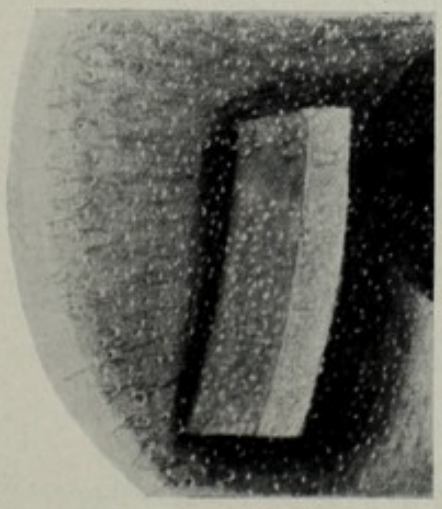
(*a*)

FIG. 97.—Diffuse epithelial dystrophy. Clinical appearances. (*After A. Meesman and Fr. Wilke* (1939). *Klin. Mbl. Augenheilk.*, **103,** 361.)

(*a*) Right eye of a man aged 69 years. The eye is quiet. An elliptical scar is seen in the middle of the cornea somewhat eccentrically. It is deep yellow in colour.

(*b*) Appearances in a boy aged 10 years. The dystrophic epithelial changes are seen as glassy, grey-white dots in direct illumination.

(*c*) and (*d*) Appearances in this boy's mother, aged 30 years (a niece of the patient depicted in Fig. 97*a*. Fig. 97*d* shows the epithelial site of the lesion, the rest of the cornea being normal.



(*b*)

(*c*)

(*d*)

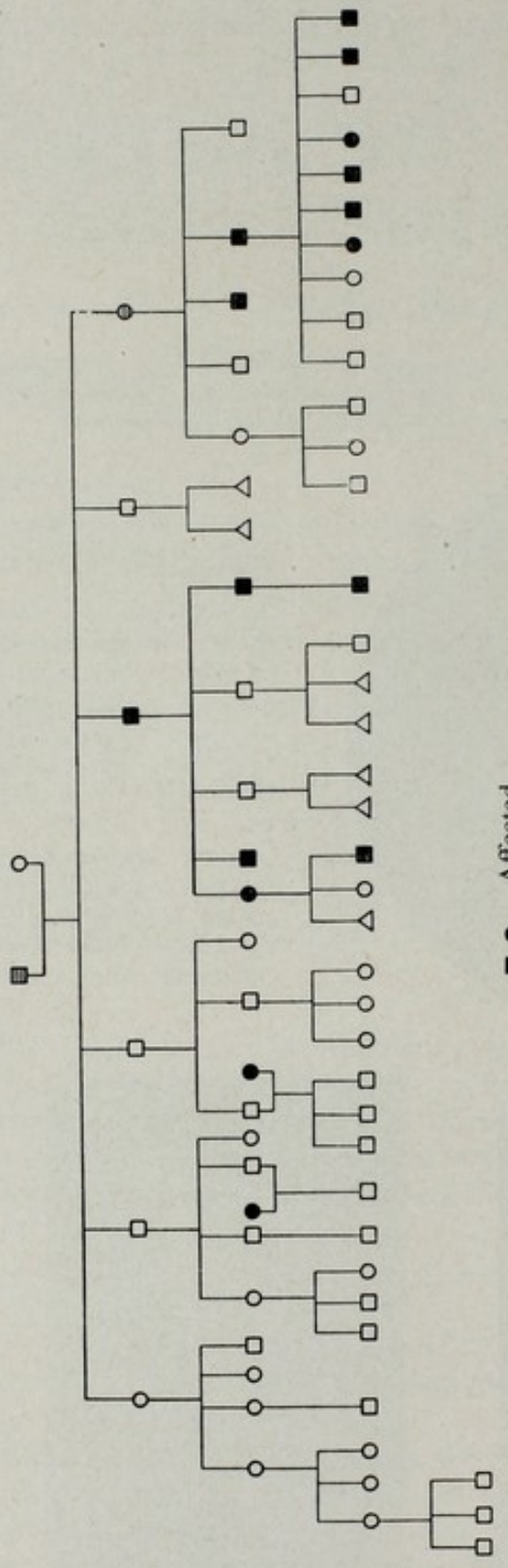


FIG. 98.—Diffuse epithelial dystrophy. Pedigree showing dominant inheritance. (*After A. Meesmann and Fr. Wilke* (1939). *Klin. Mbl. Augenheilk.*, **103**, 361.)

Juvenile epithelial dystrophy (*Kraupa's*).—Here the parenchyma tends to be involved to a slight extent in addition to the epithelium, and it is possible that the condition is congenital, or at any rate of onset early in life. It would appear that there are both dominant and recessive varieties.

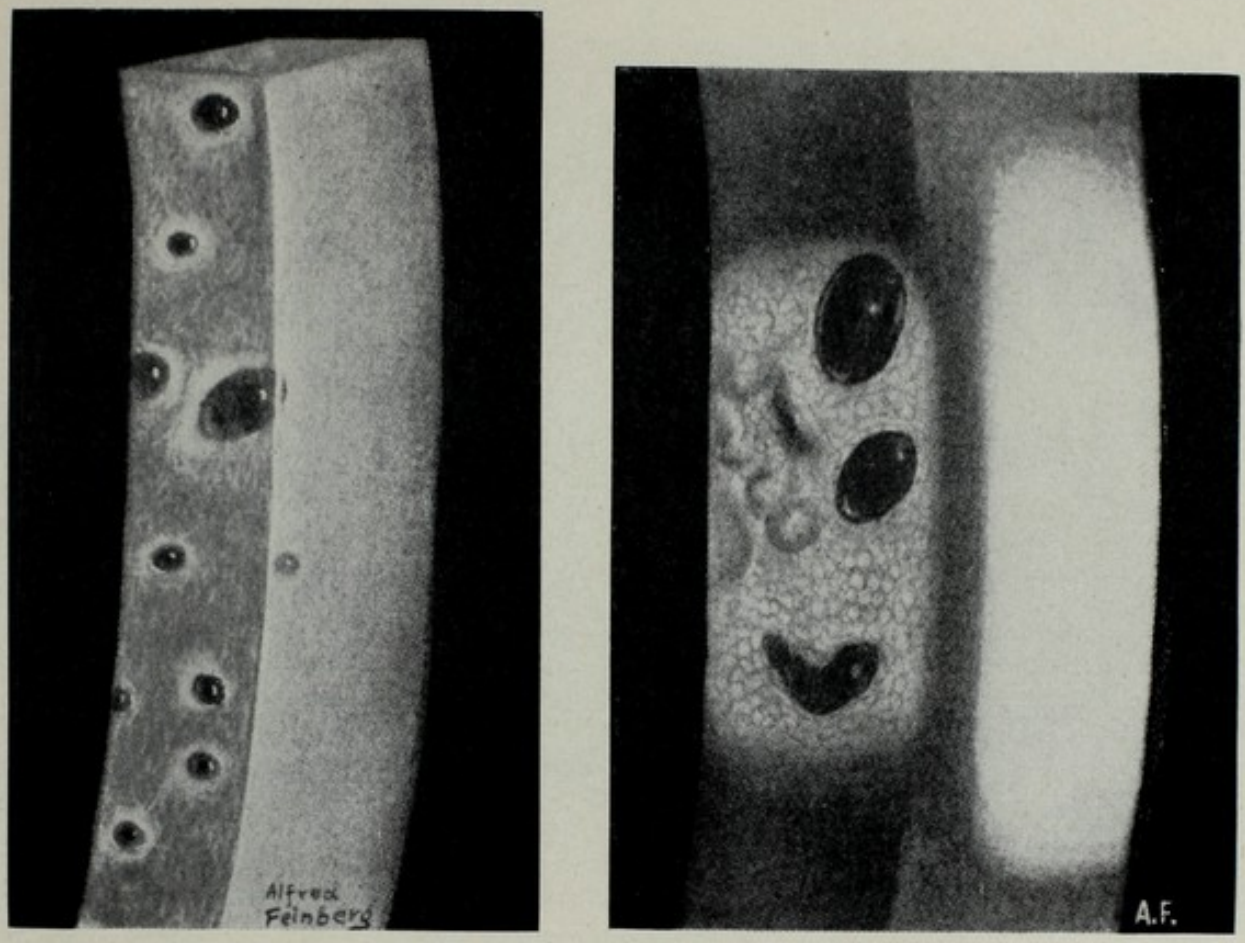
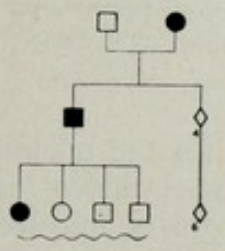


FIG. 99.—Endothelial dystrophy of the cornea. Slit-lamp appearances in a girl aged 18 years. (Magnification: × 16 and × 31 respectively.) (*After F. H. Theodore* (1939). *Arch. Ophthal.*, **21**, 626.)

FIG. 100.—Endothelial dystrophy of the cornea. Pedigree of patient illustrated in Fig. 99. Observed occurrences of the lesion over three generations. (*After F. H. Theodore* (1939). *Arch. Ophthal.*, **21**, 626.)



Dystrophies of Bowman's membrane

Ring-like dystrophy (*dystrophia annularis*).—Under this designation, Bücklers has described an apparently dominant affection characterized by early onset,

frequent "acute attacks", superficial epithelial defects, which on healing leave opacities suggestive of the macular type of dystrophy, but, different from these in being located almost entirely in Bowman's membrane with secondary epithelial and apparently no parenchymatous involvement (Fig. 101). The markedly reduced sensation and slow recovery from acute attacks may suggest neuro-paralytic

FIG. 101.—Ring-like dystrophy of cornea. (*After M. Bücklers* (1949). *Klin. Mbl. Augenheilk.*, **114**, 386.)
(*a*) Appearances in a woman aged 50 years. Irregular heaping-up of narrow lines, arcs, and rings. Radial distribution up and in. Cloudy opacification in the pupil area. A thin pigment line below.
(*b*) Optical section of the same cornea. Note wave-like superficial surface, thickened epithelium, and marked changes in Bowman's membrane. The stroma is practically clear.

keratitis, except for the bilateral involvement. The confluence of many ring-like epithelial and subepithelial lesions gives a map-like appearance in late stages. Vision becomes grossly affected relatively early. A pedigree is shown in Fig. 103.

Calcareous band-shaped dystrophy.—A genetic basis for primary calcareous band degeneration is suggested by the recorded occurrence of this affection in three sibships, once in two elderly brothers, and twice in children (Fig. 105). In one case, examined histologically, the disturbance was essentially in Bowman's membrane.

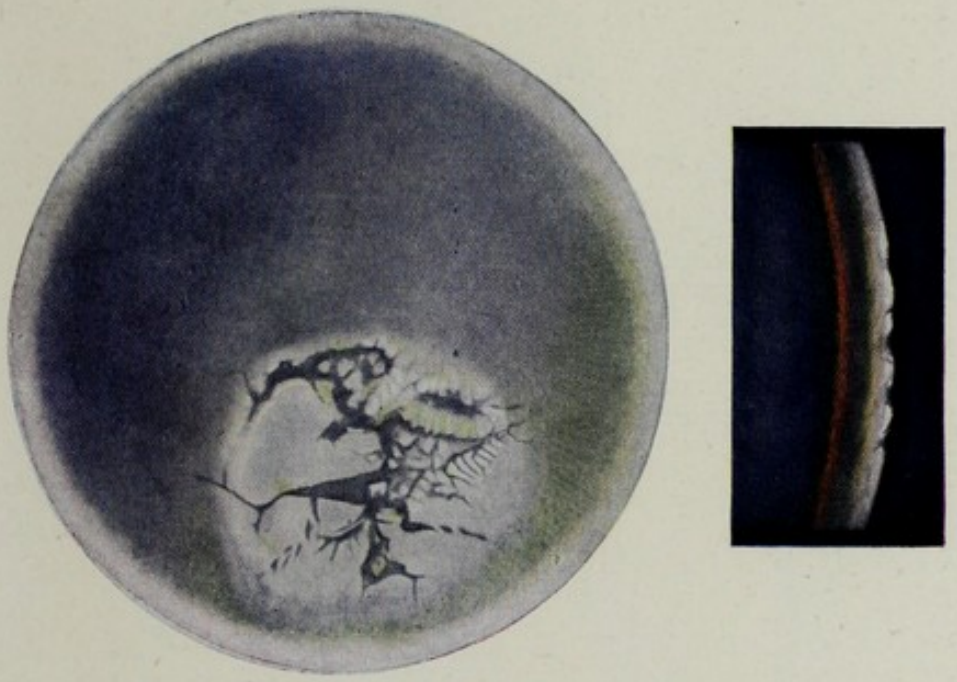


FIG. 102.—Compound endothelial and epithelial dystrophies. Clinical appearances of the senile type. (Senile epithelial dystrophy (Fuchs').) (*After J. H. Doggart* (1948). *Ocular Signs in Slit-lamp Microscopy. Fig.* 41. *London; Kimpton.*)

The appearances in the juvenile type, described by Kraupa, tend to be more acute and more marked, and include considerable milky haziness of the parenchyma.

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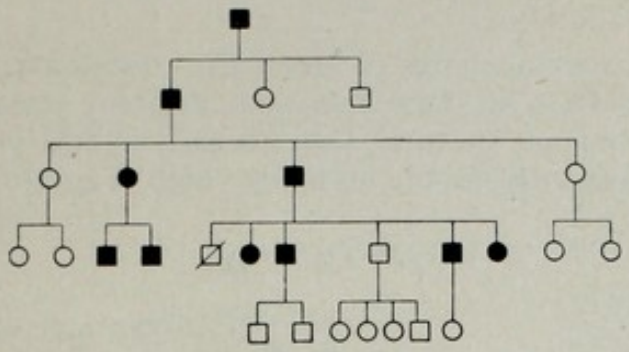


FIG. 103.—Ring-like dystrophy. Pedigree showing dominant inheritance. (*After M. Bücklers* (1949) *Klin. Mbl. Augenheilk.*, **114,** 386.)

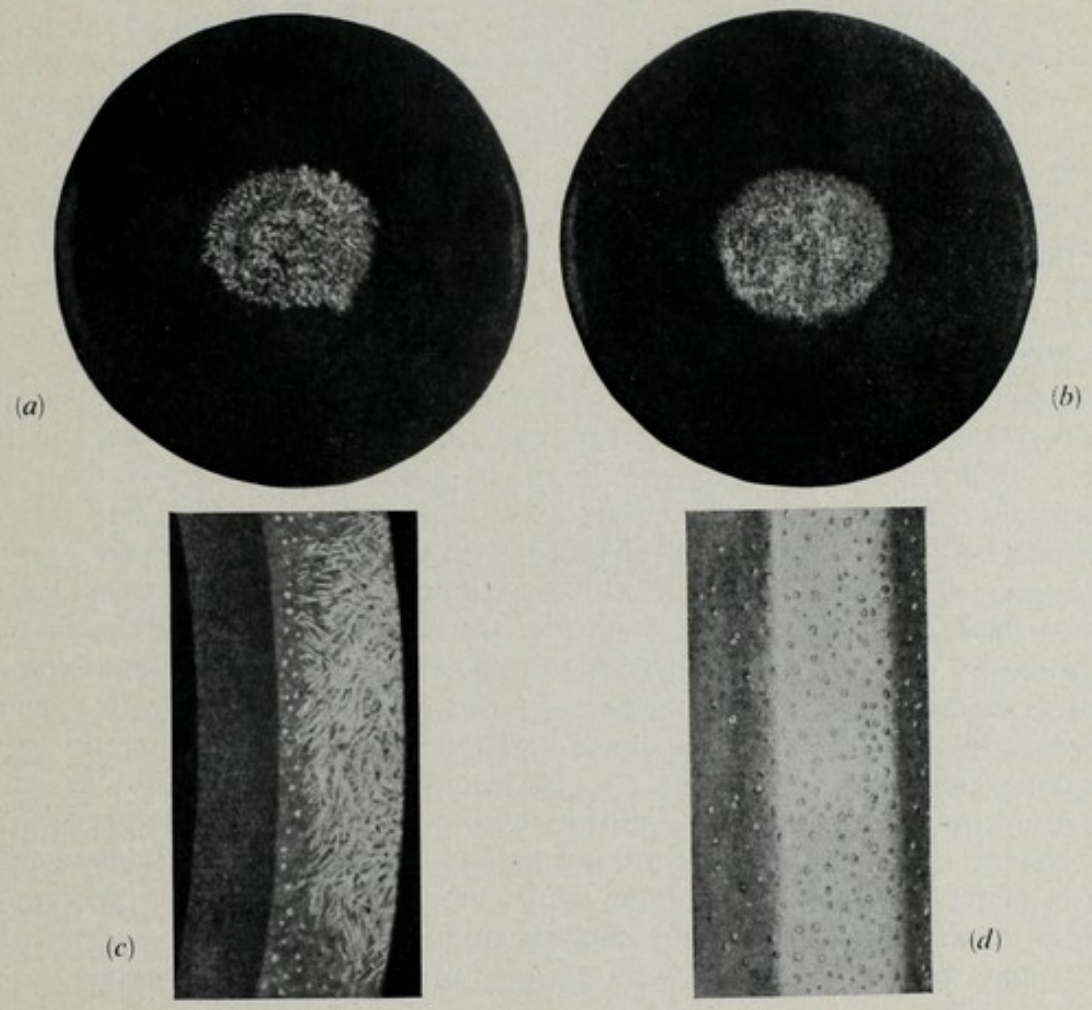
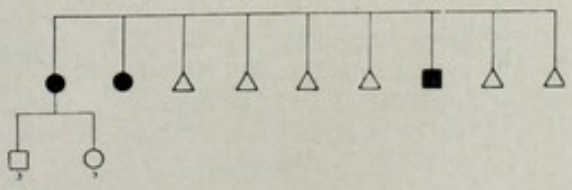


FIG. 104.—Disciform crystalline dystrophy of the cornea. (*After W. F. Schnyder* (1939). *Klin. Mbl. Augenheilk.*, **103,** 494.)
(*a*) and (*b*) Face aspects of right and left corneae showing central deposition of crystals.
(*c*) Optical section through central area showing central deposition of needle-like crystals with punctate opacities in the adjacent stroma.
(*d*) The parenchyma as seen in retro-illumination. The punctate opacities appear like drops.

FIG. 105.—Calcareous band degeneration. Pedigree showing three cases in a sibship. (*After E. B. Streiff and P. Zwahlen* (1946). *Ophthalmologica*, **111,** 129.)



Parenchymatous dystrophies

Disciform crystalline dystrophy.—An accumulation of needle-like crystals axially in the superficial layer of the parenchyma, with white dots in the adjacent stroma (Fig. 104), has been recorded as a dominant affection. Onset is early in life, progress is slow and largely asymptomatic, with steadily declining vision (Fig. 106).

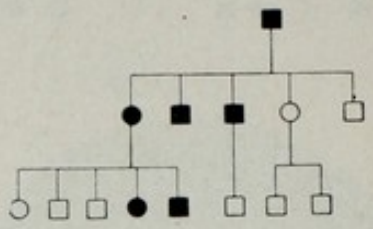


FIG. 106.—Disciform crystalline dystrophy of the cornea. Pedigree showing dominant inheritance. (*After W. F. Schnyder* (1939). *Klin. Mbl. Augenheilk.*, **103**, 449.)

Circular peripheral opacity.—A band-shaped, double-contoured, greyish-white opacity in the posterior layers of the cornea resembling folds in Descemet's membrane, has been recorded as a genetic anomaly over two generations.

Difficulties of classification

Though of considerable help clinically, the classification of corneal dystrophies into two main groups—those involving all the layers of the cornea and those largely confined to one layer—is essentially artificial. Few of the dystrophies are entirely confined to one layer only and it does not follow that even these few would be found to be so limited, if more extensive investigations were available. So far as classification is concerned it is largely in deference to traditional teaching that the three classical forms of dystrophy are described as dystrophies involving all the layers of the cornea. There is no logical reason for not describing, say, recessive macular dystrophy as a lesion of Bowman's membrane with secondary involvement of the parenchyma. In contrast there is no logical reason for not describing endothelial dystrophy as a parenchymatous lesion with the earliest changes in the endothelium. In stressing these difficulties, it is not suggested that the different corneal dystrophies are not individualized entities with characteristic courses of their own. Such a reading would be as unhelpful as it is unwarranted. There is, however, room for more detailed studies than are as yet available. Such studies may well modify the present classification in important respects.

CHAPTER 3

THE LENS

ANOMALIES IN SITE AND SHAPE

Congenital subluxation

CONGENITAL subluxation is always bilateral and this easily distinguishes the condition from traumatic subluxation of the lens. It may give no symptoms and escape detection with the undilated pupil. Iridodonesis and diplopia may, however, be present, and acute glaucoma may arise from pressure on the angle or from dislocation of the lens into the vitreous, or into the anterior chamber. It would appear that in well worked out pedigrees the affection is always dominant (Fig. 107).

Congenital subluxation with ectopic pupil

The position of the pupil is generally temporal, but may be in other directions. Within the same family, appearances are generally fairly similar, but occasionally the pupil anomaly may occur in one eye only. Some cases of partial aniridia may closely simulate the picture of subluxation of the lens with ectopic pupil. As with simple subluxation of the lens, complications are likely to develop.

In contrast to simple subluxation, inheritance would appear to be recessive (Fig. 108). There is one pedigree on record which suggests the possibility of dominant inheritance.

Delayed spontaneous subluxation of the lens (Vogt)

In some individuals subluxation of the lens, invariably downwards, occurs without apparent cause in adult life—anywhere between the ages of 20 and 70 years. A congenital abnormality of the upper part of the zonule is assumed; the symptoms and complications are not substantially different from those seen in the congenital variety of subluxation.

As yet there is only one pedigree of this affection (Fig. 109). This shows simple dominance.

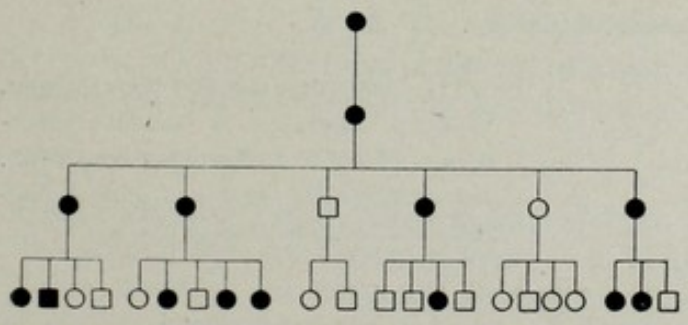


FIG. 107.—Congenital subluxation of lens. Pedigree showing dominant inheritance. (*After E. P. Cameron* (1926). *Brit. J. Ophthal.*, **10**, 384.)

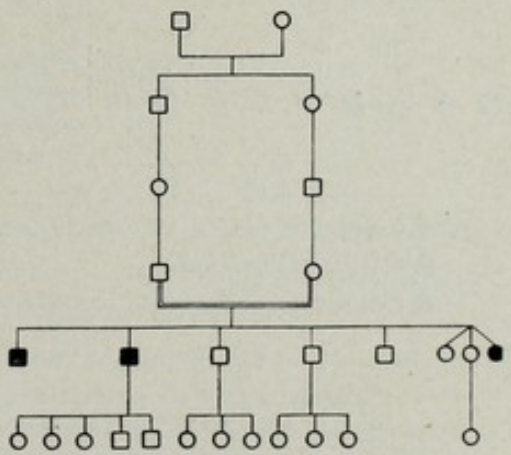


FIG. 108.—Congenital subluxation of lenses with ectopic pupils. Pedigree suggestive of recessive inheritance. (*After A. Franceschetti* (1927). *Klin. Mbl. Augenheilk.*, **78**, 351.)

Coloboma of the lens

This has been observed in typical colobomatous defects of the eye. It may, however, also occur as an aspect and possibly as a variant of subluxation of the lens (Fig. 110).

Microphakia or spherophakia

Occasionally the lens is both small and highly spherical; with a dilated pupil the margin of the lens can be seen clearly, and with the slit-lamp the zonule easily distinguished. A high degree of lenticular myopia is common, and subluxation and secondary glaucoma are not infrequent. Accommodation is affected.

The available evidence suggests that the affection is exclusively recessive (Fig. 111).

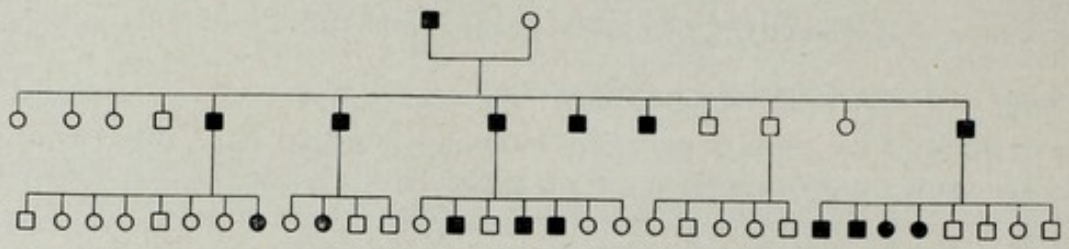
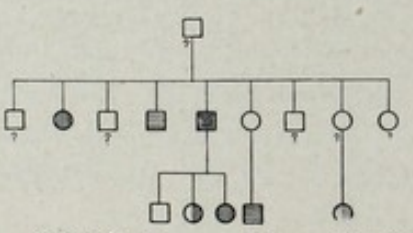


FIG. 109.—Delayed spontaneous dislocation of the lens. Pedigree showing dominant inheritance. (*After A. Vogt* (1931). *Lehrbuch und Atlas der Spaltlampenmikroskopie, 2te Aufl. Vol. II, p.* 751. *Berlin; Springer.*)



◑ ● Coloboma of lens, left sided and bilateral respectively.
■ Dislocation of lens.
■ Coloboma and dislocation of lens.

FIG. 110.—Coloboma of lens. Pedigree over two generations of a family some members of which showed coloboma or dislocation of the lens only, and others both defects. (*After F. C. Clark* (1919). *Arch. Ophthal.*, **48**, 475.)

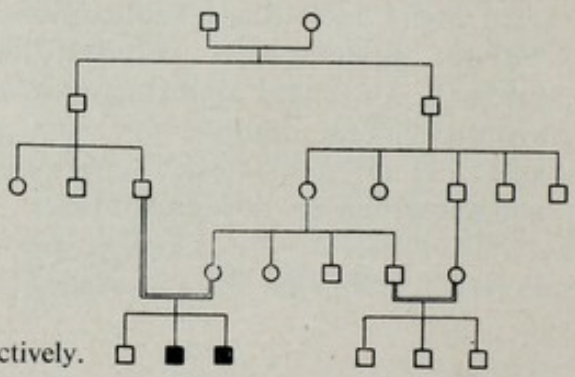


FIG. 111.—Microphakia and high myopia. Pedigree suggestive of recessive inheritance. (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 309. *The Hague; Nijhoff.*)

CATARACT

The architecture of the lens, as revealed by the slit-lamp, enables a clear distinction to be made between congenital and postnatal cataract. Only nuclear or capsular cataract can be congenital, whilst a cortical cataract must be postnatal.

Congenital Cataract

Cataract may occur as an aspect of other congenital and hereditary anomalies of the eye, as in microphthalmos, and aniridia, and presumably also in abiotrophic affections, as in some forms of retinitis pigmentosa. Frequently, however, cataract is the only or the outstanding, abnormality.

The older literature has established that hereditary congenital cataract is usually transmitted in a dominant manner, but it is difficult to apply these general findings to the individual types that have become clearly defined with the advent of slit-lamp microscopy. The fact that dominant inheritance is the one form of inheritance almost exclusively recorded for congenital cataract in general suggests that most of the individualized forms behave similarly. There is evidence that this is largely true. The possibility of a recessive mode of inheritance is clearly shown in Fig. 112.

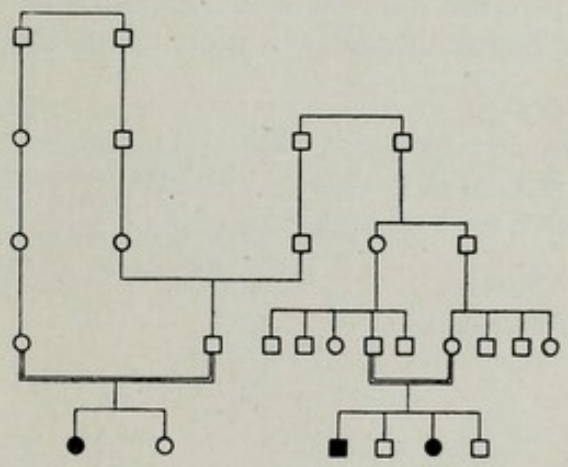


Fig. 112.—Congenital cataract. Pedigree showing recessive inheritance—apparently unusual in congenital cataract. (*After J. Saebø* (1949). *Brit. J. Ophthal.*, **33**, 601, *Figs.* 2 *and* 3.)

This is one of 17 consecutive pedigrees in which consanguinity could be established in 9 families, whilst in no family was there any evidence of dominance.

Total cataract

Total congenital cataract may be secondary to various anomalies in development. In the genetic forms inheritance appears to be dominant (Fig. 113).

These cataracts are frequently fibrous, and do not respond well to needling. The presence of nystagmus in many of the children may be secondary, but may also presumably arise from foveal hypoplasia—an assumption supported by the fact that the results of successful surgical treatment are not too good.

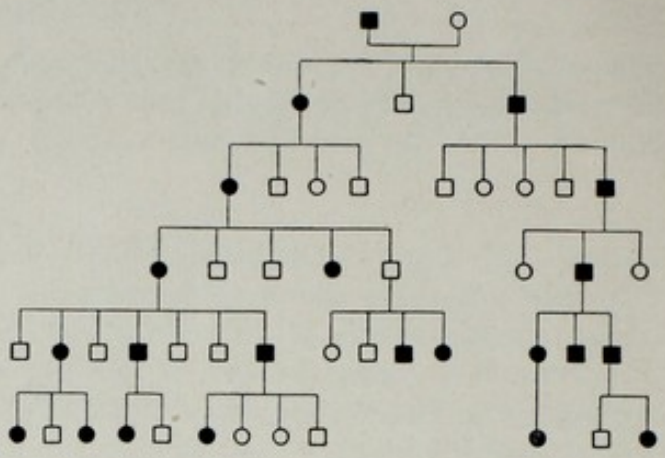


FIG. 113.—Total congenital cataract. Pedigree showing dominant inheritance. (*After M. Meissner* (1933). *Z. Augenheilk.*, **80**, 48.)

Anterior and posterior polar cataracts

Anterior polar cataracts may be minimal without any visual disturbance, or may take the variant form of pyramidal cataract with considerable visual disturbance; it may also be an aspect of other forms of congenital cataract, such as lamellar cataract. Adequate pedigrees of uncomplicated anterior polar cataract are not available. Fig. 114 suggests dominant inheritance.

In *posterior polar cataract*, too, there is a considerable range in manifestation. The evidence for dominant inheritance is more convincing (Fig. 115).

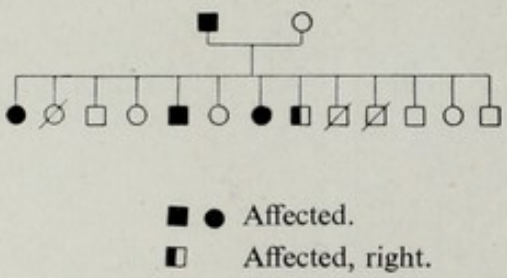


FIG. 114.—Anterior polar cataract. Pedigree suggestive of dominant inheritance. (*After A. Vogt* (1931). *Lehrbuch und Atlas der Spaltlampenmikroskopie*, 2*te Aufl. Vol.* 2, *p.* 402. *Berlin; Springer.*)

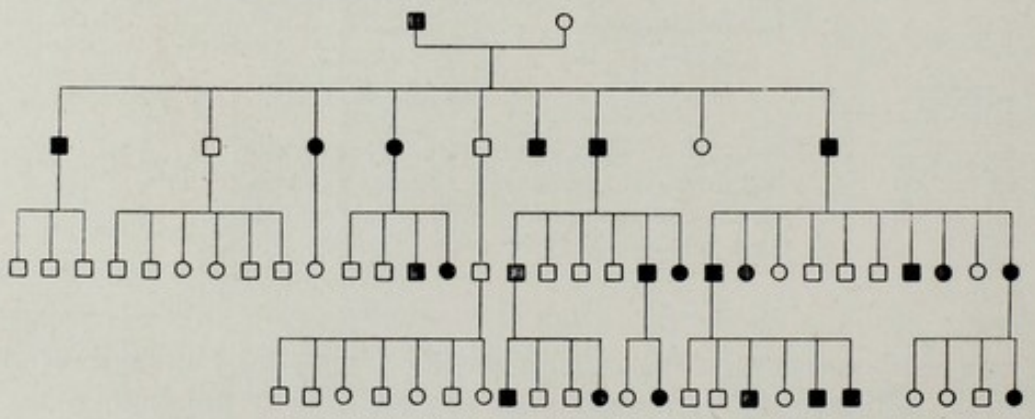


FIG. 115.—Posterior polar cataract. Pedigree showing dominant inheritance. (*After L. Ziegler and J. M. Griscom* (1915). *Trans. Amer. Ophthal. Soc.*, **14**, 356.)

Suture cataract

Anterior axial embryonal cataract hardly falls within the pathological range. It has been observed over four generations. Stellate cataract, involving both Y sutures, is also of no great clinical significance. It has been observed over two generations.

Lamellar cataract

This is a composite entity, and some forms at least are due to nutritional disturbances in the mother. Dominant inheritance has been observed repeatedly (Fig. 116 *a*); irregular dominance also occurs. A possibly recessive mode of inheritance is suggested by Fig. 116 *b*.

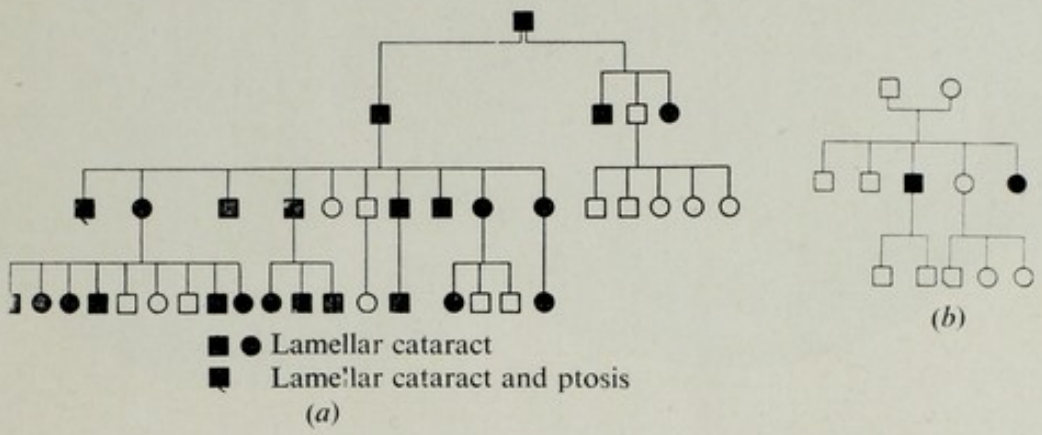


FIG. 116.—Lamellar cataract.

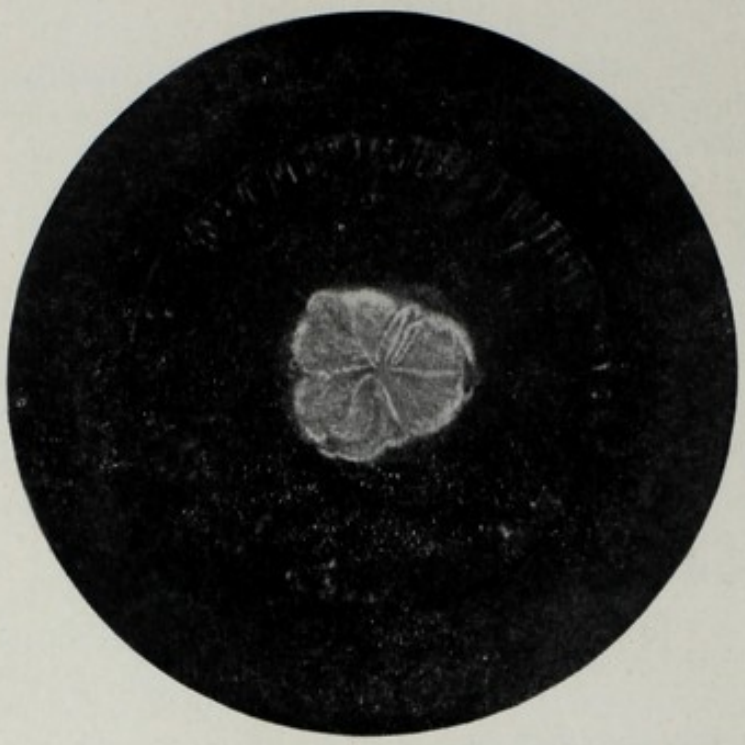
(*a*) Pedigree showing dominant inheritance. (*After E. Nettleship* (1909). *Trans. Ophthal. Soc. U.K.*, **29,** 188.)

(*b*) Pedigree suggestive of recessive inheritance. (*After J. Saebø* (1949). *Brit. J. Ophthal.*, **33,** 620.)

Central cataract

This is not always easy to distinguish from lamellar cataract, as many central cataracts have outlying riders. There are at least three distinct types. (1) In one form of central cataract the opacity is dense or patterned, with severe visual disturbances (Figs. 117 *a* and *b*). (2) There is a less severe form, which may be observable only by slit-lamp examination—the so-called cataracta pulverulenta, of which the Coppock cataract is a specially marked variety (Figs. 117 *c*, *d* and *e*). (3) Disc-shaped (ring) cataract. In this anomaly the lens is dumb-bell shaped with the centre being fibrous (Fig. 117 *f*). Clinically there is a central opacity at a distinctly deeper level than the rest of the surface of the lens, with other irregular opacities. With a small pupil the central opacity may fill the entire pupillary area; with a dilated pupil a peripheral clear zone can be seen. The lens as a whole is the shape of a ring-like life-belt. Subluxation of the lens is a frequent, and possibly a constant concomitant.

Inheritance of all these forms of central cataract would appear to be dominant (Figs. 118 *a*, *b*, *c* and *d*).



(*a*)

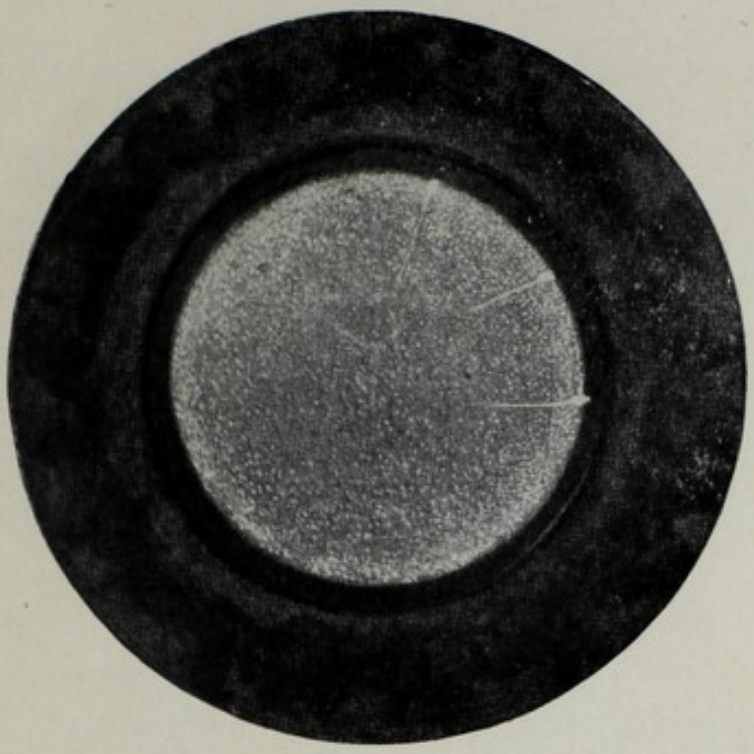
(*b*)

FIG. 117.—The clinical forms of central cataract. (*a–e after M. Bücklers* (1938). *In Handbuch der Erbkrankheiten, Ed. by A. Gütt. Vol.* 5, *p.* 125. *Leipzig; Georg Thieme.*)

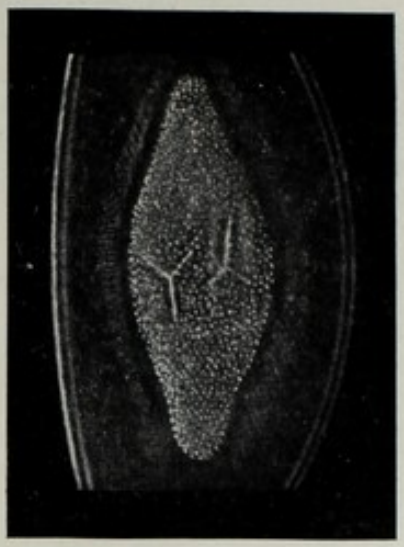
(*a*) and (*b*) Central cataract. Face view and optical section respectively in a woman aged 29 years.

(*c*)

FIG. 117 (*cont.*).—(*c*) Pulverulent cataract; moderately developed. Face view in a boy aged 12 years.



(*d*)



(*e*)

FIG. 117 (*cont.*).—(*d* and *e*) Pulverulent cataract. Face view and optical section respectively of a well-developed pulverulent cataract in a man aged 37 years.

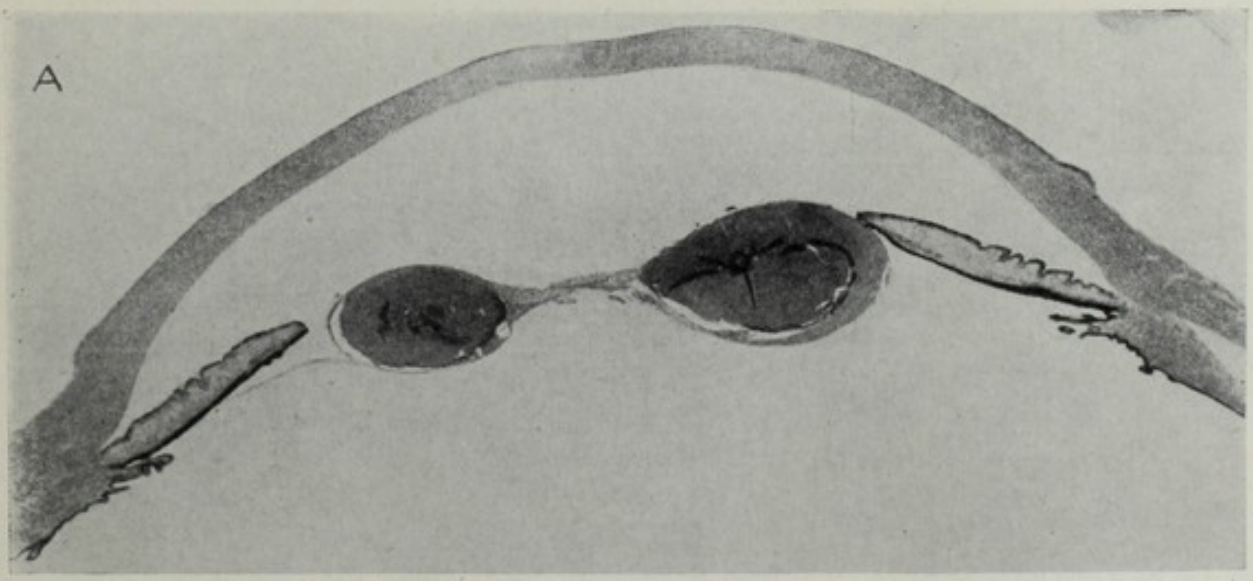


FIG. 117 (*cont.*).—(*f*) Disc-shaped cataract. Anatomical section of an eye in a girl aged 5 years. (*After E. S. Haro* (1946). *Arch. Ophthal.*, **36,** 89.)

Other forms of congenital cataract

Three forms of cataract show crystal formation (Fig. 119). They are apparently independent entities with the same dominant mode of inheritance. Figs. 120 *a*, *b* and *c*, show pedigrees of coralliform, spear-like, and floriform cataract respectively.

Lentoid formation.—Occasionally lens fibres may regenerate from capsular remains after needling operations. Genetically determined formation of multiple lentoid structures resulting in bizarre bodies in front of or behind the iris has been observed in a family with needled congenital cataract, "perinuclear" in type and dominant in inheritance (Fig. 121).

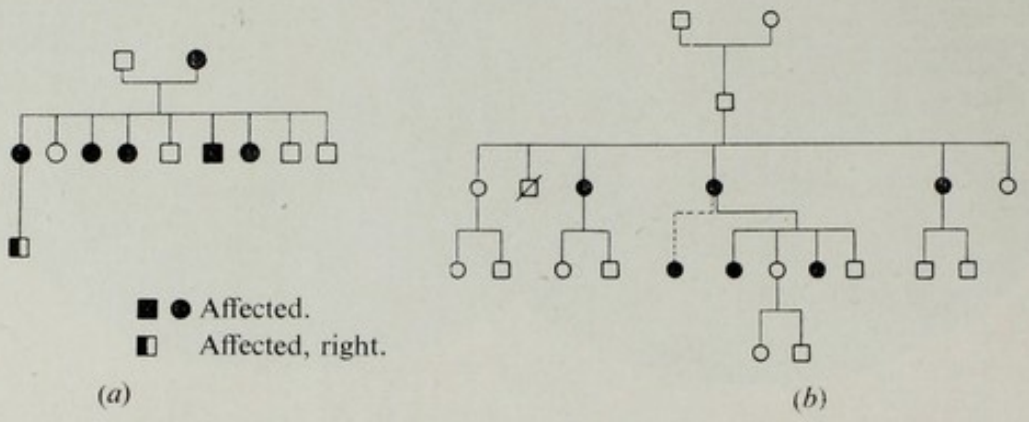


FIG. 118.—Central cataract. Pedigrees.

(*a*) Inheritance of central cataract over three generations. (*After M. Bücklers* (1938). *In Handbuch der Erbkrankheiten. Ed. by A. Gütt. Vol. 5, p. 125. Leipzig; Georg Thieme.*)

(*b*) Pulverulent cataract. Inheritance over two generations. (*After A. Vogt* (1931). *Lehrbuch und Atlas der Spaltlampenmikroskopie, 2te Aufl. Vol. II, p. 438. Berlin; Springer.*)

POSTNATAL CATARACT

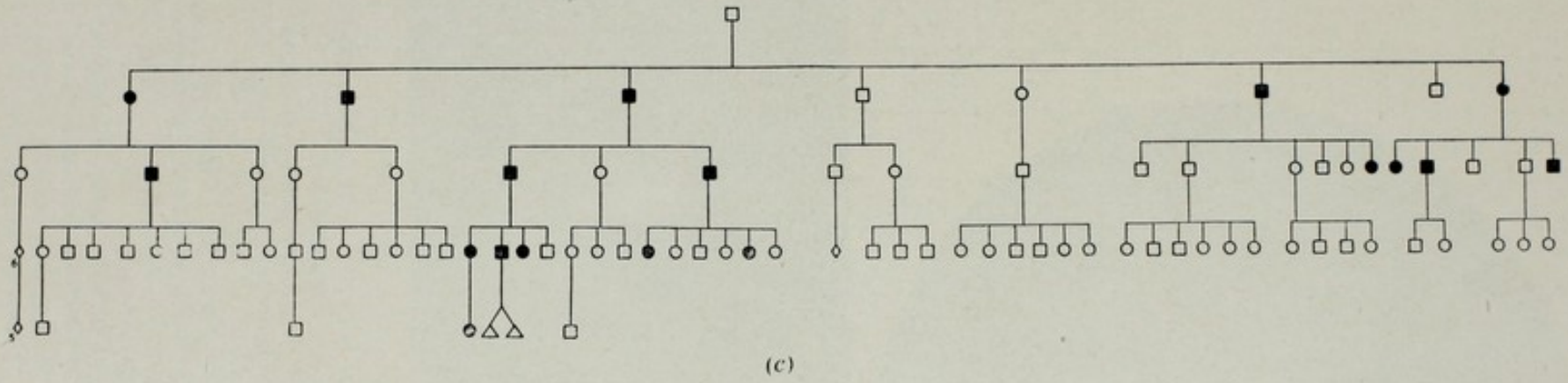
Evidence of the genetic character of postnatal cataract is readily available for the cataracts occurring early in life. For the primary cataract late in life there are no adequate pedigrees, no doubt owing to the difficulty in obtaining satisfactory information.

Coronary cataract

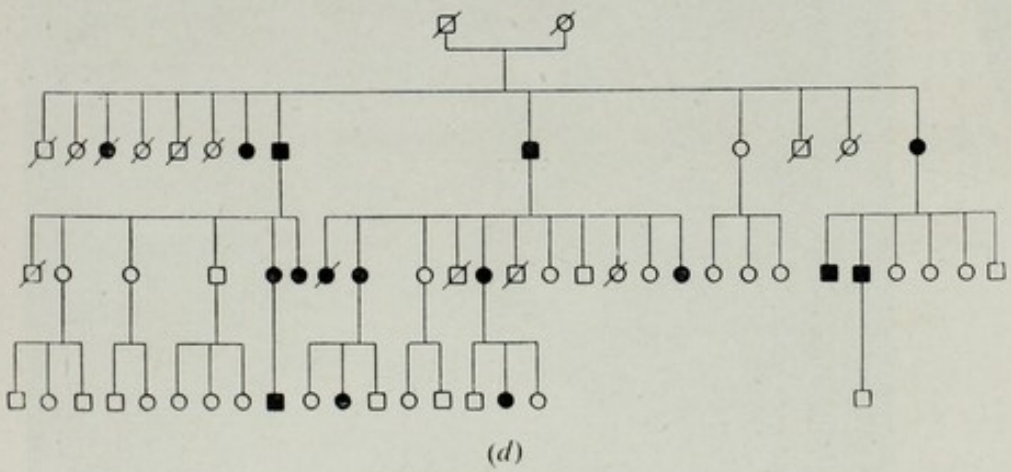
In this form, adequately described by the synonyms coronary cataract, blue dot cataract and punctate cataract, changes first appear at about puberty and are confined to the periphery of the lens, covered by the contracted pupil. As these changes are common, their inheritance must be held as unproved until there is more information than is at present available.

Pre-senile cataract of the adult nucleus

This is a well defined type with dominant inheritance. Fig. 122 *a* illustrates a pedigree in which coronary cataract, nuclear and perinuclear opacities occurred in the same family. Whether these were interchangeable, or an accidental

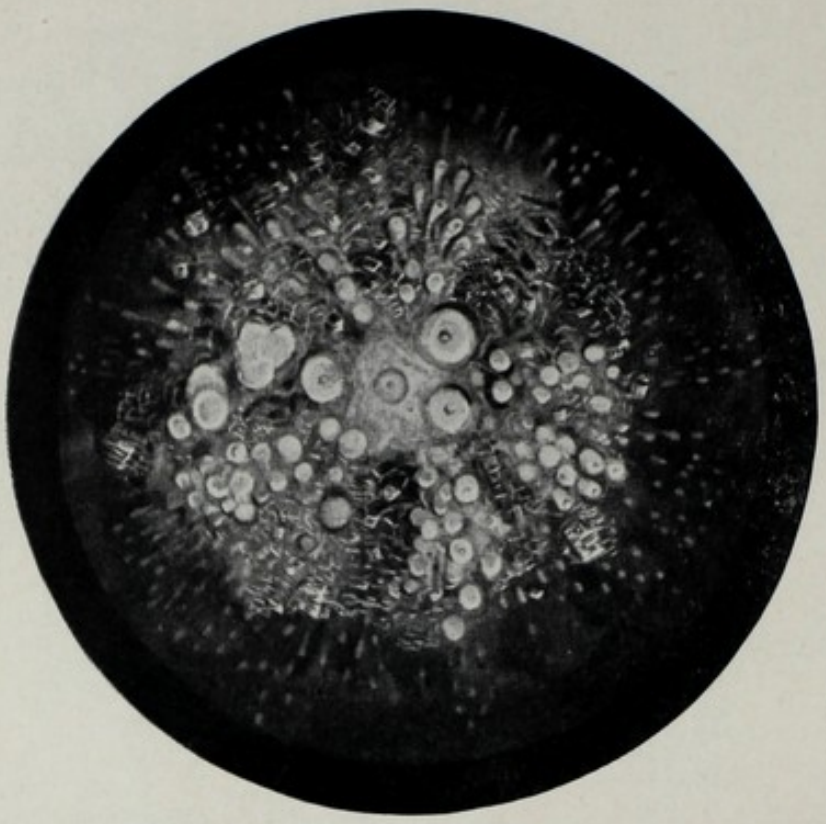


(*c*)



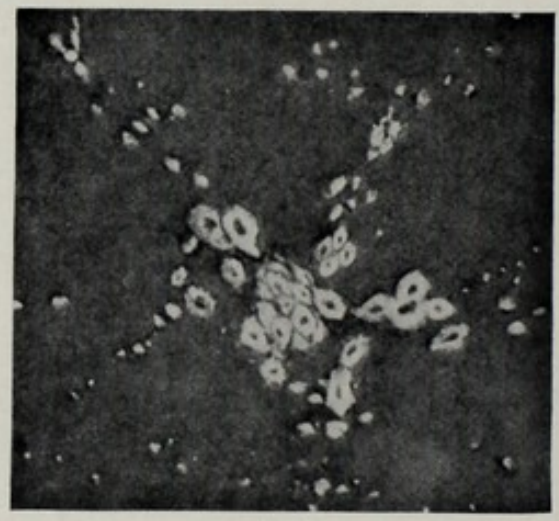
(*d*)

FIG. 118 (*cont.*).—(*c*) "Coppock" cataract. Dominant inheritance. (*After E. Nettleship and G. M. Ogilvie* (1906). *Trans. Ophthal. Soc. U.K.*, **26,** 191.)
(*d*) Disc-shaped "ring" cataract. Dominant inheritance. (*After E. S. Haro* (1946). *Arch. Ophthal.*, **36,** 82.)



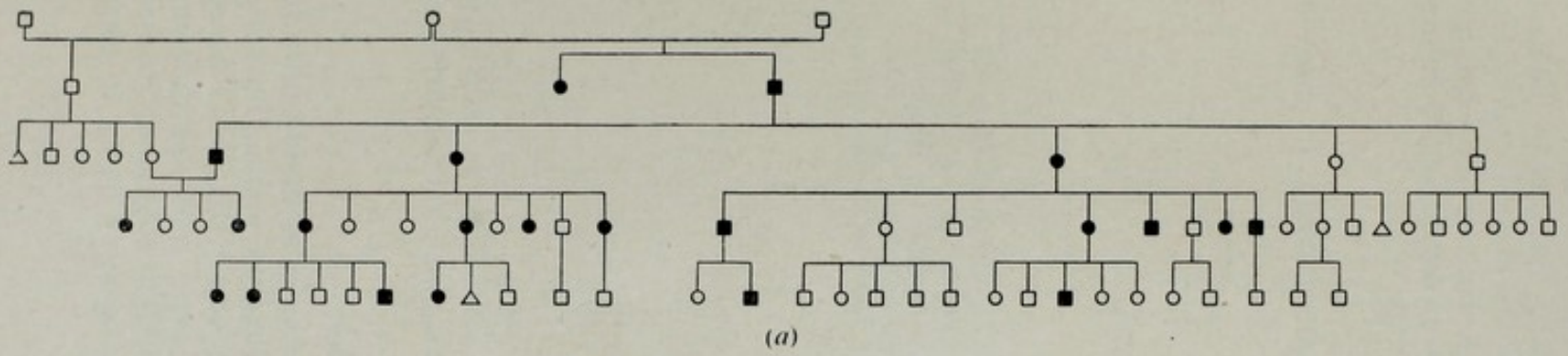
(*a*)

(*b*)

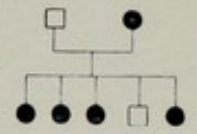


(*c*)

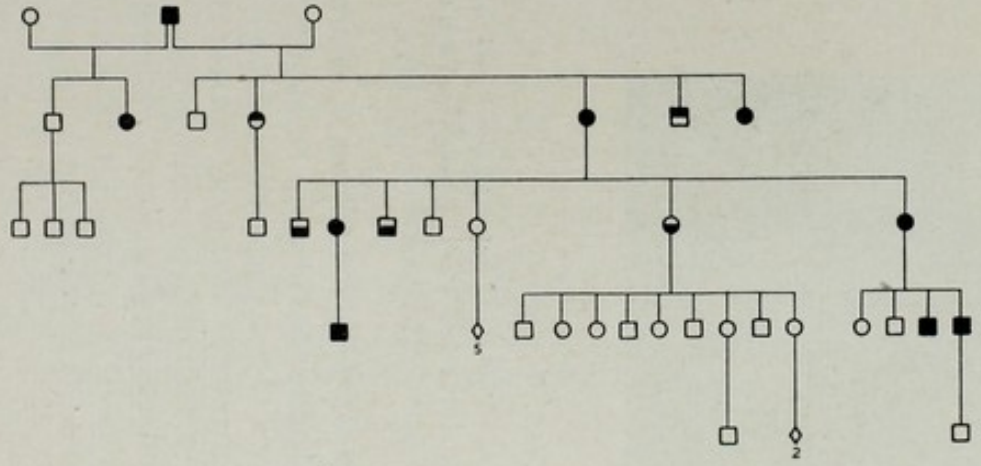
FIG. 119.—Other forms of congenital cataract. Clinical appearances.
(*a*) Coralliform. (*After M. Bücklers* (1938). *In Handbuch der Erbkrankheiten. Ed. by A. Gütt. Vol.* 5, *p.* 119. *Leipzig; Georg Thieme.*)
(*b*) Spear-like. (*After A. Vogt* (1931). *Lehrbuch und Atlas der Spaltlampenmikroskopie, 2te Aufl. Vol. II, Plate* 134. *Berlin; Springer.*)
(*c*) Floriform. (*After M. Bücklers* (1931). *In Handbuch der Erbkrankheiten. Ed. by A. Gütt, Vol.* 5 *p.* 122. *Leipzig; Thieme.*)



(*a*)



(*c*)



Spear cataract.

Incipient senile cataract.

Coronary cataract.

(*b*)

FIG. 120.—Other forms of congenital cataract. Pedigrees.

(*a*) Coralliform cataract. Pedigree showing dominant inheritance. (*After E. Nettleship* (1909). *Trans. Ophthal. Soc. U.K.*, **29**, 188.)

(*b*) Spear-like cataract. Pedigree showing dominant inheritance. (*After A. Romer* (1926). *Arch. Klaus. Stift. Vererb.*, **2**, 207. *Quoted by A. Franceschetti* (1930). *In Kurzes Handbuch der Ophthalmologie. Ed. by F. Schieck and A. Brückner, Vol. I, p.* 748. *Berlin; Springer.*)

(*c*) Floriform cataract. Pedigree showing inheritance over two generations. (*After E. Koby* (1923). *Arch. d'Ophtal.*, **40**, 492.)

combination of two genetic anomalies within the same family, is not known. Fig. 122 *b* illustrates dominant inheritance of changes in the cortex.

A pedigree in which different members were affected by opacities in the axial region of the anterior adult nucleus, and others by opacities in the foetal nucleus is shown in Fig. 122 *c*. The pedigree of a family in which some members had pre-senile cataract and others total cataract present at birth or developing in infancy is recorded in Fig. 122 *d*.

Pre-senile posterior cortical cataract

This has been observed in several members of the same sibship. Its mode of inheritance is uncertain.

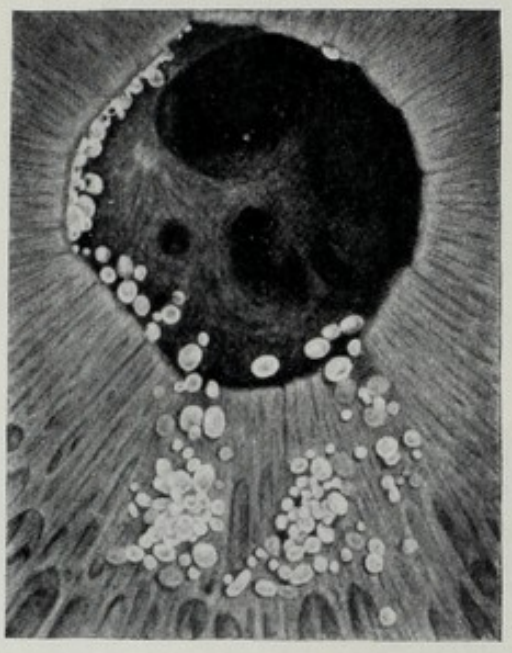


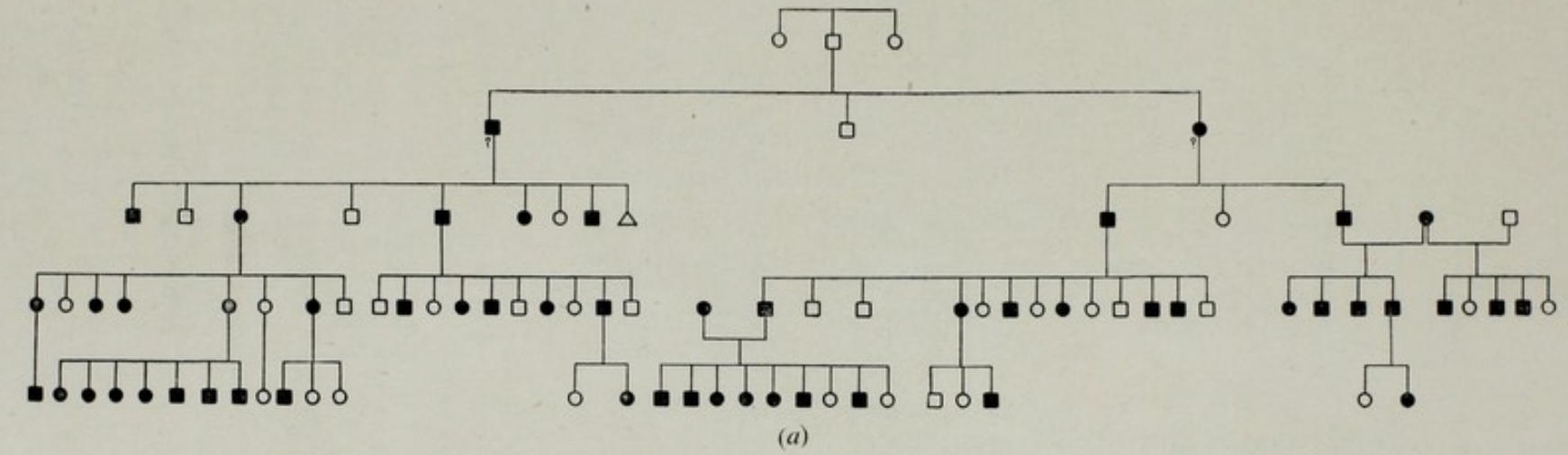
FIG. 121.—Lentoid formation. Observed in different members of a family after needling for congenital dominant "perinuclear" cataract. (*After F. Riedl* (1939). *Klin. Mbl. Augenheilk.*, **103**, 169.)

Senile cataract

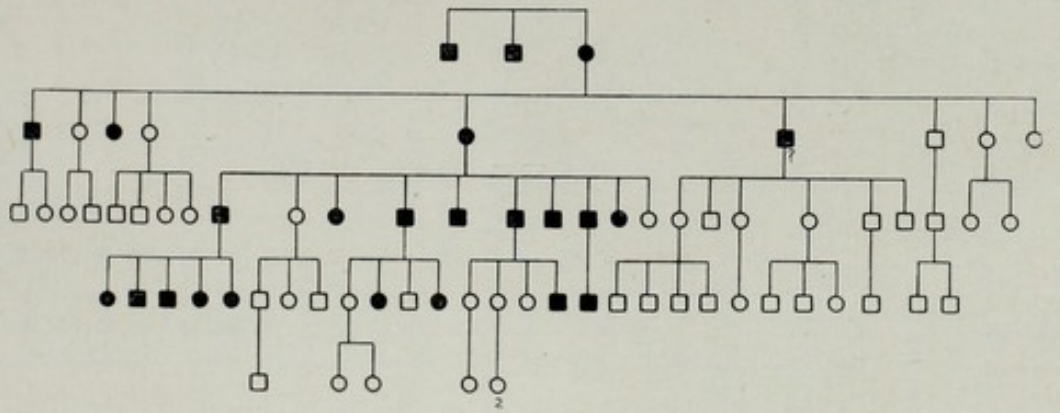
The best evidence as yet available as to the genetic basis of senile cataract is derived from the work of Vogt on the frequency of senile cataract in both members of a pair of uni-ovular twins late in life.

Relationship of the different forms of cataract to each other

Early pedigrees recorded by Nettleship, and such pedigrees as those shown in Figs. 122 *a*, *c* and *d*, suggest that whilst it is true that within given families the same type of cataract tends to appear, different clinical types tend to overlap. On balance it is unlikely that different members of such families carry genes for different types of cataract. Further clinical observations are required to determine whether the manifestation of a gene for cataract may vary considerably owing to total genic balance, or environmental factors.



(*a*)

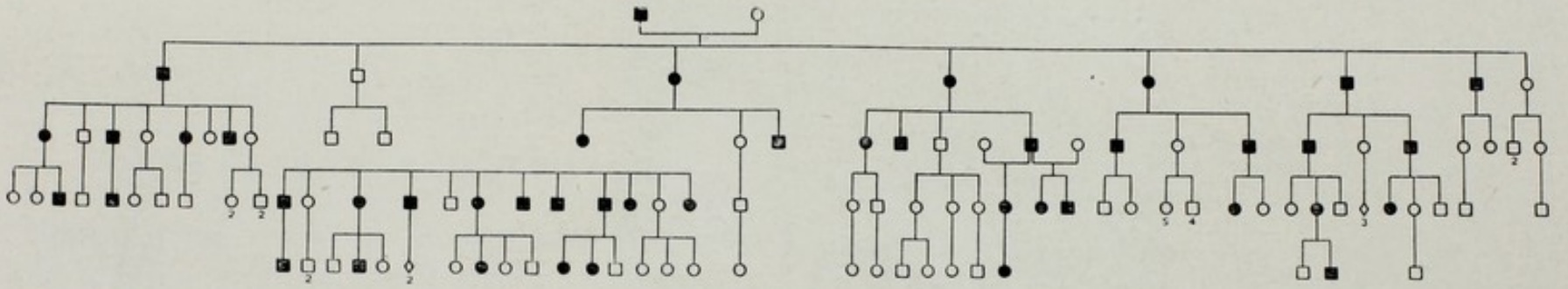


(*b*)

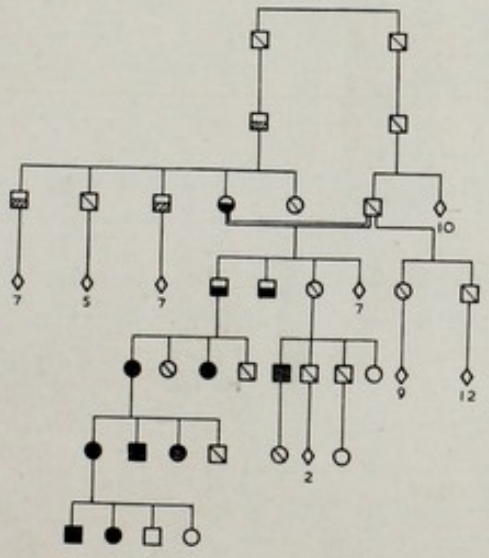
FIG. 122.—Pre-senile cataract of the adult nucleus.

(*a*) Pedigree of family in which coronary cataract, nuclear and perinuclear opacities occurred in different members. (*After K. T. A. Halbertsma* (1928). *Klin. Mbl. Augenheilk.*, **80,** 794.)

(*b*) Dominant inheritance of presenile cortical changes. (*After I. L. Johnstone* (1947). *Brit. J. Ophthal.*, **31,** 385.)



(*c*)



(*d*)

FIG. 122 (*cont.*).—(*c*) Pedigree of a family in which opacities of either adult or foetal nucleus occurred. (*After F. C. Lutman and J. V. Neel* (1945). *Arch. Ophthal.*, **33**, 341.)
(*d*) Pedigree of a family in which pre-senile cataract occurred in some members and total congenital or infantile cataract in others. (*After Th. Redl* (1949). *Klin. Mbl. Augenheilk*, **114**, 24.)

- Reputed affected with pre-senile cataract.
- Observed as affected with pre-senile cataract.
- Observed as affected with congenital or infantile total cataract.
- Reputed normal.
- Observed as normal.

CHAPTER 4

THE UVEAL TRACT

THE IRIS

A LARGE number of anomalies of the iris of no pathological significance are recognized. They appear to have a genetic basis, and some, at any rate, are aspects of the wider issue of colour of the iris. It is possible that some of the more marked physiological variants, such as some forms of hypoplasia of the mesodermal layers are abortive forms of aniridia. Clinical and genetic evidence is, however, as yet fragmentary.

ANIRIDIA

The concept of aniridia must be extended to include atypical iris colobomas as well as fully formed aniridia. Even this latter type shows considerable variations, as a variable amount of tissue may be present at the root. That atypical iris colobomas are part of the picture of aniridia has been brought out by a number of pedigrees. Fig. 123 *a* is illustrative, showing three fully developed cases of aniridia in a family in which nine others showed extensive atypical colobomas. In other pedigrees, aplasia of the anterior mesodermal layer of the iris and small peripheral defects in the posterior layer, or polycoria appear as a variant of complete aniridia (Fig. 123 *b*).

Aniridia is inherited in a dominant manner. Such pedigrees as are recorded to show irregular dominance may well have contained cases of rudimentary atypical colobomas.

Aniridia is generally associated with other extensive anomalies, the most significant being aplasia of the macula. The lack of macular development has been brought forward to support the view that aniridia is determined by failure in ectodermal development. The occasionally associated buphthalmos is probably a secondary feature consequent on maldevelopment of the angle.

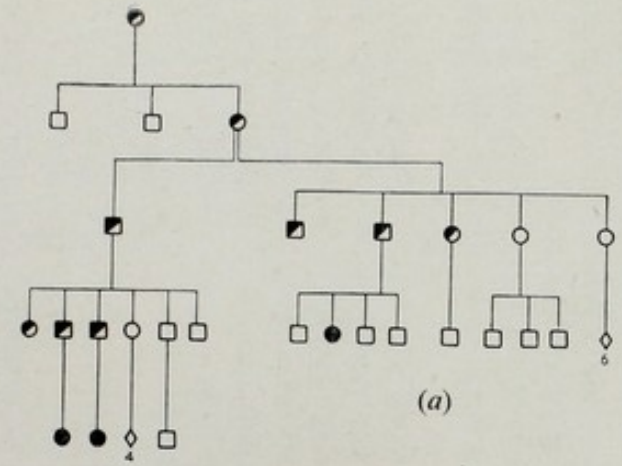
It is possible that there is also a recessive form of aniridia. Judging by Japanese pedigrees, it would appear that these recessive cases, in contrast to the dominant cases, have a fully developed macula.

There is also the possibility that some forms of atypical coloboma of the iris are independent of aniridia. Fig. 124 shows the pedigree of a family in which atypical colobomas, unilateral, bilateral or merely minimally developed, occurred. Assuming that such pedigrees illustrate a variety of atypical colobomas independent of aniridia, a possible embryological explanation would lie with the non-closure of secondary fissures in the optic vesicle. Such a reading would also facilitate an understanding of isolated cases without a genetic basis.

OTHER ANOMALIES

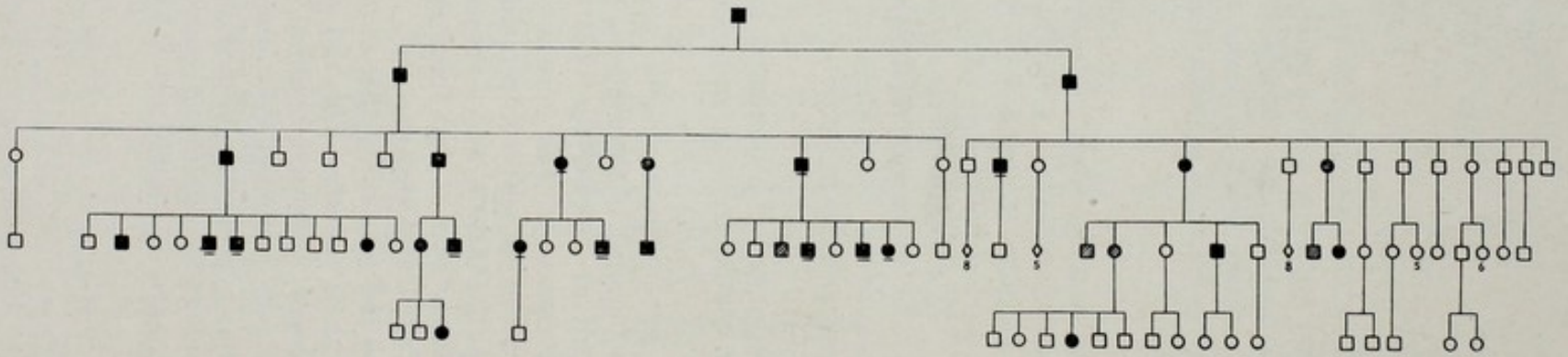
Pupil anomalies

Polycoria.—This has been observed over two generations, probably as an aspect of hypoplasia of the mesodermal layers, or of atypical coloboma of the iris or of



(*a*)

● Aniridia.
◩ ◐ Atypical coloboma of iris.



■ ● Aniridia.
■ ● Aniridia with ectopia lentis.
▨ ◎ Variable degrees of hypoplasia of iris, including polycoria and atypical colobomas.

(*b*)

FIG. 123.—Aniridia. Two pedigrees illustrative of dominant inheritance and of the range of anomalies in families with aniridia.
(*a*) Pedigree showing the occurrence of atypical coloboma of the iris in some members of the family and aniridia in others. (*After S. Snell* (1908). *Trans. Ophthal. Soc. U.K.*, **28,** 149.)
(*b*) Pedigree showing different members of a family with aniridia, aniridia with ectopia lentis, and variable degrees of hypoplasia of iris including polycoria and atypical colobomas. (*After P. H. Beattie* (1947). *Brit. J. Ophthal.*, **31,** 649.)

aniridia. When such defects were observed towards the periphery of the iris they have been designated as congenital iridodialysis; in one family they have been recorded over three generations.

Ectopic pupils.—This anomaly is generally seen in association with congenital dislocation of the lens. A dominant mode of inheritance for uncomplicated ectopic pupil has been recorded by Waardenburg (Fig. 125). The extent of the deformity varies considerably in different members of the family. Ectopic pupils may be vertical in shape, simulating a cat's pupil. It would appear that there may also be a recessive variety.

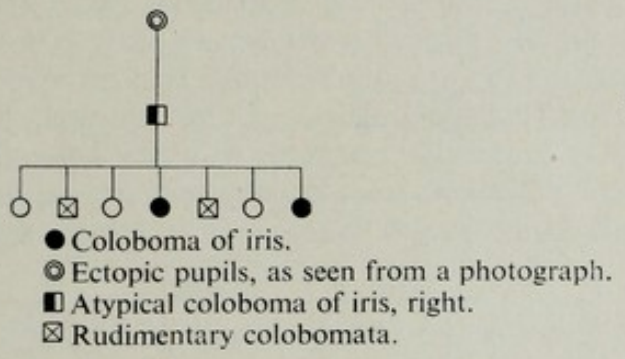


FIG. 124.—Atypical coloboma of the iris. Pedigree showing the range of defects—some minimal—observed in one family. (*After K. T. A. Halbertsma* (1928). *Klin. Mbl. Augenheilk.*, **80**, 794.)

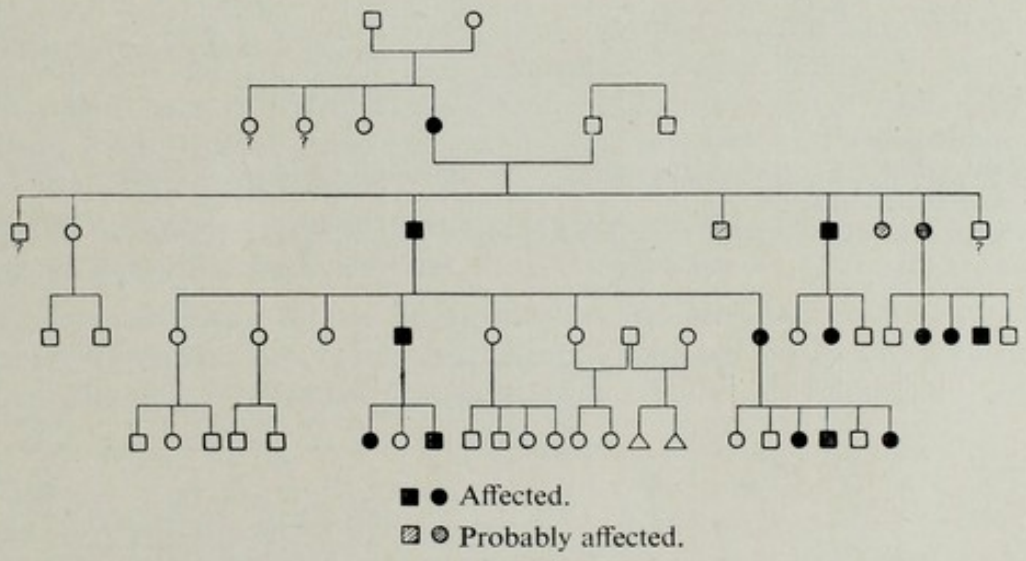


FIG. 125.—Ectopic pupils. Pedigree showing dominant inheritance. (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 196. *The Hague; Nijhoff.*)

Anomalies in pupil reactions

Non-reacting pupils.—Miotic non-reacting pupils have been observed by Waardenburg in a family with recessive total ophthalmoplegia. The anomaly has also been seen in two sibships without external ophthalmoplegia. Non-reacting pupils without miosis have also been observed in a sibship.

Anomalies in iris structure

Hyperplasia.—Hyperplasia of the mesodermal layers, giving the appearance of doubling of the mesodermal part of the iris, has been recorded as dominant in inheritance.

Hyperplasia of the ectodermal layer of the iris, taking the form of flocculi iridis, has been observed in a presumably dominant mode of inheritance (Fig. 126 *a*).

Hypoplasia.—Hypoplasia of the ectodermal layers is probably part of the aniridia complex. It was observed in an eye which showed a translucent iris with intact stroma, the fellow eye showing aniridia.

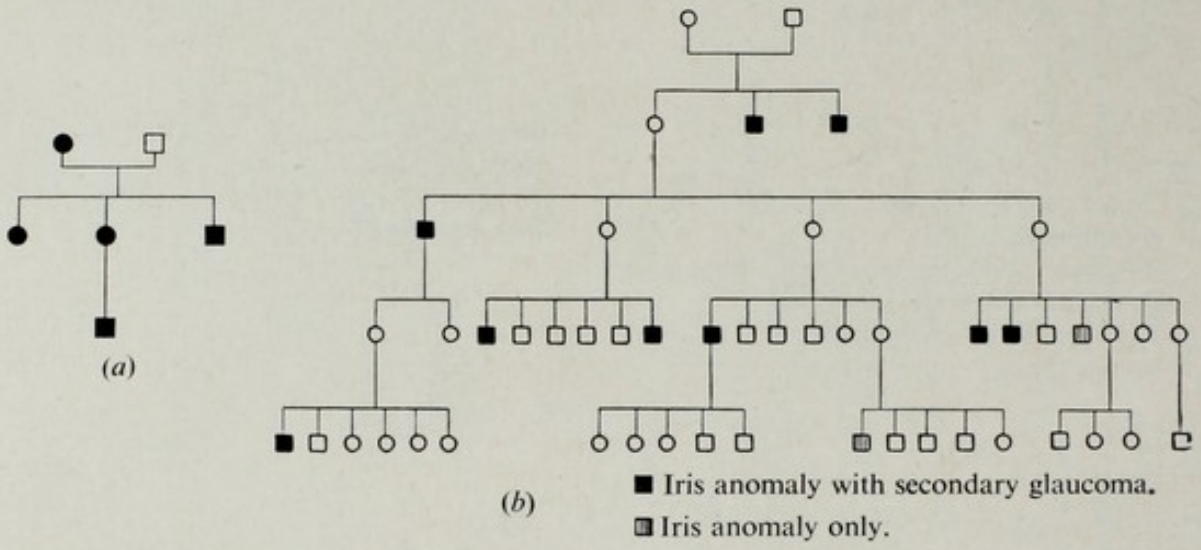


FIG. 126.—Anomalies in iris structure.
(*a*) Pedigree showing dominant inheritance of flocculi iridis (*After R. E. Fröhlich* (1924). *Arch. Rass.—u. Ges-Biol.*, **15**, 249.)
(*b*) Pedigree showing sex-linked inheritance of hypoplasia of the iris complicated by secondary glaucoma. (*After S. G. Frank-Kamenetzki* (1925). *Klin. Mbl. Augenheilk.*, **74**, 133.)

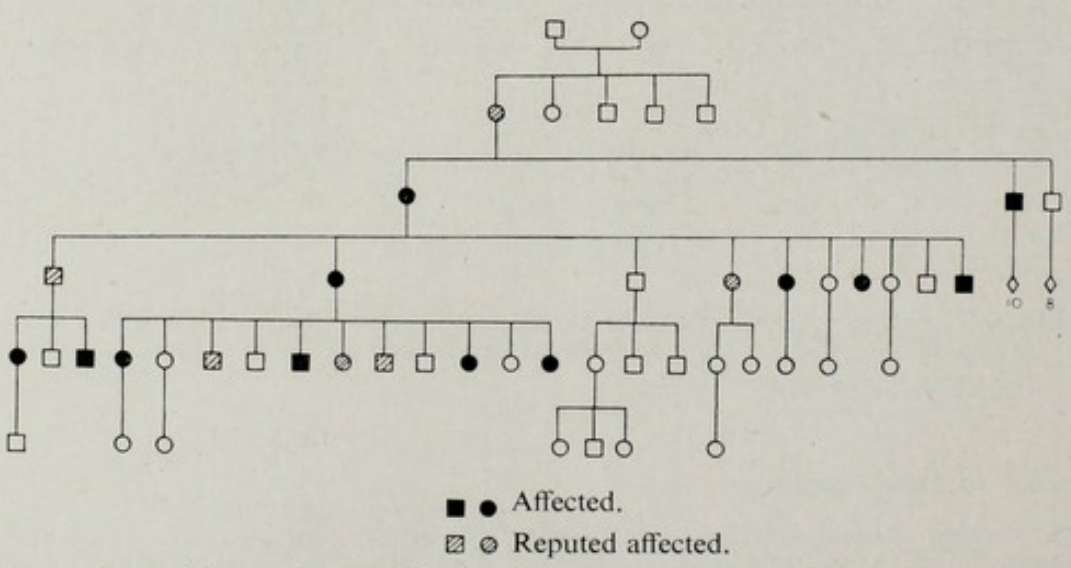


FIG. 127.—Widespread anomalies in the anterior segment of the eye. Pedigree of a family in which a wide range of anterior segment anomalies was inherited in a dominant manner. (*After H. F. Falls* (1949). *Amer. J. Ophthal.*, **32**, 41.)

Hypoplasia of the mesodermal layers has also been observed as dominantly inherited. In one pedigree in which recessive sex-linkage was seen, secondary glaucoma appeared frequently. (Fig. 126 *b*).

Persistent pupillary membrane.—This has been observed as a hereditary anomaly in cases showing other and extensive congenital anomalies of the eye. It may also appear as an isolated hereditary anomaly.

Heterochromia of the iris.—This has been observed as a dominant feature. It has also been noted in uniovular twins.

Widespread anomalies in the anterior segment of the eye

Fig. 127 is a pedigree of a family with dominant inheritance of widespread anomalies throughout the anterior segment of the eye. The iris anomalies ranged over corectopia, pseudo-polycoria, slit pupil, iridotasis, dyscoria and ectopic pupil. The cornea in some members of the pedigree showed opacities and embryotoxon; the lens was ectopic, and occasionally anterior polar cataract was present. Buphthalmos was also observed. Members of this family differed considerably in the degree of involvement they showed. (These cases may well have been extreme examples of embryotoxon discussed on page 102.)

THE CHOROID

Congenital Defects

Atypical choroidal coloboma

As distinct from anomalies seen with typical colobomatous defects involving the choroid, there is the relatively rare atypical choroidal coloboma—atypical in position rather than in form. These atypical colobomas have been observed in association with macular colobomas, and there is on record a brief note which suggests that a child with an atypical iris and choroidal coloboma had a healthy mother, but a maternal grandmother who was likewise affected.

Macular coloboma

That many congenital central fundus defects are inflammatory reactions rather than maldevelopments can hardly be doubted. Some of the lesions seen in toxoplasmosis simulate pigmented colobomas closely. A developmental basis is

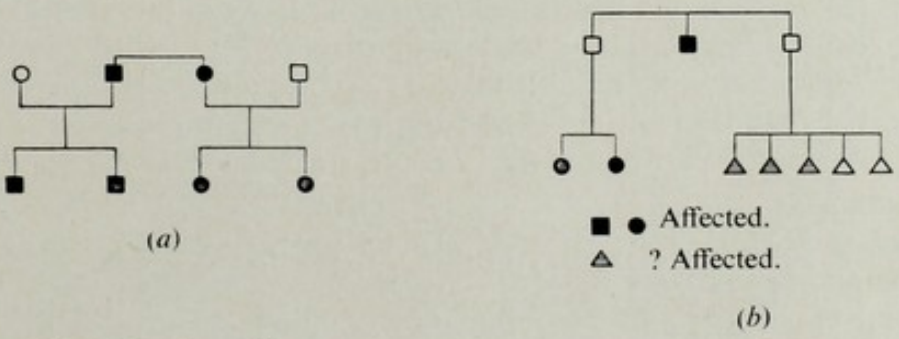


Fig. 128.—Macular coloboma.
(*a*) Pedigree suggestive of dominant inheritance. (*After W. Clausen* (1921 *and* 1928). *Klin. Mbl. Augenheilk.*, **67**, 116, *and* **81**, 385.)
(*b*) Pedigree suggestive of irregular dominance. (*After K. Schott* (1921). *Klin. Mbl. Augenheilk.*, **67**, 415.)

likewise obvious from the occasional association of macular coloboma with both typical and atypical choroidal coloboma, or colobomatous defects of the disc with microphthalmos. Pigmented macular colobomas have been observed in a uniovular twin, and several times over two generations (Fig. 128 *a*), and once over three generations (in a family in whom there was present associated apical dystrophy of hands and feet). Irregular dominance is suggested by the pedigree shown in Fig. 128 *b*.

Congenital choroideremia

It is possible that there is a congenital form of choroideremia characterized by total absence of choroidal vessels with tufts of venae vorticosae breaking the uniform glistening white scleral reflex. Nothing is known of the inheritance of this presumed congenital total choroideremia.

Abiotrophic Lesions

Choroideremia

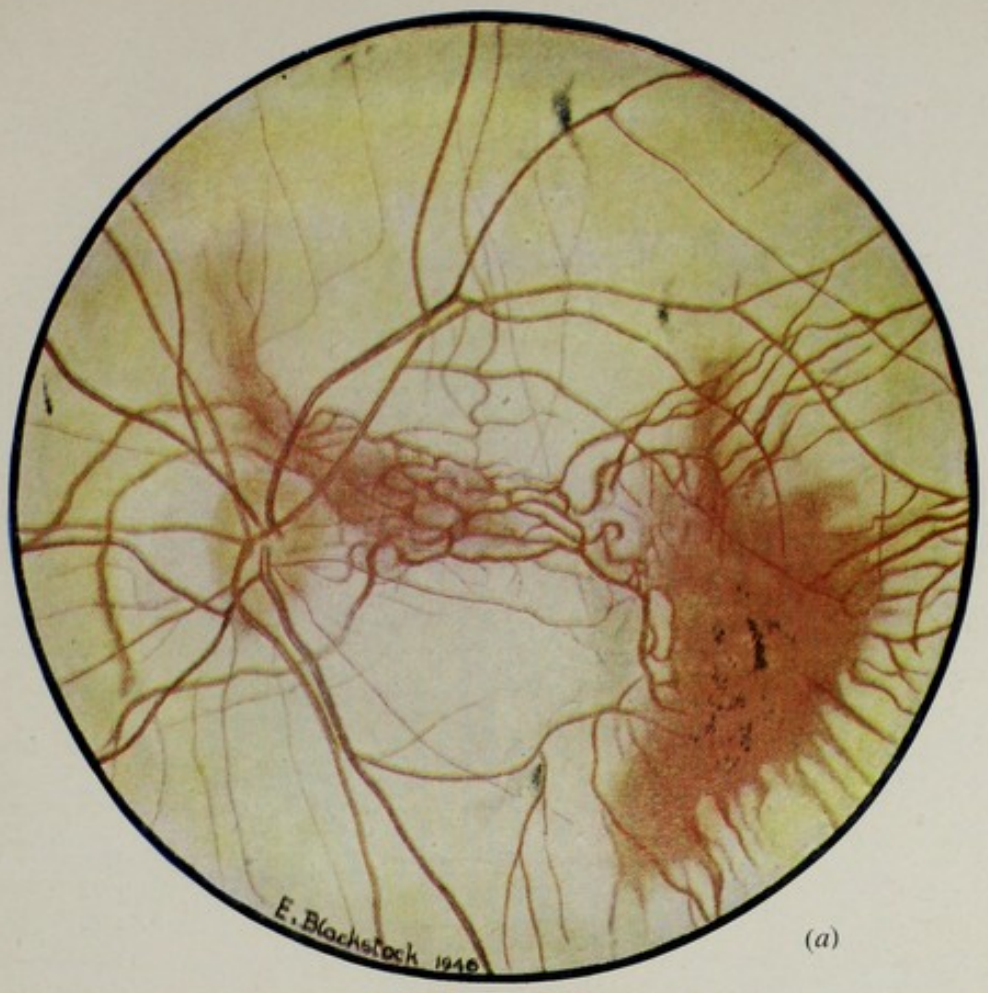
Choroideremia was considered by Leber to be an acquired and not a congenital affection, and subsequent workers have tended to regard it as a variant of "atypical retinitis pigmentosa". The affection, confined almost entirely to men, is actually abiotrophic in character and inherited in an intermediate sex-linked manner so that it is seen in women in a mild form ("atypical retinitis pigmentosa") and in men in the severe and fully developed form. Fig. 129 shows the fundi of a man fully affected and his sister slightly affected. Vision was, of course, grossly affected in the case of the man; in the case of the sister vision was full and all visual functions normal. The intermediate sex-linked mode of inheritance is clearly shown by Fig. 130. Affected men have heterozygous daughters. These daughters have no, or minimal, visual troubles, but their fundi betray the heterozygous state. Such daughters pass on their one pathogenic gene to some of their daughters, whilst the theoretical expectation that 50 per cent of their sons are fully affected is borne out.

The clinical picture, as elaborated by McCulloch, may briefly be summed up in the following terms:

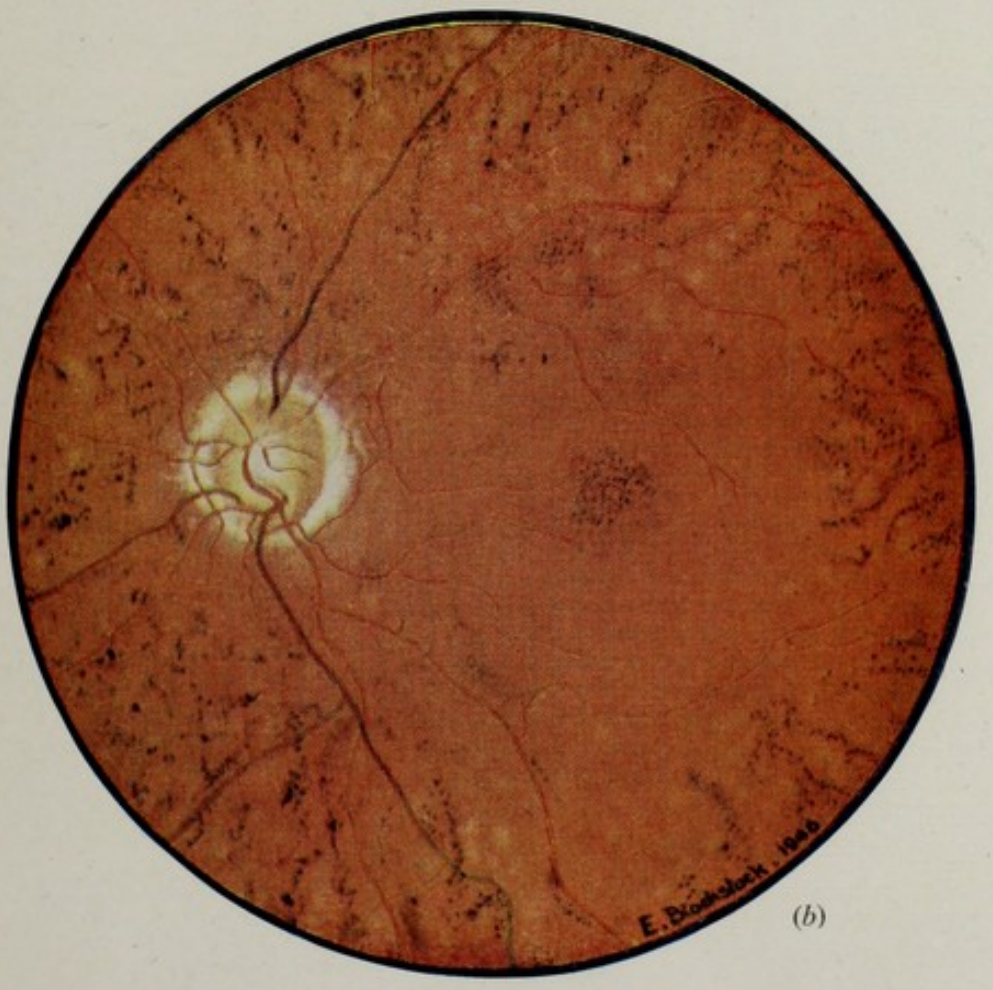
Subjective signs.—All patients have good vision until the onset of disease. This may occur early in childhood, but generally between the ages of 10 and 30 years. The earliest symptoms are those of progressive night-blindness, which ultimately becomes absolute. Field defects, at first essentially peripheral, and subsequently in the nature of a ring scotoma develop. Central vision is not affected until some 35 years or more after the onset of the affection.

Ophthalmoscopic changes.—The earliest changes are irregular pigmentary disturbances, such as is seen in female heterozygotes. Atrophic changes develop subsequently and appear earliest at the equator, where exposure of brilliant white sclera occurs. (This was also observed in one of the women.) Scleral exposure coincides with the development of night-blindness. The retinal vessels remain normal and show no sheathing. The disc does not become atrophic until late.

Other ocular changes.—During the course of the affection myopia tends to develop. Colour vision is apparently normal and lens opacities are uncommon.



(*a*)



(*b*)

FIG. 129.—Choroideremia. Fundus appearances. (*After C. McCulloch and R. J. P. McCulloch* (1948). *Trans. Amer. Acad. Oto-laryng.*, **53,** 160.)

(*a*) Fully developed choroideremia as seen in an affected man aged 40 years.

(*b*) Appearances in a sister aged 30 years—a heterozygous woman.

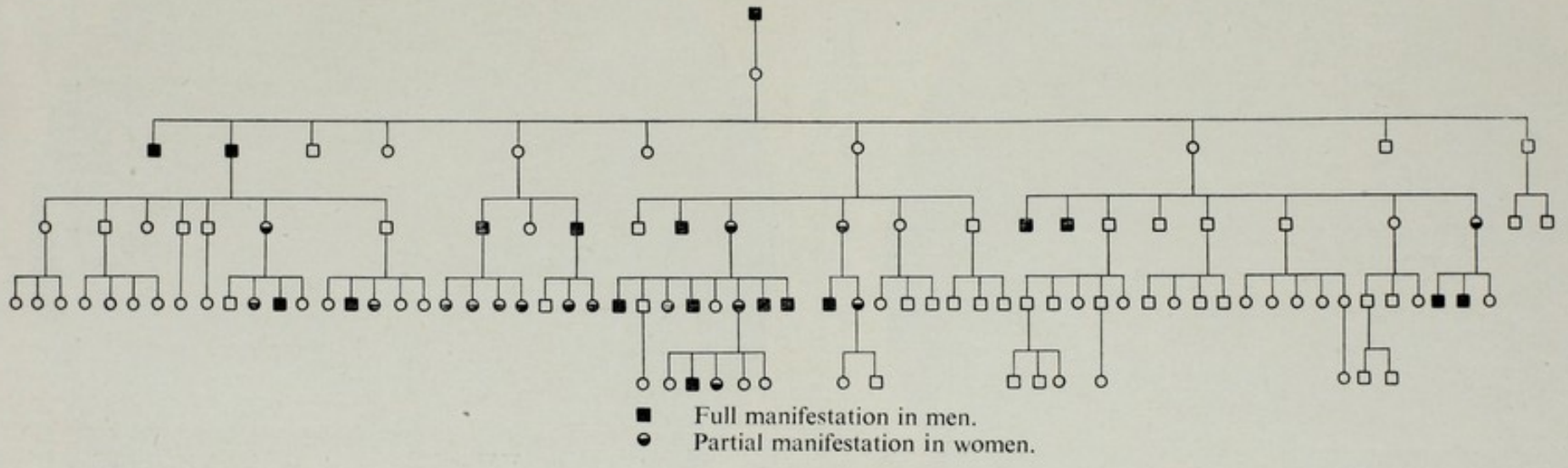


FIG. 130.—Choroideremia. Pedigree showing intermediate sex-linked inheritance. (*After C. McCulloch and R. J. P. McCulloch* (1948). *Trans. Amer. Acad. Oto-laryng.*, **53**, 160.)

Relationship to retinitis pigmentosa.—There is no evidence of retinitis pigmentosa in other members of the family.

Choroidal sclerosis

At least two well-defined clinical types can be distinguished: in one the whole of the choroid is involved (generalized choroidal sclerosis) and in the other the lesion is confined to the central area (central choroidal sclerosis).

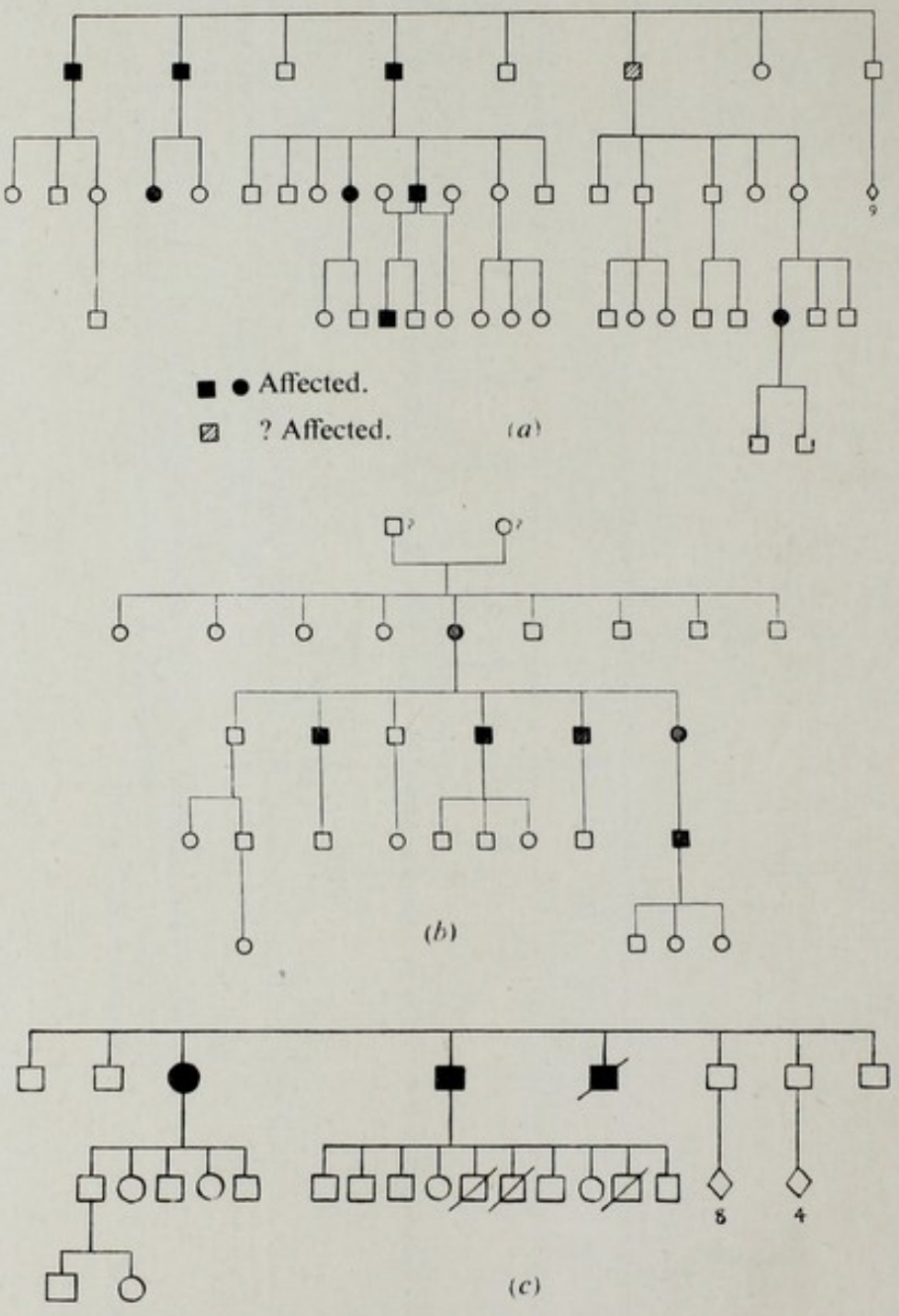


FIG. 131.—Generalized choroidal sclerosis. Pedigree charts.
(*a*) Dominant inheritance. (*After A. Tobler-Berg* (1937). *Eine Familie mit dominanter Vererbung von atypischer Retinitis pigmentosa. Geneva; Thesis.*)
(*b*) Dominant inheritance. (*After J. François* (1949). *Ophthalmologica*, **118,** 14.)
(*c*) Possibly recessive inheritance. (*After A. Sorsby* (1939). *Brit. J. Ophthal.*, **23,** 433.)

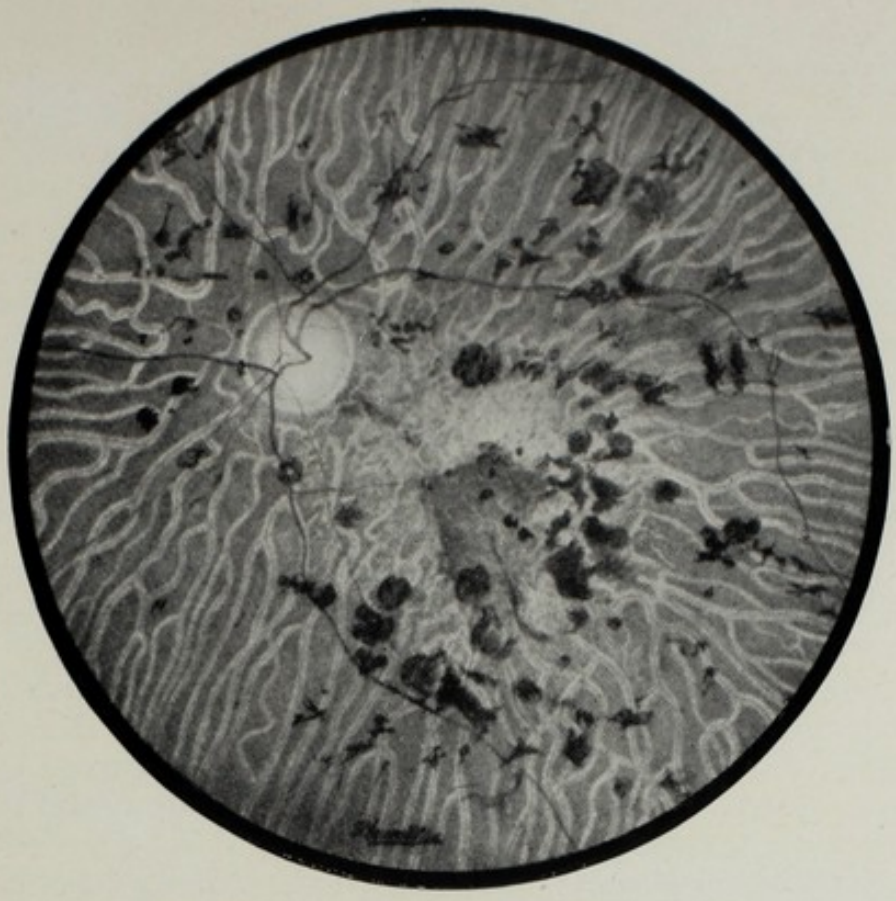


FIG. 132.—Generalized choroidal sclerosis. Fundus appearances. (*After A. Sorsby* (1939). *Brit. J. Ophthal.*, **23**, 433.)

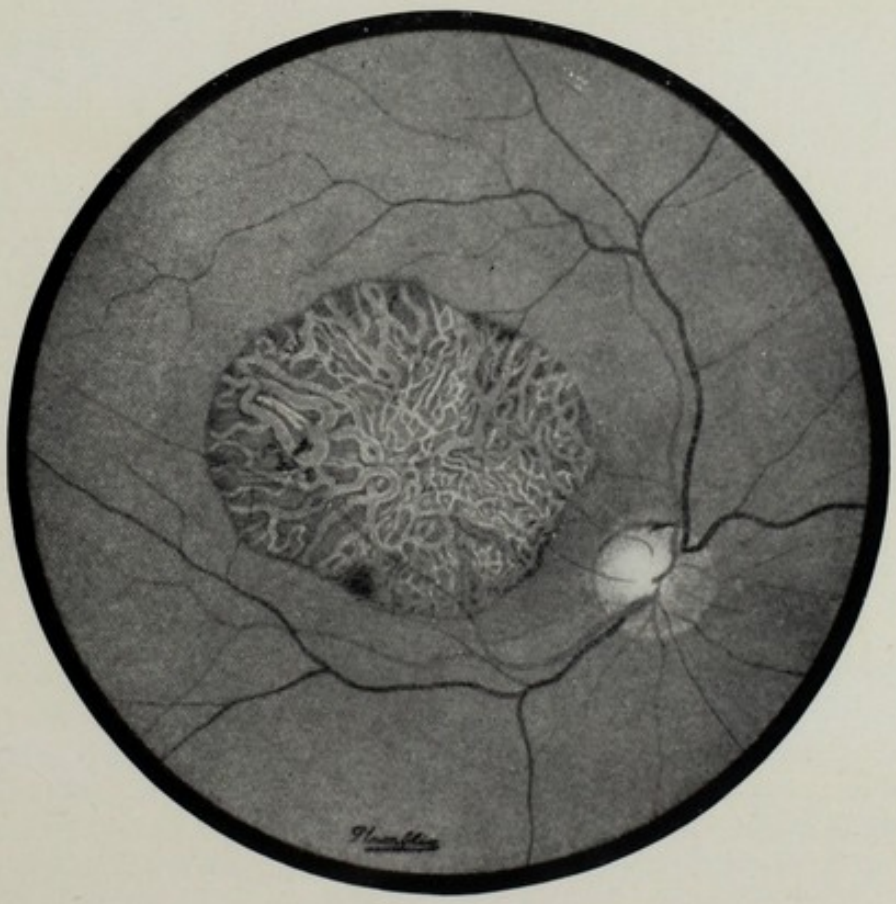


FIG. 133.—Central choroidal sclerosis. Fundus appearances. (*After A. Sorsby* (1939). *Brit. J. Ophthal.*, **23**, 433.)

To face page 148

Generalized choroidal sclerosis.—Many of the records in the literature on "atypical retinitis pigmentosa" are probably examples of generalized choroidal sclerosis. The outstanding feature is the conversion of the choroidal vessels into white streaks, with pigmentary disturbances reminiscent of retinitis pigmentosa as subsidiary aspects. The fundus appearances are shown in Fig. 132. A dominant mode of inheritance in atypical retinitis pigmentosa (obviously choroidal sclerosis from the illustrations) is shown in Fig. 131 *a*, and another dominant pedigree is shown in Fig. 131 *b*. A possible recessive mode of inheritance is suggested by the occurrence in a brother and sister without any suggestive history in antecedents, or affection in the descendants (Fig. 131 *c*).

Central choroidal sclerosis.—This affection has passed in the literature under the name of central senile areolar choroidal atrophy. Fig. 133 shows the ophthalmoscopic appearance in a man aged 63 years. Fig. 134 shows the pedigree, which lends no support to any reading of dominant inheritance. Likewise there is no definite support for recessive inheritance in the absence of a history of consanguinity. Similar lesions were also observed in two sisters, aged 71 and 73 years, once again with no suggestive history in the antecedents, no affected descendants, and no history of consanguinity. The affection, though observed in elderly patients, appears to develop at about the age of 20 years judging by the history obtained in these four cases. The earliest changes, as available from a record on one of the affected sisters well before middle age, were those of "central chorioretinitis".

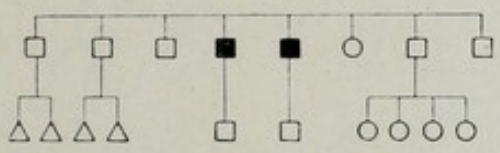


FIG. 134.—Central choroidal sclerosis. Pedigree chart of the two brothers whose fundi are shown in Fig. 133. (*After A. Sorsby* (1939). *Brit. J. Ophthal.*, **23**, 433.)

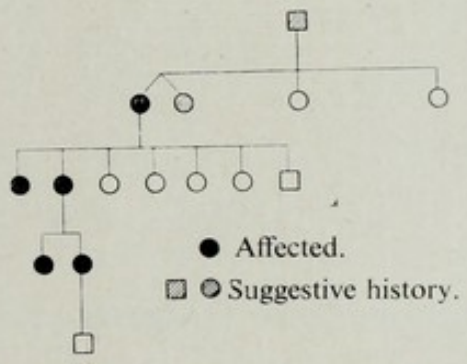


FIG. 135.—Sarcoma of choroid. Pedigree showing dominant inheritance. (*After R. C. Davenport* (1927). *Brit. J. Ophthal.*, **11**, 443.)

Peripapillary choroidal sclerosis.—From the one case on record when the affection was observed in two sisters with a negative family history, nothing definite can be said as to the mode of inheritance.

The clinical course of the different varieties of choroidal sclerosis is as yet undetermined owing to the paucity of studies on the subject. The fully developed picture in which choroidal vessels are converted into white streaks corresponds to the exceptionally severe and rare cases of retinal arteriosclerosis, which would run on to obliteration of the retinal vessels. Whilst the early stages of retinal arteriosclerosis are well known, those of choroidal sclerosis are not. It is possible that

the earliest sign of choroidal sclerosis is the development of white dots lying deeply in the retina. Subsequently slaty-blue choroidal haemorrhages appear. When these absorb there is exposure of the sclerosed choroidal vessels. At a later stage still it is possible that these sclerosed vessels become absorbed, exposing the sclera.

To what extent choroidal sclerosis may be a secondary feature in primary retinal dystrophy is as yet undetermined.

Neoplasms

Sarcoma of the choroid

This has been observed once in two brothers, once over two generations, and twice over three generations. Fig. 135 gives the most fully worked out pedigree.

CHAPTER 5

THE RETINA

CONGENITAL ANOMALIES

Opaque Nerve Fibres

Inheritance over two generations has been recorded by a number of observers (Fig. 136). With the available data autosomal dominance would appear to be the most likely mode of transmission.

Many ocular and general abnormalities have been recorded in association with opaque nerve fibres. These are probably accidental findings, for there is nothing in the hereditary cases to support any other reading. The relationship of extensive

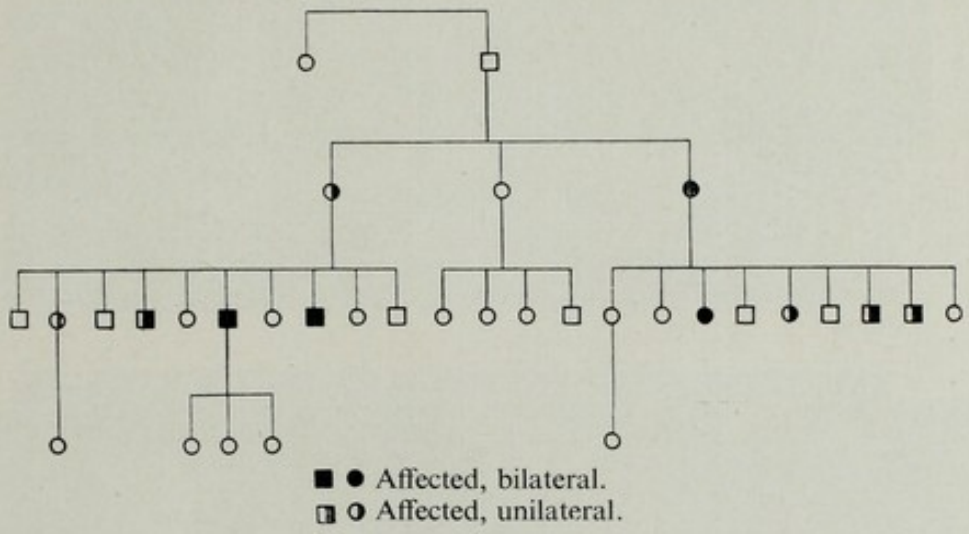


Fig. 136.—Opaque nerve fibres. Pedigree over two generations. (*After E. A. Cockayne* (1936). *Brit. J. Ophthal.*, **20**, 569.)

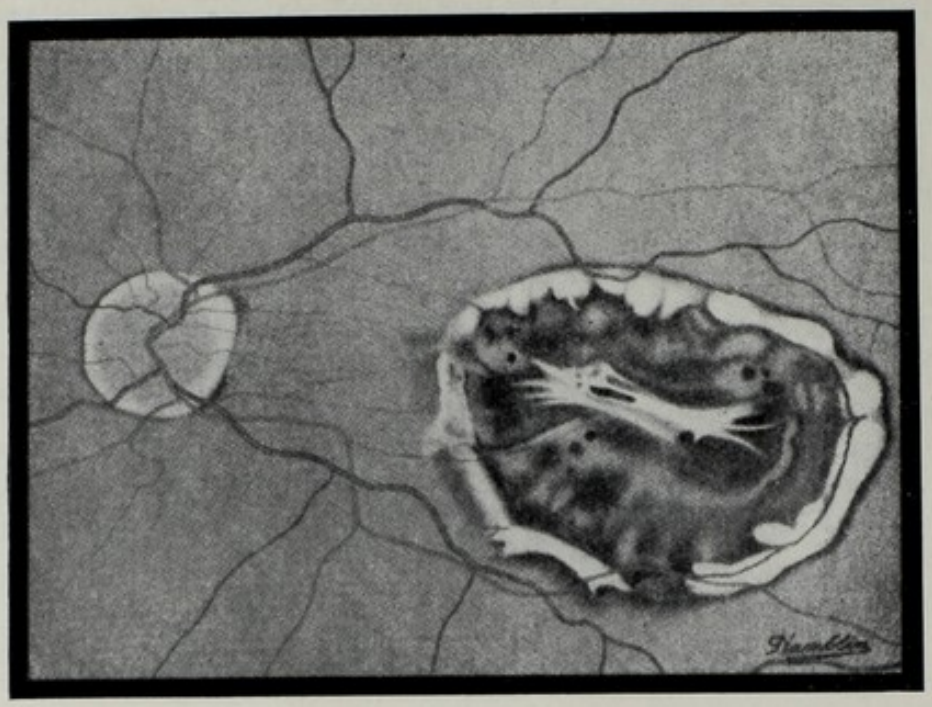
opaque nerve fibres with high myopia, frequently unilateral, is more definite, but also requires further clarification.

Congenital Macular Defects

Four clinical types of lesions at the macula, proved or presumed to be congenital in origin, are recognized. Their clinical appearances are shown in Fig. 137 *a–g*. Of these, coloboma of the macula (Fig. 137 *a*) is known pathologically as primarily a choroidal defect, and as such is discussed under congenital defects of the choroid (*see* p. 145). The remaining three affections have not been observed at birth, but their stationary course and their occurrence in children suggest that they are in fact congenital. That they are retinal in character, rather than choroidal, is also an assumption.

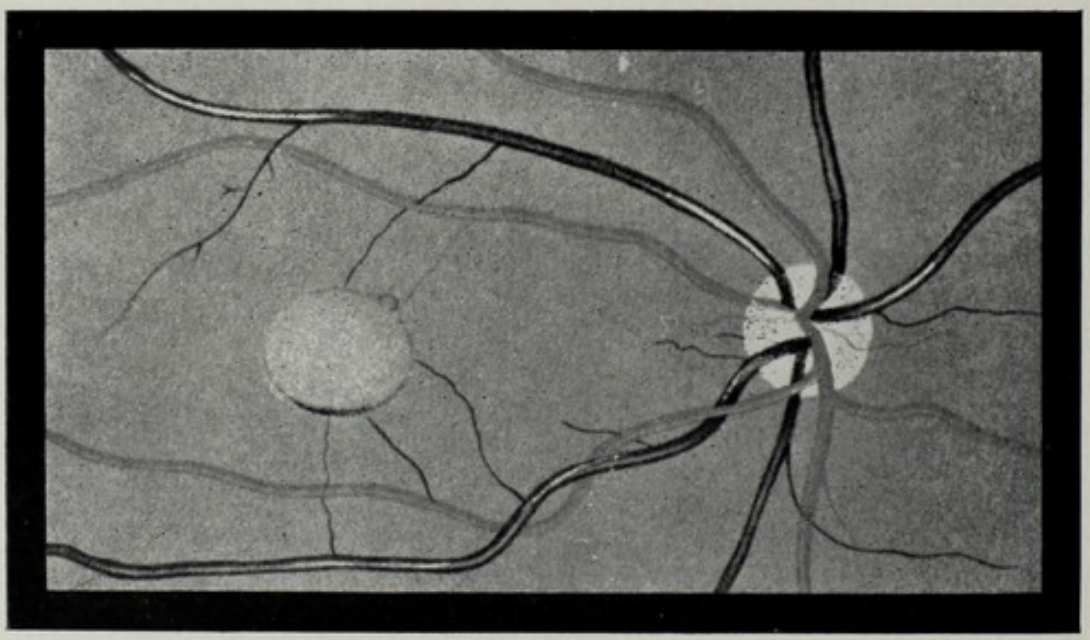
Congenital macular and paramacular atrophic defect (*Best's disease*) (Figs. 137 *b*, *c* and *d*)

For many years regarded as an irregularly dominant affection confined exclusively to the particular family studied by Best and his successors, other cases are



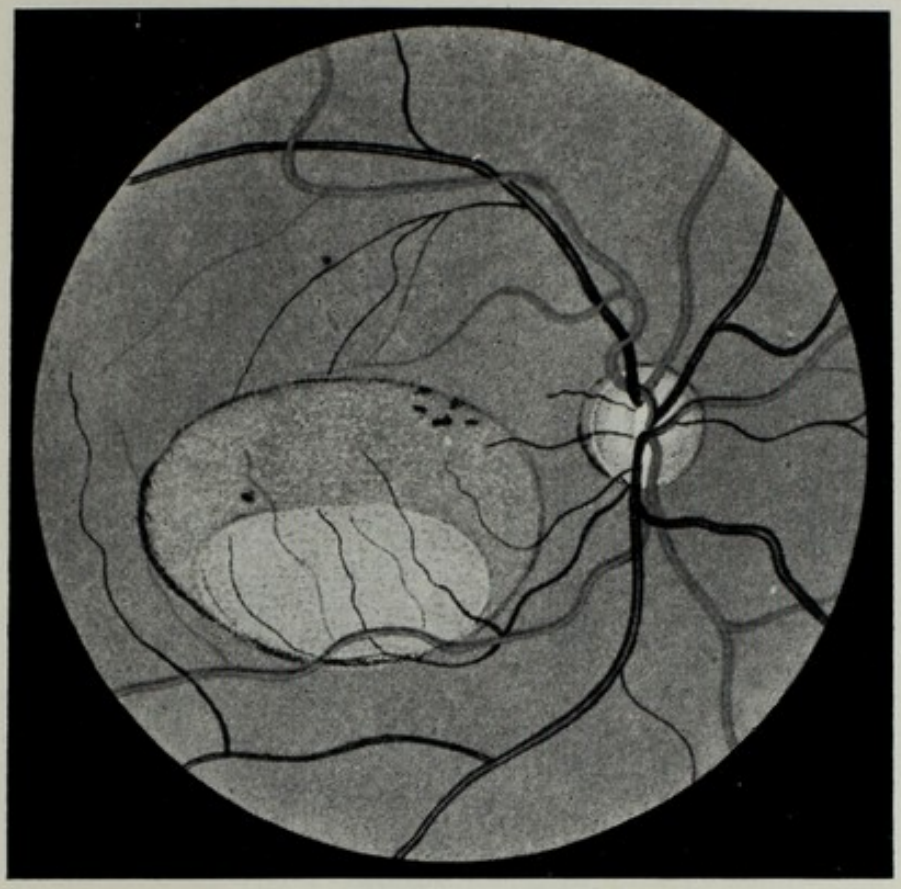
(*a*)

FIG. 137.—Congenital macular defects. Ophthalmoscopic appearances. (*a*) Pigmented macular coloboma. (*After A. Sorsby* (1935). *Brit. J. Ophthal.*, **19**, 65.)

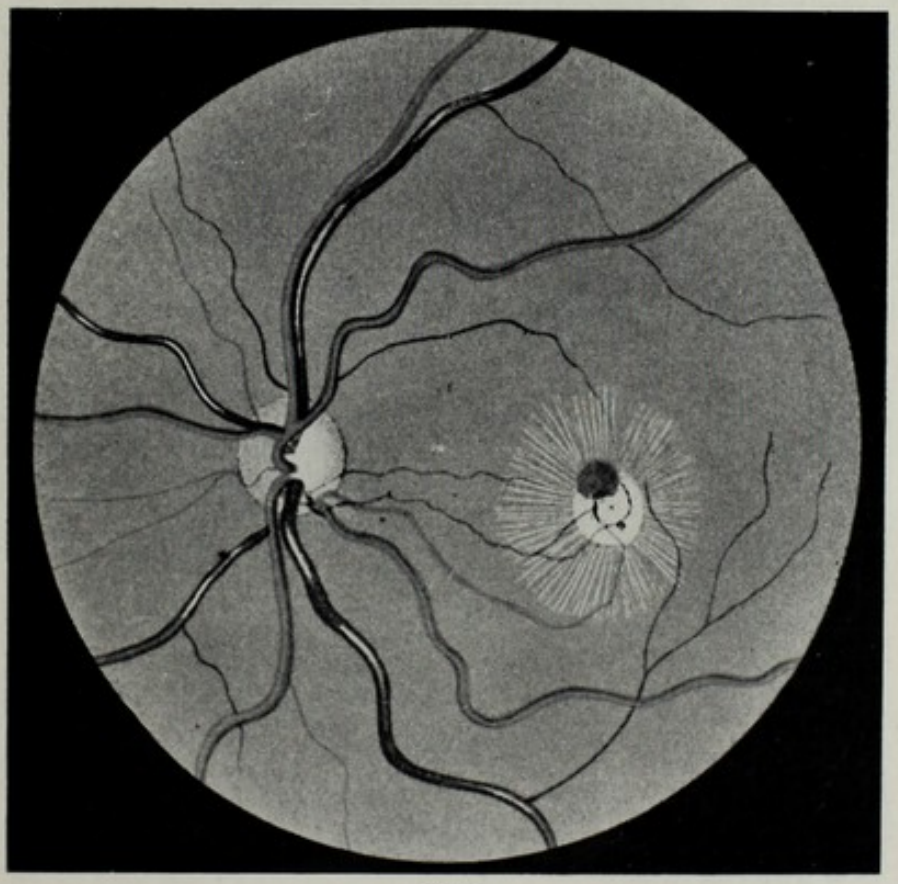


(*b*)

FIG. 137 (*cont.*).—(*b*), (*c*), and (*d*) Congenital macular and paramacular atrophic defect (Best's disease). Appearances seen in three members of an affected family. (*After F. Best* (1905). *Z. Augenheilk.*, **13**, 199.)

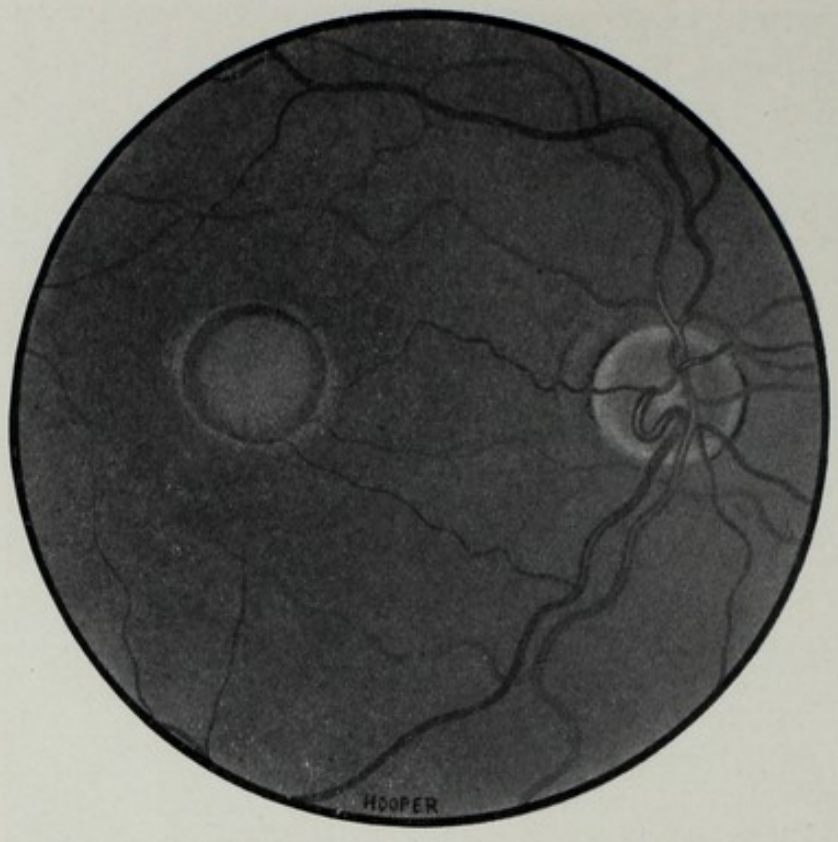


(*c*)



(*d*)

(*e*)



(*f*)

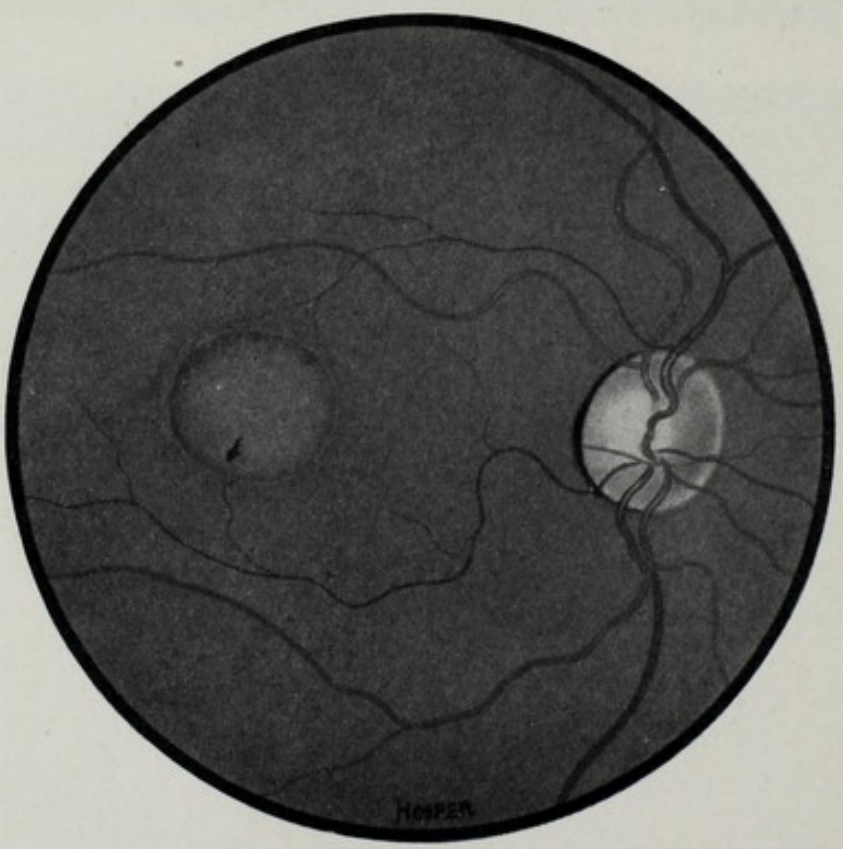
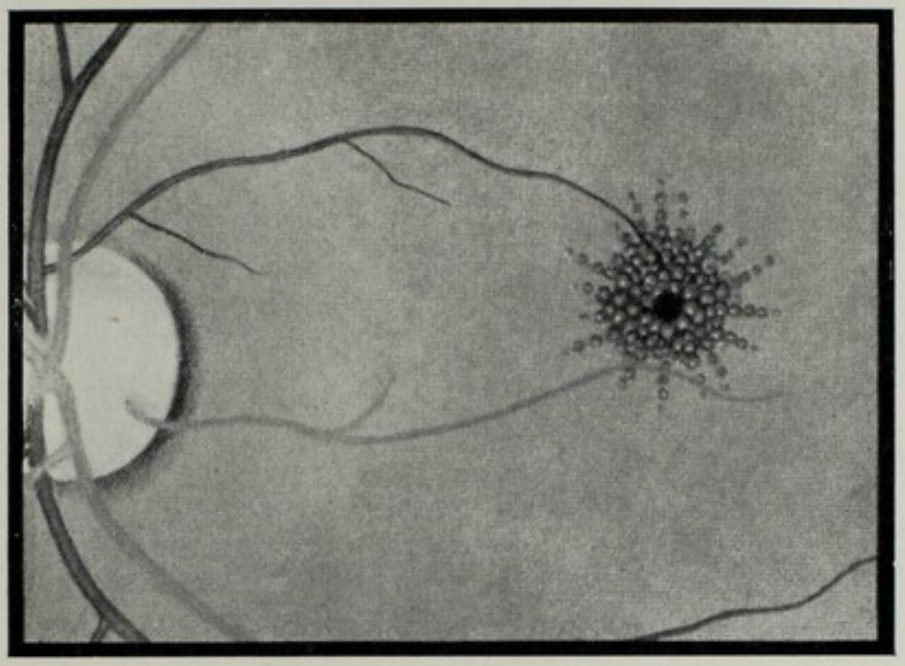


FIG. 137 (*cont.*).—(*e*) and (*f*) "Hole" at macula. Ophthalmoscopic appearances as seen in a brother and sister recorded in pedigree Fig. 139. (*Personal observation. Royal Eye Hosp., No.* 50/5063.)

now being reported. The significant clinical aspects are the stationary nature of the lesion, and the frequently good central vision, despite the extensive ophthalmoscopic changes. In the family studied by Falls there was regular autosomal dominance (Fig. 138).



(*g*)

FIG. 137 (*cont.*).—(*g*) Rosette figure. Unusual reaction observed in the sibship recorded in Fig. 140. (*After A. L. Brown* (1928). *Amer. J. Ophthal.*, **11**, 190.)

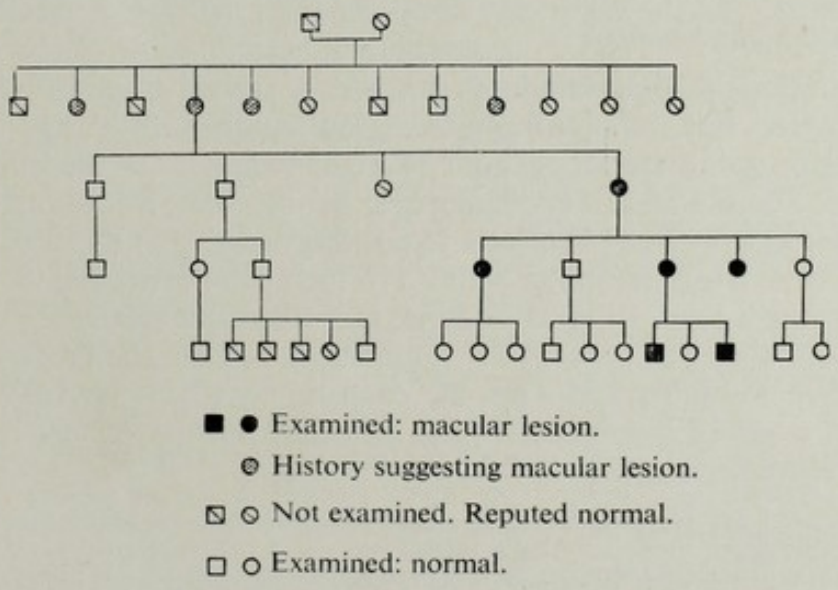


FIG. 138.—Congenital macular and paramacular atrophic defect (Best's disease). Pedigree showing dominant inheritance. (*After H. F. Falls* (1949). *Amer. J. human Genet.*, **1**, 96.)

"Hole" at macula (Figs. 137 *e* and *f*)

To what extent this is a variant of Best's disease is not known. It is also not known whether central vision, which is generally good, remains unaffected. It is

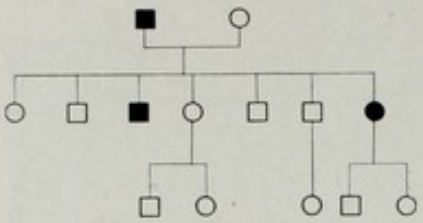


FIG. 139.—"Hole" at macula. Pedigrees suggestive of dominant inheritance. (*Cases illustrated in Figs.* 137 *e and f. Personal observation.*)

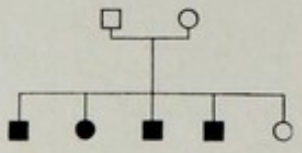


FIG. 140.—Rosette figure at macula. Pedigree of an affected sibship. (*After A. L. Brown* (1928.) *Amer. J. Ophthal.*, **11**, 190.)

likely that the "holes" are translucent cysts, and that vision becomes defective only after they have burst with subsequent pigmentary degenerative changes. Fig. 139 suggests dominant inheritance.

Rosette figure at the macula (Fig. 137 *g*)

From the single sibship on record (Fig. 140), nothing definite can be said on the mode of inheritance. It may be noted that this pedigree is not inconsistent with irregular dominance, and as such may have a similar mode of inheritance to that seen in the other three congenital hereditary macular defects.

CONGENITAL STATIONARY NIGHT-BLINDNESS

Uncomplicated night-blindness

Congenital stationary night-blindness occupies a special place in human genetics because of the fact that it has contributed exceptionally well-worked-out pedigrees. In 1838, Cunier published an account of night-blindness in the offspring of one Jean Nougaret, born 1637 at Vendémian near Montpellier. Nettleship, in collaboration with Truc and with the help of a local clergyman, completed this pedigree in 1907. There were ten generations with 2,116 members, of whom 135 were known to have been night-blind. Fig. 21 is an extract from this pedigree. The dominant mode of inheritance is obvious. A number of other pedigrees of dominant inheritance are available and they all conform to type (Fig. 141). There is no suggestion or irregular dominance in any of them, or of any ocular complications. There is no disability apart from the night-blindness.

Much has been written concerning the excess of unaffected over affected individuals in the Cunier-Truc-Nettleship pedigree. The expected ratio of 1 : 1 is not borne out by 134 affected to 255 normal in the affected branches of the family. As information on the earlier generations is largely from hearsay, it is of course possible that many affected members who died young were not reckoned amongst those affected. The rather complicated theoretical explanations which have been advanced seem unwarranted.

Night-blindness with myopia

Sex-linked recessive.—Fig. 142 *a* is taken from another famous pedigree, the Pfluger-Amman-Kleiner pedigree. The mode of inheritance is clearly that of recessive sex-linkage. A characteristic feature in this pedigree—and in some pedigrees recorded by Nettleship—(Fig. 142 *b*) was the presence of myopia ranging from 6 D to 11 D. Astigmatism was not uncommon, as also was some degree of visual defect. It is not unlikely that the pedigree of sex-linked recessive myopia recorded by Worth falls into this category. In one of Nettleship's pedigrees, an affected woman appeared.

Autosomal recessive.—Fig. 142 *c*, an extract from yet a third well-known pedigree (the Gassler pedigree), shows autosomal recessive inheritance. It is uncertain whether the myopia or the night-blindness differs from features as seen in sex-linked recessive inheritance. In the Gassler pedigree, the myopia varied between 9 D and 16 D and corrected vision varied between 6/60 and 6/18.

Night-blindness with abnormal fundus coloration

In Oguchi's disease there is a characteristic greyish reflex on ophthalmoscopic examination. After an hour or more in a dark room the normal fundus coloration appears—the Mizuo sign. Only a few cases have been recorded in Caucasians; the affection appears to be fairly prevalent amongst Japanese. The available pedigrees show a high rate of consanguinity and suggest recessive inheritance.

Fundus albi punctatus

Lauber in 1910 sought to differentiate between retinitis punctata albescens, which he regarded as a progressive affection of the retinitis pigmentosa group, and fundus albi punctatus, which he considered to be a congenital stationary affection with no complications beyond night-blindness. The exact status is still uncertain.

It is unlikely that any further substantial clarification of the various affections with night-blindness will be achieved until finer methods of examination than those used clinically at the present are employed.

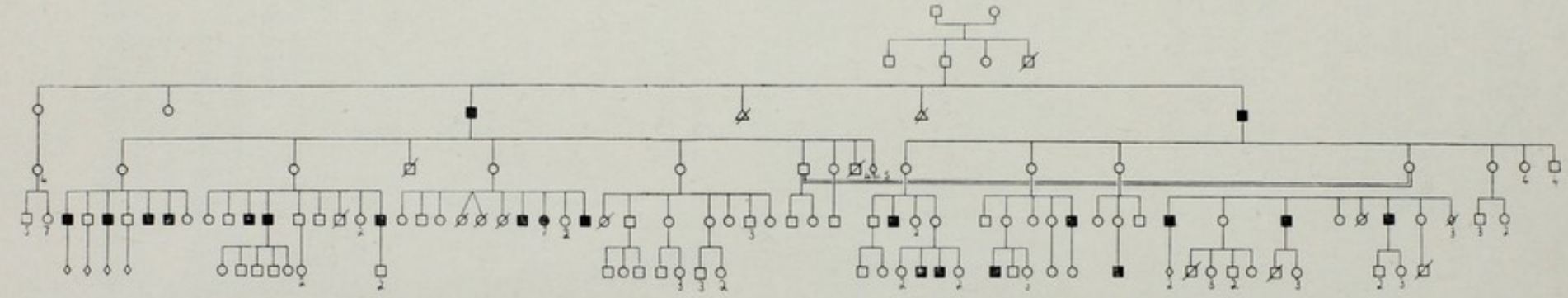
Anomalies of Colour Vision

In trichromatic vision any colour (or spectral light) can be matched by a mixture of three primary colours (or spectral lights). Dichromats can match any light with a mixture of two primary lights. In monochromatic vision any light can be matched by any other light, merely by adjusting intensities.

Normal trichromatic vision is present in about 92 per cent of men and about 99·5 per cent or more of women. Of the 8 per cent or so defectives amongst men, most have trichromatic vision: they match a light with a mixture of three primary lights, but their trichromatic coefficient curves are of a different shape and their colour vision differs in some details from the normal trichomats (anomalous trichromatism). Only 2·6 per cent of men are dichromats. Monochromats are rare, and there does not appear to be any definite excess of men over women.

Monochromatism (total colour-blindness; day blindness)

Total colour-blindness is an aspect of a severe symptom-complex, which



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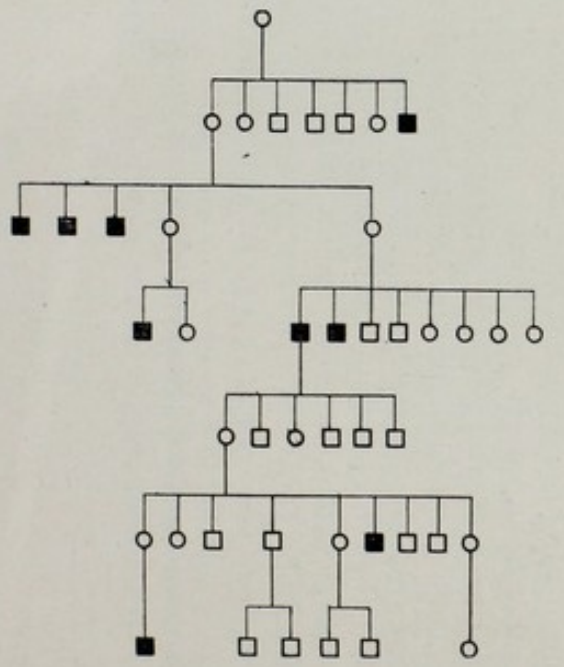
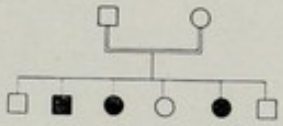


(*a*)



(*c*)

FIG. 142.—Night-blindness with myopia.
(*a*) Recessive sex-linkage. (*After W. Kleiner* (1923). *Arch. Rass. u. Ges-Biol.*, **15,** H.I.)
(*b*) Recessive sex-linkage. (*After E. Nettleship* (1912) *Trans. Ophthal. Soc. U.K.*, **32,** 21.)
(*c*) Autosomal recessive inheritance. Extract from an extensive pedigree. (*After V. J. Gassler* (1925). *Arch. Klaus-Stift. Vererb.*, **1,** 259.)

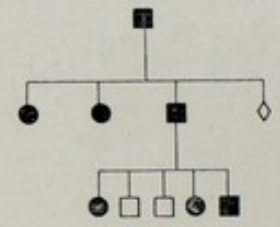


FIG. 141.—Uncomplicated night-blindness. Dominant inheritance. (*After W.T. Atwool* (1895). *Roy. Ophthal. Hosp. Rep.*, **14,** 260.)

includes photophobia, low visual acuity, and nystagmus. Luminosity curves and such scanty histological evidence as is available suggest that cones are lacking and that vision depends exclusively on rods.

The familial occurrence of the affection was noted by Nettleship as early as 1880, when he also stressed the frequences of consanguinity in the parents. The available pedigrees show it as essentially a familial affection, and there are a not inconsiderable number of isolated cases. A high degree of consanguinity is recorded (23 per cent in the material analyzed by Lina Peter, and 33 per cent in the Dutch material investigated by Waardenburg). It is said that the condition is more prevalent in Japan, where a consanguinity rate of over 80 per cent has been recorded in this affection. In isolated cases it has been shown that consanguinity may be present far back.

A Japanese pedigree involving three collateral sibships is shown in Fig. 143 *a*. Isolated cases in collateral branches are shown in Fig. 143 *b*. In each case the

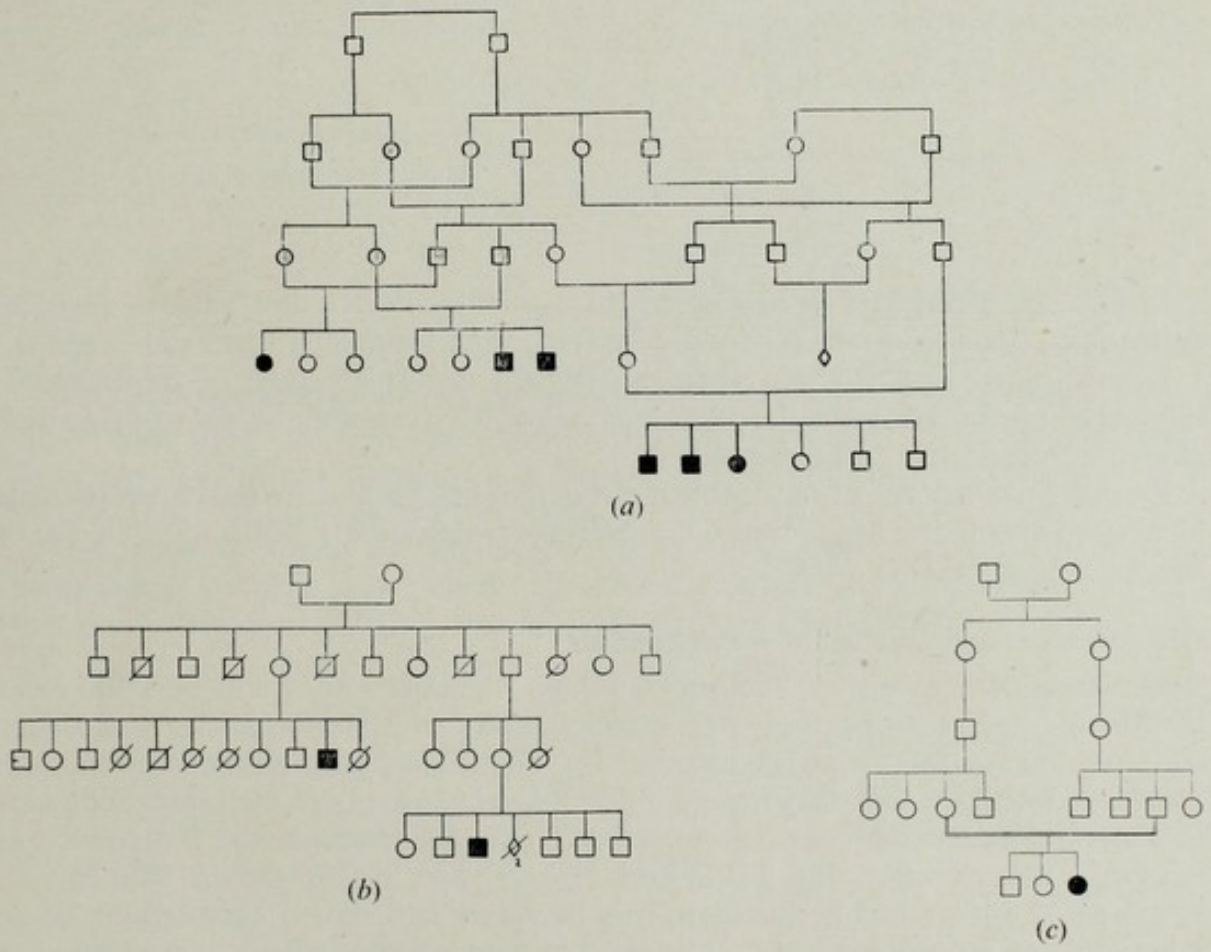


FIG. 143.—Total colour blindness.
(*a*) Recessive inheritance in three collateral branches of a family heavily intermarried. (*After T. Maeda in T. Komai* (1934). *Pedigrees of Hereditary Diseases in the Japanese Race. Kyoto.*)
(*b*) Inheritance in two isolated cases with a common ancestor. (*After L. Peter* (1926). *Arch. Klaus-Stift. Vererb.*, **2**, 143.)
(*c*) Isolated case in a sibship derived from a second-cousin marriage. (*After Vogt* (1922). *Klin. Mbl. Augenheilk.*, **69**, 121.)

parents were not consanguineous, but both the mothers had a common descent. In contrast, consanguinity of parents is shown in an isolated case in Fig. 143 *c*.

Several pedigrees suggest the possibility that the condition may occasionally be dominant.

The pedigree recorded in Fig. 144 shows the occurrence of the affection in all the four members of a sibship; two of the members also suffered from labyrinthine deafness, which appears to have been inherited independently in a dominant manner. The parents of the affected sibs were unrelated.

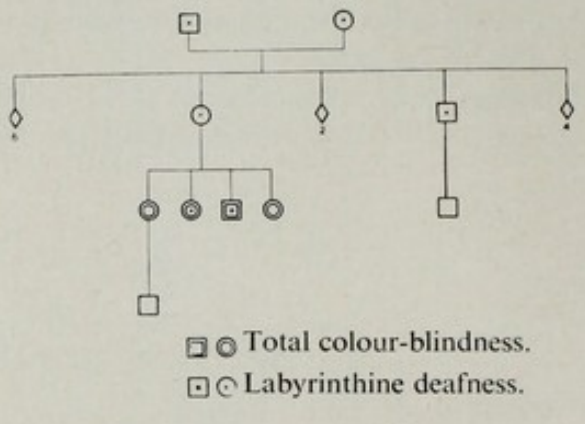


FIG. 144.—Total colour-blindness, inherited presumably in a recessive manner, with independent inheritance of dominant labyrinthine deafness. (*After S. Ry. Andersen* (1946). *Acta Ophthalmologica*, **24**, 99.)

In this last pedigree, as in many others, mental defect and various physical deformities, such as syndactyly and club foot, were frequently observed.

According to Franceschetti there is also an incomplete type of total colour-blindness: all the symptoms are less marked and vision may be up to 6/24. This affection, too, is said to be recessive.

Recently a cone type of monochromatic vision has been described. Such patients have good vision and are no more troubled than dichromats. Nothing is known of the genetics of this disturbance.

Dichromatism and anomalous trichromatism

The hereditary nature of "colour-blindness" has been known since 1778. John Dalton and two of his brothers were affected, and Dalton reported "extraordinary facts relating to the vision of colours" in 1794. The early observers were well acquainted with the fact that the condition occurred largely in men, and Sedgwick in 1861 recognized the essentials of what is now called sex-linked inheritance in relation to this affection. Fig. 145 is from Horner, who in 1876 showed that colour-blindness is transmitted in the same way as Nasse had shown haemophilia to be inherited, and he also explained the apparent contradiction of direct transmission from father to son, for in his pedigree where this occurred the mother was a carrier.

The large number of pedigrees on colour-blindness show almost without exception regular recessive sex-linkage. Such pedigrees as appeared to depart from this mode of linkage were shown by Döderlein and by Schiotz to be largely due to incomplete or mistaken statements. "Colour-blindness" is, in fact, one of the outstanding examples of sex-linkage. It has a special place in medical genetics as

it was one of the conditions which appeared to invalidate the application of Mendelian rules to Man, until the discovery of sex-linkage in Drosophila turned an apparently insuperable objection into a brilliant confirmation.

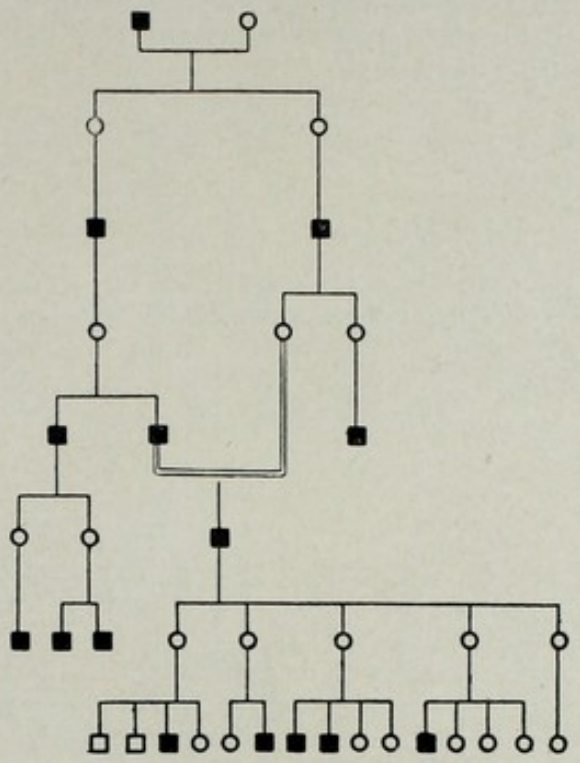


FIG. 145.—Dichromatism. Early pedigree showing recessive sex-linked mode of inheritance. (*After W. D. Horner* (1876). *In Treasury of Human Inheritance, Ed. by K. Pearson. Vol. II by Julia Bell. Fig.* 589. *London; Cambridge University Press* (1933).

Dichromatism

The older literature made no distinction between protanopia and deuteranopia, or between dichromatism and anomalous trichromatism. Most recent observers agree on a distribution such as is shown in the following table from Waaler, derived from an investigation on 9,049 boys and 9,072 girls.

That all these forms are sex-linked has to be accepted from the fact that the older literature does not record any inheritance but sex-linkage, and the more recent investigators conform to the older findings (Figs. 146 *a*, *b*, *c* and *d*).

Condition	Percentage distribution			
	Boys		Girls	
Protanopia	0·88	1·92	–	0·033
Protanomaly	1·04		0·033	
Deuteranopia	1·03	6·09	0·011	0·401
Deuteranomaly	5·06		0·39	
"Colour-blind"		8·01		0·434

Most of the exceptions to the usual transmission by an affected man through his carrier daughters to 50 per cent of his grandsons, find their explanation in the theoretical possibilities of transmission of recessive sex-linkage discussed in Section I, Chapter 3. In some cases the heterozygous (carrier) state of the clinically unaffected mother must be assumed. In others it can be reasonably deduced from a study of her pedigree.

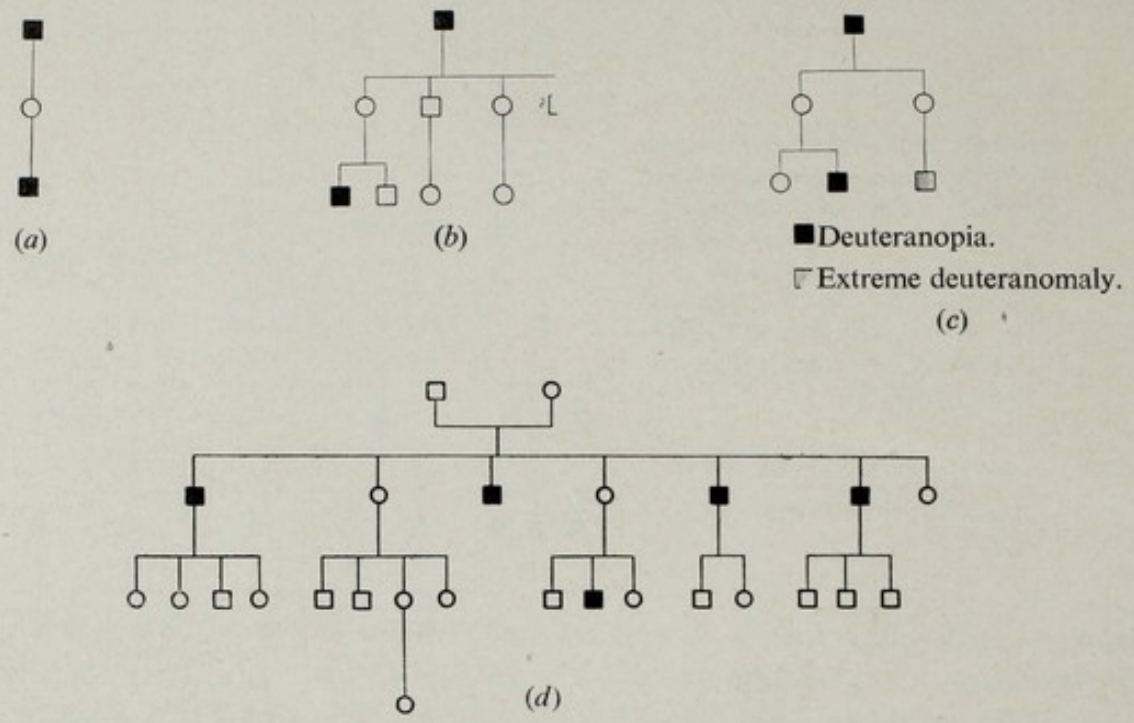


FIG. 146.—Deuteranopia and protanopia. Pedigrees showing recessive sex-linkage.
(*a*) Protanopia. (*After W. Brunner* (1930). *Arch. Ophthal.*, **124**, 1. (*Fig.* 23).)
(*b*) Protanomaly. (*After W. Brunner, Ibid.* (*Fig.* 22).)
(*c*) Deuteranopia. (*After W. Brunner. Ibid.* (*Fig.* 20).)
(*d*) Deuteranomaly. (*After E. Wolfflin* (1923). *Arch. ges. Physiol*, **201**, 214.)

There are cases of colour-blind daughters of clinically unaffected parents. Theoretically this could not come about unless the father was affected and the mother a carrier. To explain these cases on the adage *pater semper incertus* is an easy—all too easy—way out of a difficulty. It is more likely that all such cases are to be explained by the occasional full expression of the heterozygous state. There is ample evidence that female heterozygotes are not always completely normal in their colour vision, and apparently they can be phenotypically fully affected. This is shown by such facts as the occurrence of a colour-blind daughter of a colour-blind father and a mother who is apparently not a carrier. Fig. 147 shows such a pedigree. On the one hand, the two affected grandsons of an affected man conform to rule in so far as their mothers are unaffected. On the other hand, the affected daughter should be homozygous, in which case her son ought to be affected—but he is not. It may be assumed that the daughter is indeed heterozygous and in spite of this manifests the affection. Presumably the total genic balance comes into question in such cases.

The Cunier pedigree of colour-blindness transmitted exclusively through women (Fig. 36) is as yet the only one of its kind. As already noted on page 44 this is explained by the postulate that such women are XXY in constitution.

It may therefore be taken that recessive sex-linkage with occasional expression in heterozygous women explains all aspects of inheritance in dichromatism.

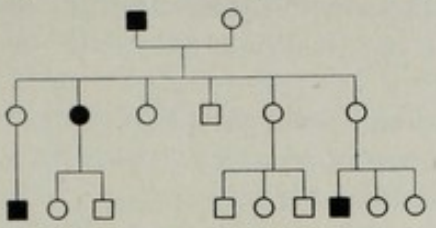


FIG. 147.—"Colour-blindness". Pedigree chart showing an affected heterozygous woman. (*After H. W. Siemens* (1926). *Klin. Mbl. Augenheilk.*, **76**, 769.)

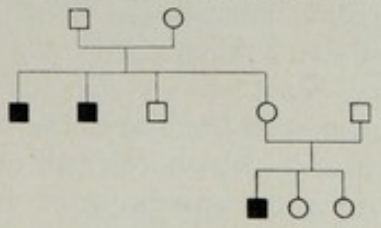


FIG. 148.—Anomalous trichromatism. Sex-linked inheritance in tritanomaly. (*After H. Hartung* (1926). *Klin. Mbl. Augenheilk.*, **76**, 229.)

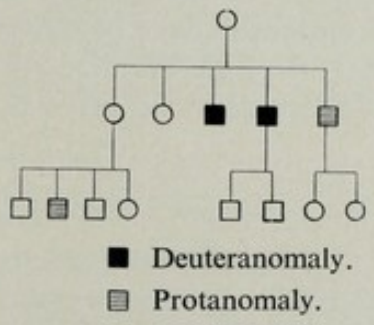


FIG. 149.—Deuteranomaly and protanomaly transmitted independently by a woman carrier of both genes. (*After W. Brunner* (1930). *Arch. Ophthal.*, **124**, 1.)

Anomalous trichromatism

Deuteranomaly, protanomaly and tritanomaly.—Sex-linked recessive inheritance applies to tritanomaly (Fig. 148) as it does for deuteranomaly and for protanomaly.

It is an old observation that within the same family, the same type of anomaly of colour vision occurs. There are, however, exceptions, and these have helped to elucidate the relationship of the different anomalies of colour vision to each other.

Deuteranomaly and deuteranopia.—In a pedigree of Wölfflin 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 mother an X chromosome carrying deuteranopia. On the assumption that the two genes are allelomorphs, deuteranomaly is dominant over deuteranopia.

Protanomaly and protanopia.—Similar relationships have been established between these two affections.

Deuteranomaly and protanomaly.—In a pedigree of Brunner (Fig. 149) a woman had 2 normal daughters and 3 sons, two of whom showed deuteranomaly and one protanomaly. It is assumed that the mother—who was clinically unaffected—carried both these genes but on different loci on her two X chromosomes. This

supposition is strengthened by the fact that her daughter transmitted protanomaly to one of her sons. The two affections are therefore inherited independently.

The general conclusions that these and similar pedigrees allow are:

(1) Deuteranopia and protanopia are genetically distinct entities, the gene for each being carried by the non-homologous portions of the X chromosome.

(2) The gene determining deuteranopia is allelomorphic to that determining deuteranomaly. Likewise the gene for protanomaly is an allele of that for protanopia.

(3) The gene determining normalcy is dominant over the pathogenic alleles; and of these the allele which determines the less severe anomaly is dominant over that for the more severe anomaly.

These relations are shown schematically as follows:

Normal > deuteranomaly > deuteranopia

Normal > protanomaly > protanopia

(4) It is likely that similar considerations apply to tritanomaly and tritanopia.

Extreme anomalous trichromatism

It is uncertain whether extreme deuteranomaly and extreme protanomaly are distinct entities or merely anomalous states observed under conditions of fatigue. If they are genetically distinct, they are determined by alleles, and their position as regards dominance would presumably be between the anomalous state and the anopia state.

ABIOTROPHIES

The classical forms of abiotrophic affections of the retina are retinitis pigmentosa and macular dystrophy. Less common abiotrophic affections are gyrate atrophy of the retina and choroid, choroideremia, and the affection known as Doyne's choroiditis. Retinitis pigmentosa has a characteristic pigment reaction, while the lesion in macular dystrophy is also pigmentary, there is mottling and atrophy instead of bone corpuscle reaction. In gyrate atrophy the reaction is almost entirely one of atrophy with exposure of white sclera. In choroideremia, fundamentally the same reaction is present, but on a more extensive scale with occasional bone corpuscle pigment. In Doyne's choroiditis, pigment proliferation is present, but in addition there are whitish "exudates", or possibly large colloid bodies. In all these affections the reaction is, therefore, essentially one of atrophy and relatively fine pigmentary disturbances, except that in Doyne's choroiditis an approach to an exudative reaction is observed.

In recent years a considerably wider range of reactions have come to be recognized in the abiotrophic lesions. Angioid streaks with the not infrequently associated haemorrhages and exudates bear no similarity to the classical reactions. In choroidal sclerosis the conversion of the choroidal vessels into white streaks (Figs. 132 and 133) is yet another unusual abiotrophic reaction. Still more striking are the exudative reactions recorded in macular dystrophy (Fig. 159) while in the generalized fundus dystrophy recently described oedema, haemorrhages and exudates can be observed in the early stages and massive pigmentary proliferation in the late stages (Fig. 163).

The variety of abiotrophic reactions is therefore so wide as to simulate almost any type of fundus reaction traditionally associated with affections of environmental origin. These developments have extended the range of abiotrophic lesions to considerably beyond the limited range of affections regarded as such in the past.

In retinitis pigmentosa it has been known for many years that the age of onset of the affection varies considerably in different families and that there are several modes of inheritance. In macular dystrophy the tendency has been to regard the classical form described by Stargardt as occurring in late childhood or at puberty, as an exclusive chronological and genetic type. That this view as to the age onset is untenable was shown by Behr, who stressed the occurrence of macular dystrophy later in life. He held that macular dystrophy occurs at the critical periods of development: the first dentition, adolescence, early adult life, the climacteric, and possibly also in old age. Though somewhat schematic, Behr's teaching has the merit of emphasizing that in the macular dystrophies, perhaps even more than in retinitis pigmentosa, there is no one age at which the lesion may occur, and that the classical Stargardt form is merely one of many possible varieties. Likewise, though the recessive type is much the commonest, almost every other form of inheritance may occur. It is not unlikely that the range of modes of inheritance in the macular dystrophies is no less than in retinitis pigmentosa.

The Retinitis Pigmentosa Group

Four, and possibly six, modes of inheritance of retinitis pigmentosa without generalized associations are recognized. The relative frequency of these different types of unassociated retinitis pigmentosa is known only in broad outline, and clinical differences as between these different groups are as yet ill-defined.

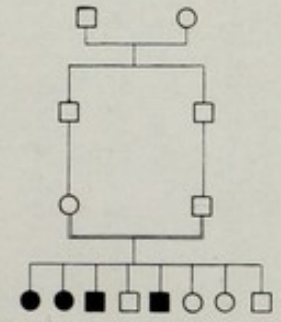
Genetic varieties

Recessive.—Published pedigrees of retinitis pigmentosa tend to emphasize the exceptional families in which large numbers are affected and the affection is transmitted over several generations. There is, however, no doubt that the relatively infrequently recorded pedigrees of recessive inheritance stand for the bulk of the cases. In a consecutive series of 41 pedigrees of retinitis pigmentosa, Usher found that all but one were recessive. Fig. 150 *a* illustrates a typical pedigree.

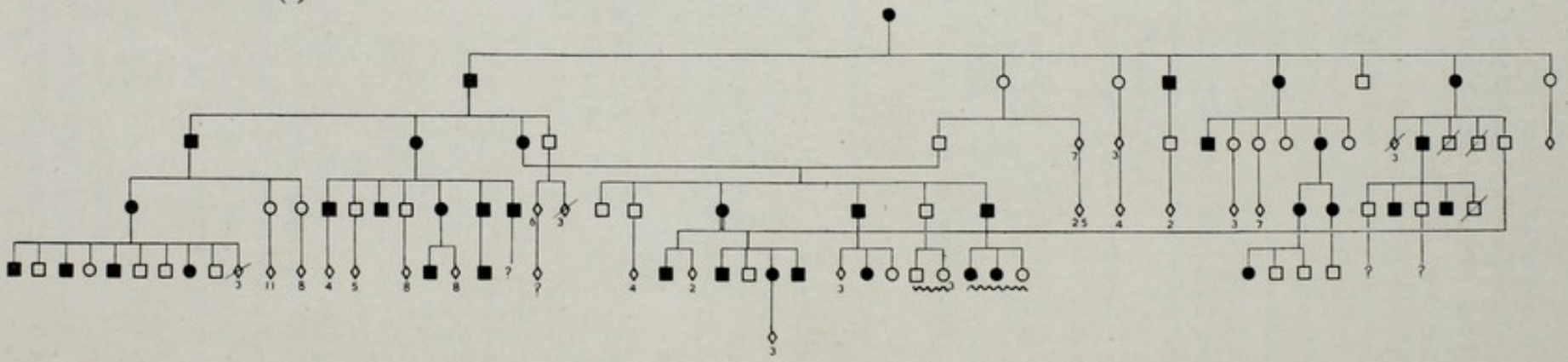
Dominant.—The very large number of pedigrees published tend to give an exaggerated importance to the frequency of this mode of inheritance. In all the published pedigrees a striking feature has been the regular mode of inheritance without any skipping of a generation (Fig. 150 *b*).

Sex-linked recessive.—Relatively few pedigrees are available. Fig. 150 *c* illustrates the typical mode of inheritance. Available evidence would seem to suggest that retinitis pigmentosa with this mode of inheritance is a particularly severe affection. It would also seem that in some families the female heterozygotes are affected.

Intermediate sex-linked.—Falls and Cotterman have drawn attention to this variety of retinitis pigmentosa. They hold that, as in choroideremia, female heterozygotes can be recognized by ophthalmoscopic changes of no pathological importance. There is a characteristic highly glistening retinal reflex, somewhat

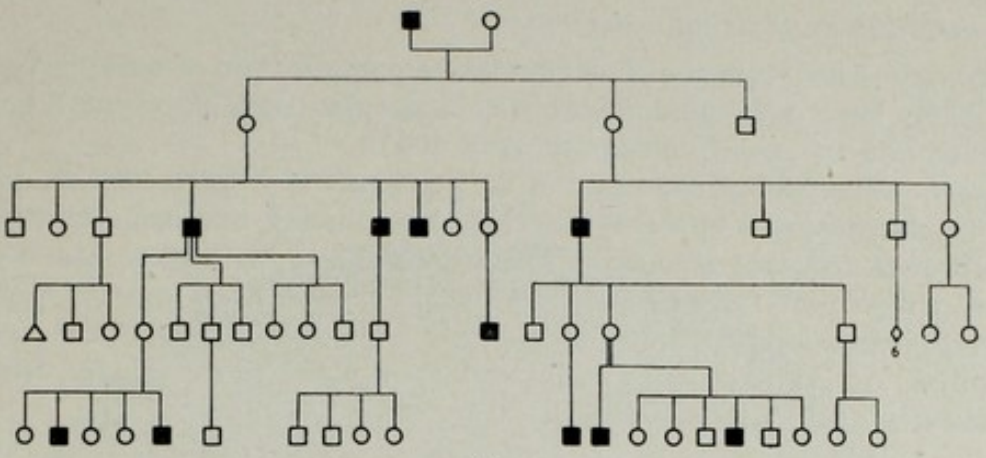


(*a*)



(*b*)

FIG. 150.—Retinitis pigmentosa.
(*a*) Recessive inheritance. (*After E. Nettleship* (1908). *Royal Ophthal. Hosp. Rep.*, **17**, 1.)
(*b*) Dominant inheritance. (*After E. Nettleship. Ibid.*)



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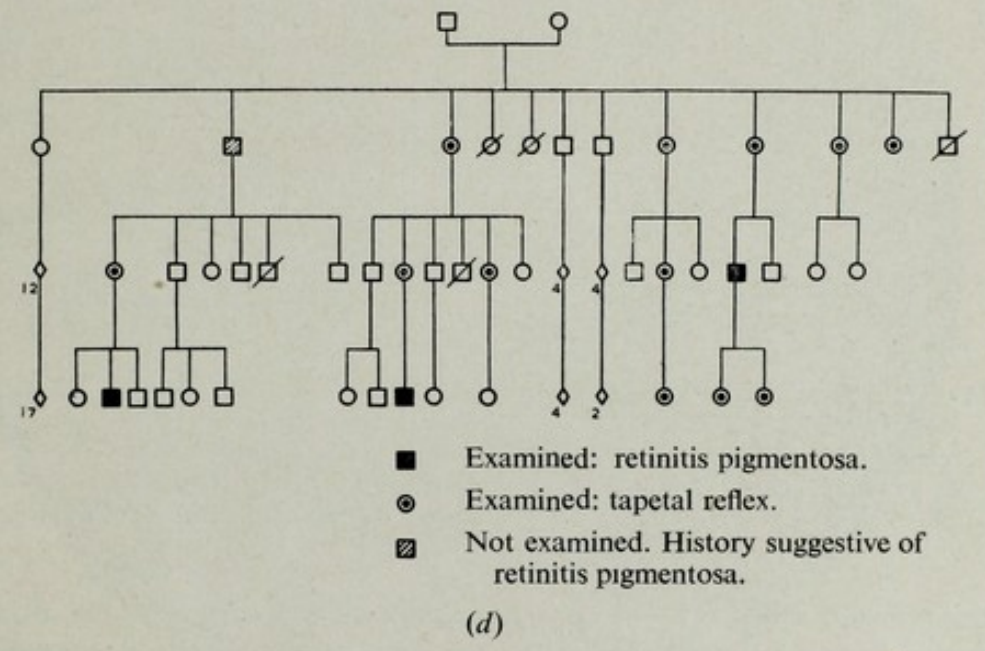


(*d*)

FIG. 150 (*cont.*).—(*c*) Recessive sex-linked inheritance. (*After C. H. Usher* (1935). *Trans. Ophthal. Soc. U.K.*, **55**, 164.)
(*d*) Intermediate sex-linked inheritance. (*After H. F. Falls and C. W. Cotterman* (1948). *Arch. Ophthal.*, **40**, 685.)

reminiscent of the tapetal reflex of animals. Fig. 153 illustrates the range of such possible retinal reflexes. The exact significance of this heterozygous manifestation has still to be assessed.

Apart from these four modes of inheritance there are two further possibilities suggested by Haldane.

Dominant partial sex-linkage.—Fig. 39 supports such a reading if cross-over is assumed.

Recessive partial sex-linkage.—The evidence for this mode of inheritance is less convincing. Fig. 38 is one of the pedigrees used to support that reading—a reading that cannot be maintained in the light of any single pedigree, but only from a collection of similar pedigrees. This raises the complicated issue of selected material.

Ocular associations of retinitis pigmentosa

Glaucoma.—The frequency of glaucoma as a complication of retinitis pigmentosa has probably been over-rated. There is evidence that such glaucoma is genetically determined and not merely incidental (Fig. 151).

Cataract.—The general assumption that cataract is a secondary manifestation in retinitis pigmentosa is probably not valid. It is possible that cataract is a frequent and perhaps a constant association of dominant retinitis pigmentosa. Fig. 152 *a* shows a pedigree of fully developed cataract in dominant retinitis pigmentosa over three generations. In most individuals with dominant retinitis pigmentosa lens changes appear to develop early and to progress fairly rapidly, irrespective of the severity of the fundus lesion.

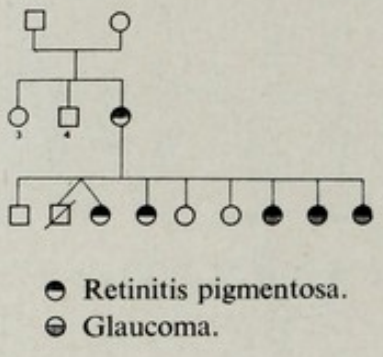


FIG. 151.—Retinitis pigmentosa associated with glaucoma. (*After A. A. Bradburne* (1916). *Ophthal. Rev.*, **35**, 65.)

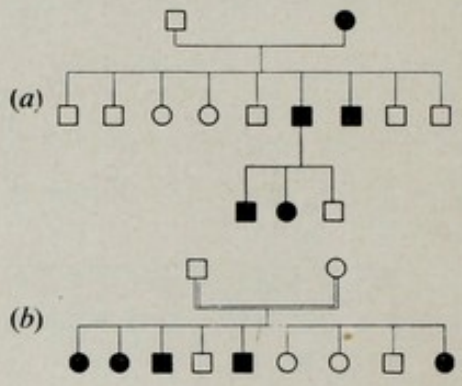
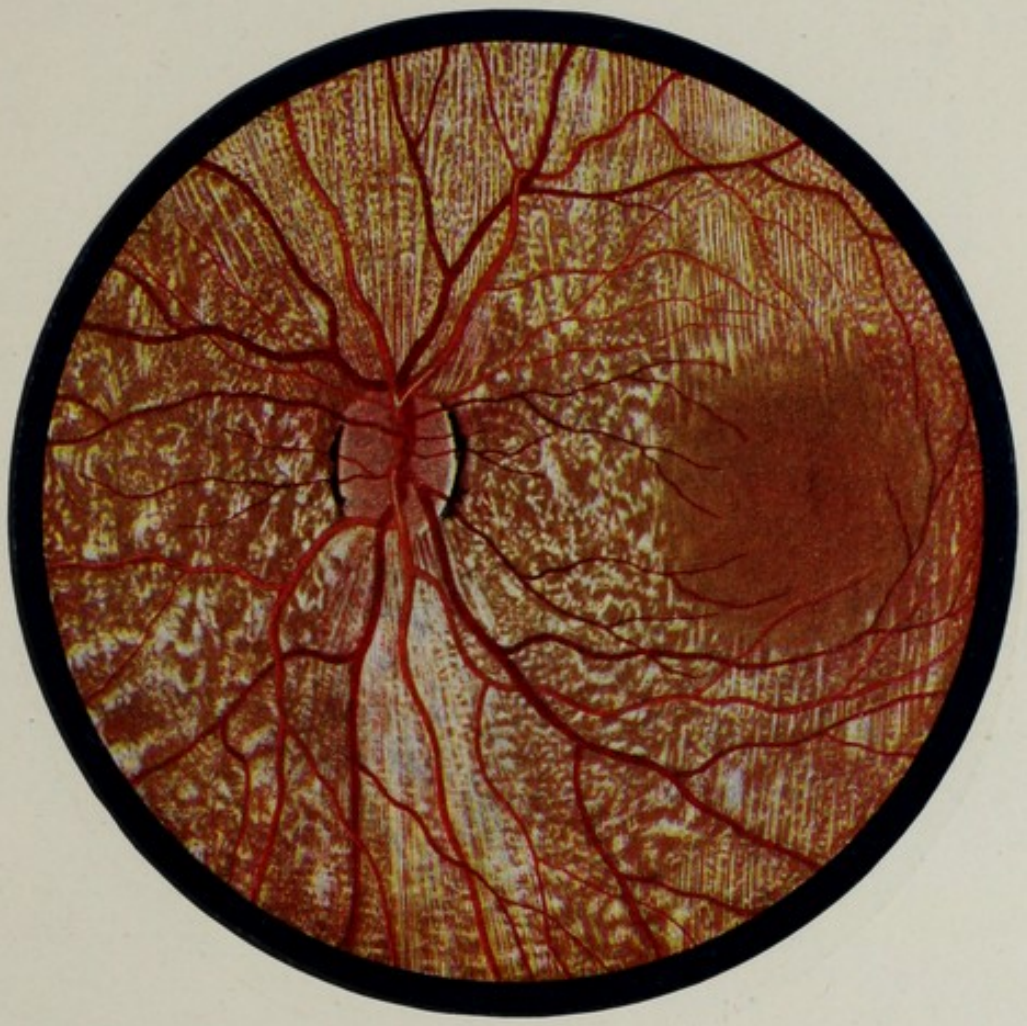


FIG. 152.—Retinitis pigmentosa with cataract. (*a*) Dominant inheritance. (*Personal observation. Royal Eye Hospital No.* 36/537.) (*b*) Recessive inheritance. (*After L. H. Savin. Hitherto unpublished. Royal Eye Hospital No.* 0/9476.)

Cataract would appear to be less common in recessive retinitis pigmentosa. It is, however, possible that there is a variety of recessive retinitis pigmentosa in which cataract is a constant association. Fig. 152 *b* illustrates such a pedigree.

It would therefore appear that whilst at least four different genes are responsible for the picture of retinitis pigmentosa in different families, there may be as many as seven and possibly eight distinct forms of retinitis pigmentosa. Intensive combined clinical and genetic studies are necessary for the elucidation of these problems. It is not unlikely that such ill-defined entities as "atypical retinitis pigmentosa" and retinitis punctata albescens will become more intelligible in the light of such studies.

Ophthalmoplegia.—There are case records of external ophthalmoplegia with or without ptosis associated with "atypical retinitis pigmentosa". Occasionally present at birth, the onset is most frequently at about puberty and the fundus lesion may be a macular dystrophy or "atypical reginitis pigmentosa" or both in combination. Nystagmus is present in the congenital cases. The affection has been seen in sibs, but the exact genetic status is uncertain. The association of elements of bulbar palsy with retinal changes recalls the retinal changes seen in the hereditary spino-cerebellar ataxias.



(*a*)

FIG. 153.—Retinitis pigmentosa. Intermediate sex-linked inheritance. Range of fundus appearance in women.
(*a*) Appearance in a girl, aged 10 years, whose father had retinitis pigmentosa. (*After W. Adams Frost* (1902). *Trans. Ophthal. Soc. U.K.*, **22**, 208.)

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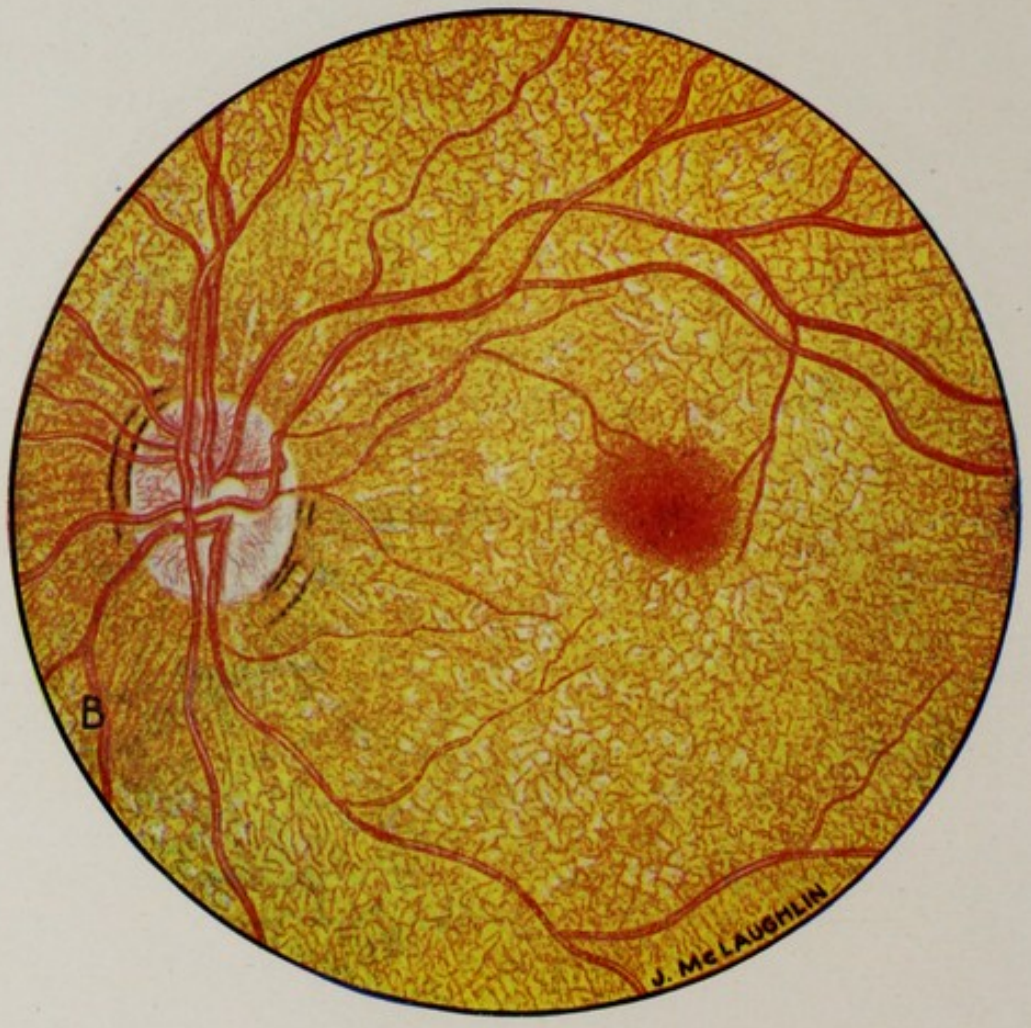
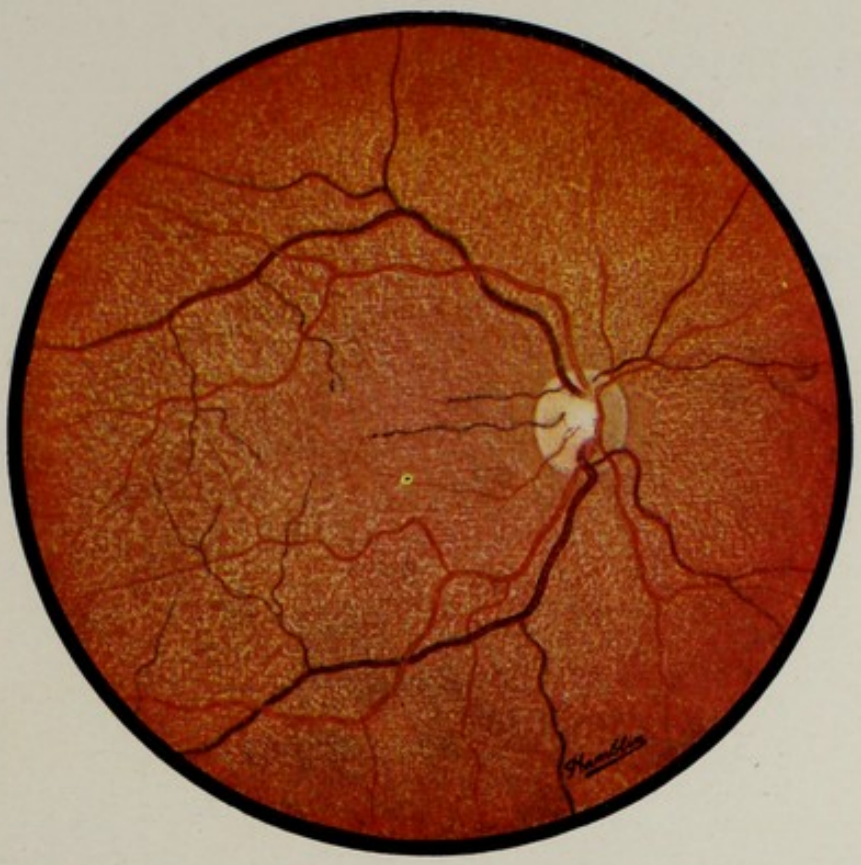


(*b*)

FIG. 153 (*cont.*).—(*b*) Fundus reflex in a woman in the family with intermediate sex-linked retinitis pigmentosa described by Falls and Cotterman. (*After H. F. Falls and C. W. Cotterman* (1948). *Arch. Ophthal.*, **40**, 685.)

(*c*)



(*d*)

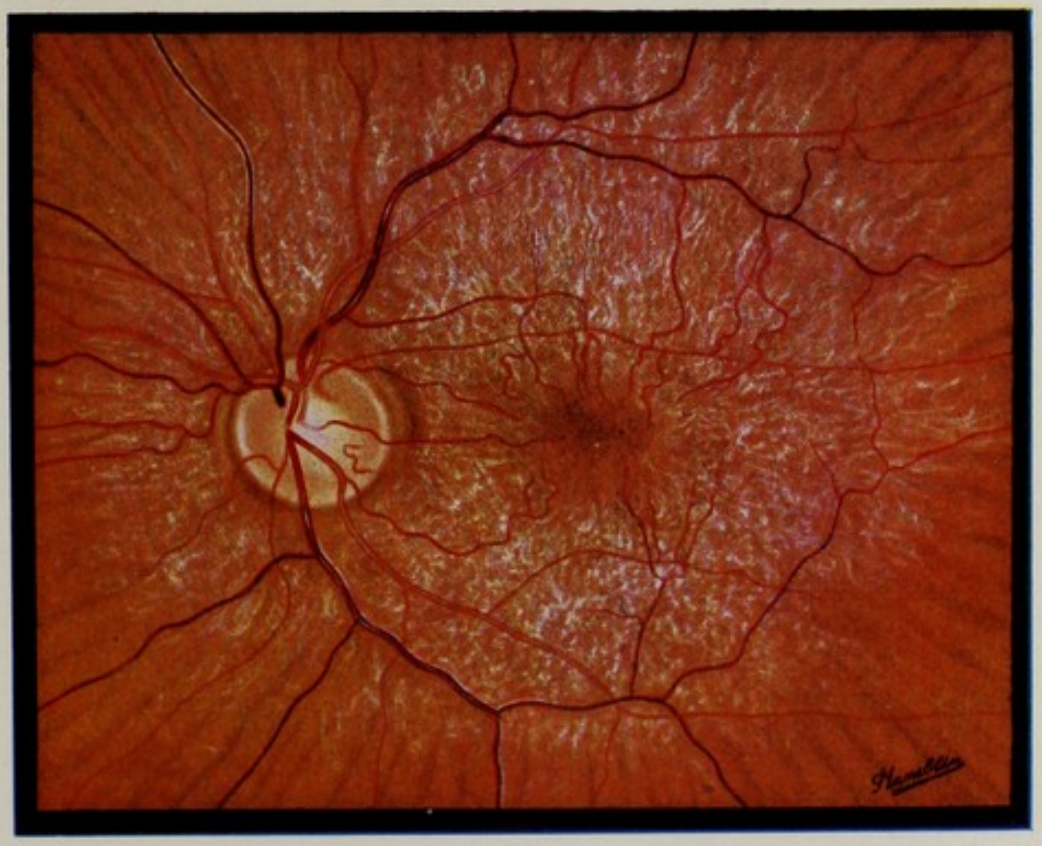


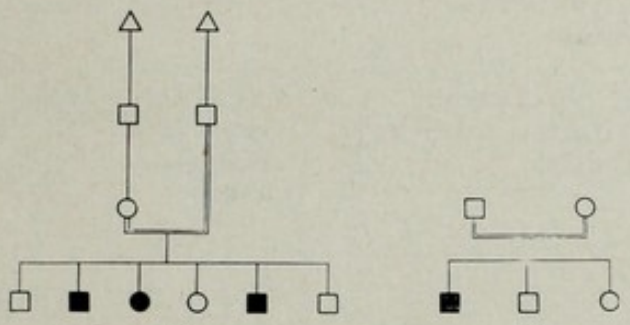
FIG. 153 (*cont.*).—(*c*) "Tapetal reflex" in a woman (whose family history is not recorded) described by Ida Mann. (*After I. Mann* (1937). *In Developmental Abnormalities of the Eye. London; Cambridge University Press.*)
(*d*) Fundus appearances in a woman aged 24 years with normal visual functions. She is a member of a family showing intermediate sex-linked retinitis pigmentosa. (*J. A. F. Roberts and A. Sorsby. Publication pending.*)

Unusual forms of retinitis pigmentosa

Retinitis pigmentosa with macular dystrophy.—The mode of inheritance of this affection is not known. Clinically it is sharply delineated from uncomplicated retinitis pigmentosa by the fact that central vision suffers early, with a consequent early total blindness. Figs. 154 *a* and *b* show a pedigree that suggests recessive inheritance.

Inverse retinitis pigmentosa.—In all probability this is also recessive. Fig. 155 illustrates a pedigree.

Unilateral retinitis pigmentosa.—There is nothing to suggest that the rare cases of unilateral retinitis pigmentosa represent a partial manifestation of the hereditary forms of retinitis pigmentosa. The available literature reveals neither an excessive incidence of consanguinity amongst the parents of such individuals, nor any definite family history of the affection. Some of the cases are probably of environmental origin, and the consequence of mechanical or chemical injury. Others may represent a somatic mutation.



(*a*) (*b*)

FIG. 154.—Retinitis pigmentosa with macular dystrophy.

(*a*) Pedigree suggestive of recessive inheritance. (*After A. Sorsby* (1941). *Brit. J. Ophthal.*, **25,** 524.)

(*b*) An isolated case with parental consanguinity. (*After A. Sorsby* (1940). *Brit. J. Ophthal.*, **24,** 485.)

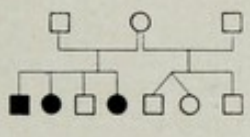


FIG. 155.—Inverse retinitis pigmentosa. Pedigree suggestive of recessive inheritance. (*After A. Sorsby* (1940). *Brit. J. Ophthal.*, **24,** 478.)

THE MACULAR DYSTROPHIES

Macular dystrophies have to be distinguished from generalized fundus dystrophies which begin at the macula. Generalized choroidal sclerosis may, and the generalized fundus dystrophy described below does, begin as a central lesion. Doyne's choroiditis is probably an incompletely studied form of generalized fundus dystrophy, whilst central changes seen in angioid streaks have systemic associations.

Ophthalmoscopically the macular dystrophies, like the retinitis pigmentosa group, appear to be one entity, but like this group, they are in fact a complex of several distinct affections, *see* Table VII.

Macular dystrophies with atrophic reactions

Typically the macular dystrophies show fine pigmentary reactions, producing an appearance of a mottled, atrophic area. (Figs. 157, *a–e*)

TABLE VII

The Macular Dystrophies: Tentative Classification

Dystrophies with atrophic reaction

Mode of Inheritance	Juvenile		Adult		Senile
	Recessive	Dominant	Recessive	Dominant	?
Frequency –	Commonest	Rare	Fairly common	Rare	?
Age of onset	Puberty	Early in childhood	About 30	About 40–50	Late in life
Effect on central vision	Rapid loss	Rapid loss	Variable	?	Steady loss
Effect on peripheral vision	None	Some involvement	None	?	None
Localization –	Central with slight paramacular involvement	Tends to become generalized	Central and paramacular	? The early stages of a generalized lesion	Mainly central

Dystrophies with exudative reactions

Mode of inheritance	Juvenile		Adult ("Doyne's choroiditis")		Senile
	Recessive	Dominant	Dominant		?
Frequency	Rare		Rare		?
Age of onset	Early in life		About 40		Late in life
Effect on central vision	Slowly progressive but vision may remain good		Steady loss		Steady loss
Effect on peripheral vision	None	?	? None		None
Localization	Central with considerable paramacular extensions		? Exclusively central and paramacular or ? an aspect of generalized fundus dystrophy		Mainly central

Stargardt, in establishing macular dystrophy as an isolated ocular lesion independent of the somewhat similar macular lesions seen in the previously recognized cerebro-macular degenerations, precipitated a considerable discussion as to whether these dystrophies were abortive forms of the more severe neurological disturbances. This possibility can now be dismissed. Families affected with macular dystrophy show a consistent clinical picture, and none of their members develops neurological complications. Furthermore, the neurological affections are now recognized as generalized lipoid dystrophies and there is nothing to suggest that the macular dystrophies are lipoid disturbances.

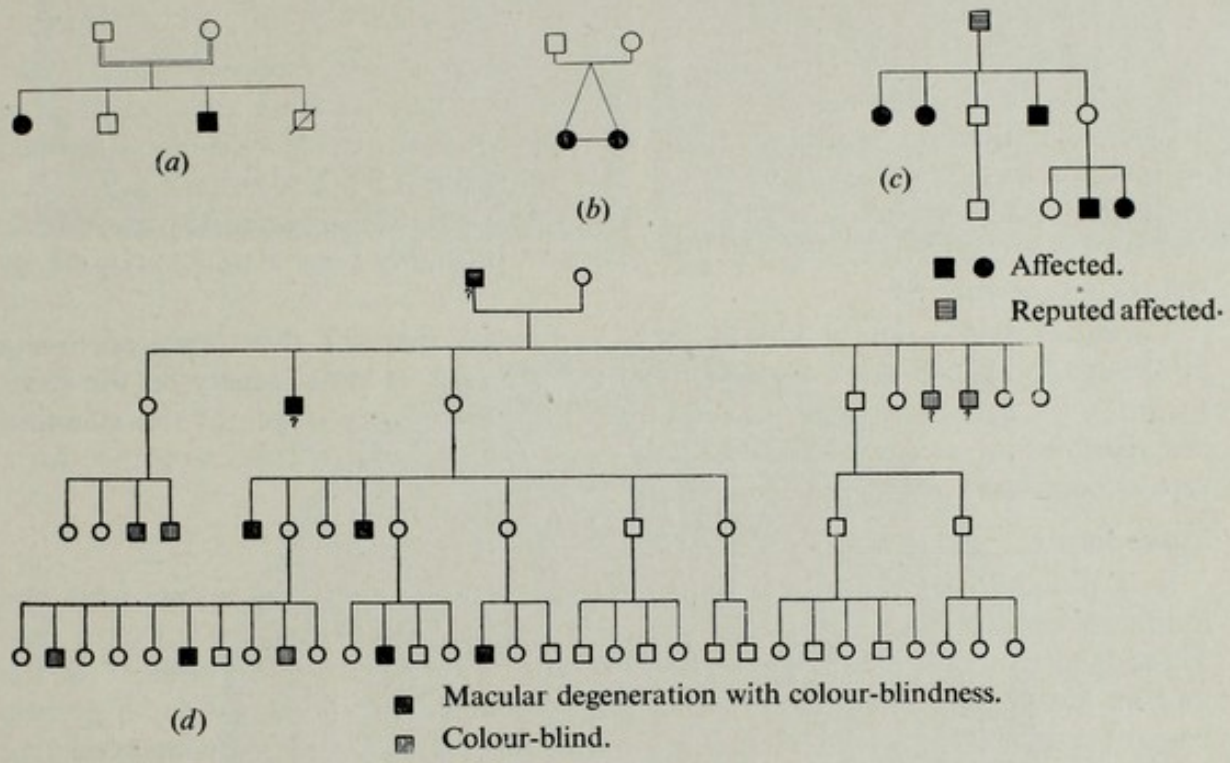


FIG. 156.—Macular dystrophies with atrophic reactions. Juvenile forms. Pedigrees.
(*a*) Pedigree showing recessive inheritance. (Stargardt's disease). (*After H. Neame* (1935). *Proc. R. Soc. Med.*, **28,** 526, *and personal communication.*)
(*b*) Pedigree chart showing the occurrence of the affection in a uniovular twin. (*Personal observation.* Fig. 157 *a* illustrates the appearances observed in this twin.)
(*c*) Pedigree suggestive of irregular dominance. (*After A. Sorsby* (1940). *Brit. J. Ophthal.*, **24,** 469. Figs. 157 *b*, *c*, and *d*, illustrate appearances in this family.)
(*d*) Pedigree chart showing recessive sex-linkage. (*After K. T. A. Halbertsma* (1928). *Klin. Mbl. Augenheilk*, **80,** 794.)

Juvenile forms

Recessive type.—This is the classical type described by Stargardt (Fig. 157 *a*). Onset is fairly sudden and occurs late in childhood, generally at about the ages of 10–14 years. Typically, central vision declines rapidly, but occasionally it is not severely affected, and may perhaps remain good. Perimacular involvement is not uncommon, and minor peripheral pigmentary disturbances are sometimes present. Generally, however, the picture is clear cut: a sharply localized, strictly symmetrical mottling of both maculae with rapid decline in central vision and no further complications. The recessive character is well established (Fig. 156 *a* and *b*).

Dominant type.—This is rare, and appears to develop at an earlier age than the recessive type. It is likely that onset is less abrupt, the course more relentless and the end-result distinctly poorer than with the recessive type owing to extensive perimacular involvement (Fig. 157 *b*, *c*, and *d*). Irregular dominance is probably not uncommon (Fig. 156 *c*).

Recessive sex-linked type.—Judging by a pedigree shown in Fig. 156 *d* the possibility of this mode of inheritance has to be considered. In this particular pedigree anomalies in colour vision were present, possibly as independent affections.

Adult forms

Recessive type.—Fig. 158 *a* is a pedigree that suggests recessive inheritance. It would appear that there is a recessive affection beginning at about the age of 30 years with marked ophthalmoscopic changes which are not necessarily correlated with the amount of visual disturbance. The ophthalmoscopic picture (Fig. 157 *e*) is essentially more varied and more generally extensive than that seen in juvenile recessive macular dystrophy, but the affection probably runs a milder course, as well as setting in later.

Dominant type.—The evidence for a dominant macular dystrophy occurring at about the age of 40 or 45 years is not conclusive. It rests largely on the cases recorded by Behr, and they may well have been the early stages of the affection described below as a generalized fundus dystrophy. There is fuller evidence for a type occurring at about the age of 20 (Fig. 158 *b*).

Senile forms

It is not unlikely that some of the fine pigmentary macular lesions seen late in life are abiotrophic in character. There is, as yet, however, no evidence for this. There is also no definite evidence for the possibility that "colloid bodies" at the macula are genetic in character. The best evidence available as yet for a genetic basis of central lesions seen in the elderly has come from sibships showing exudative reactions.

Macular dystrophies with exudative reactions

Occasionally, exudative reactions are seen in particular families (Fig. 159). It would appear that, as in the macular dystrophies with atrophic reactions, three main types may be distinguished.

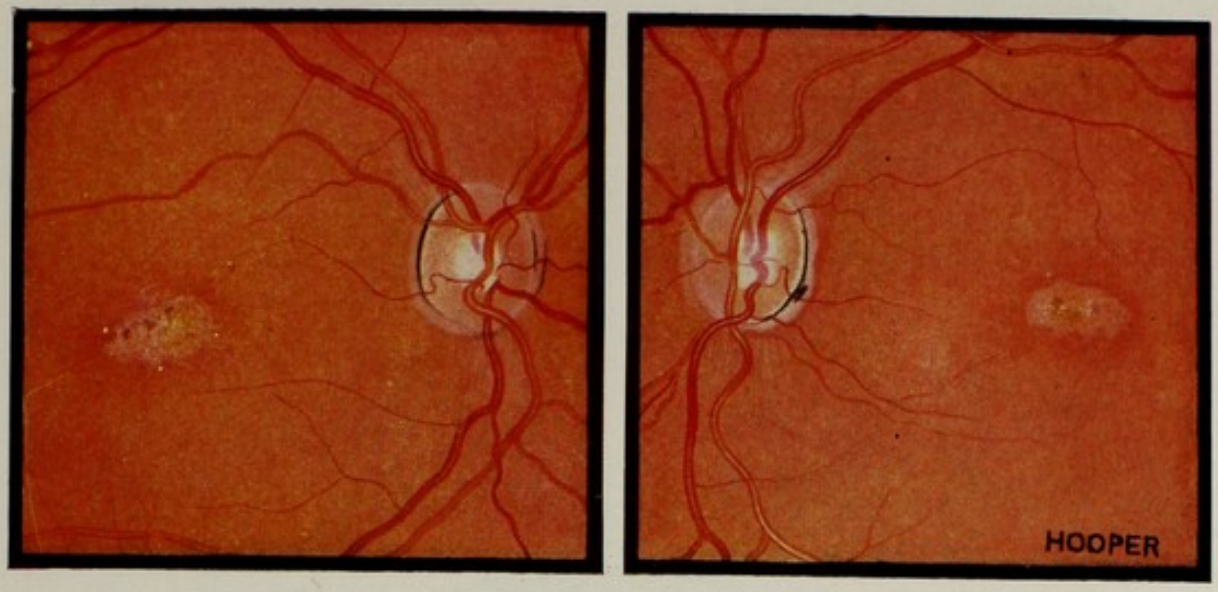
Juvenile forms

Recessive type.—Ophthalmoscopic appearances are illustrated in Fig. 159 *a* and *b*. The pedigree, suggestive of recessive inheritance, is shown in Fig. 160 *a*.

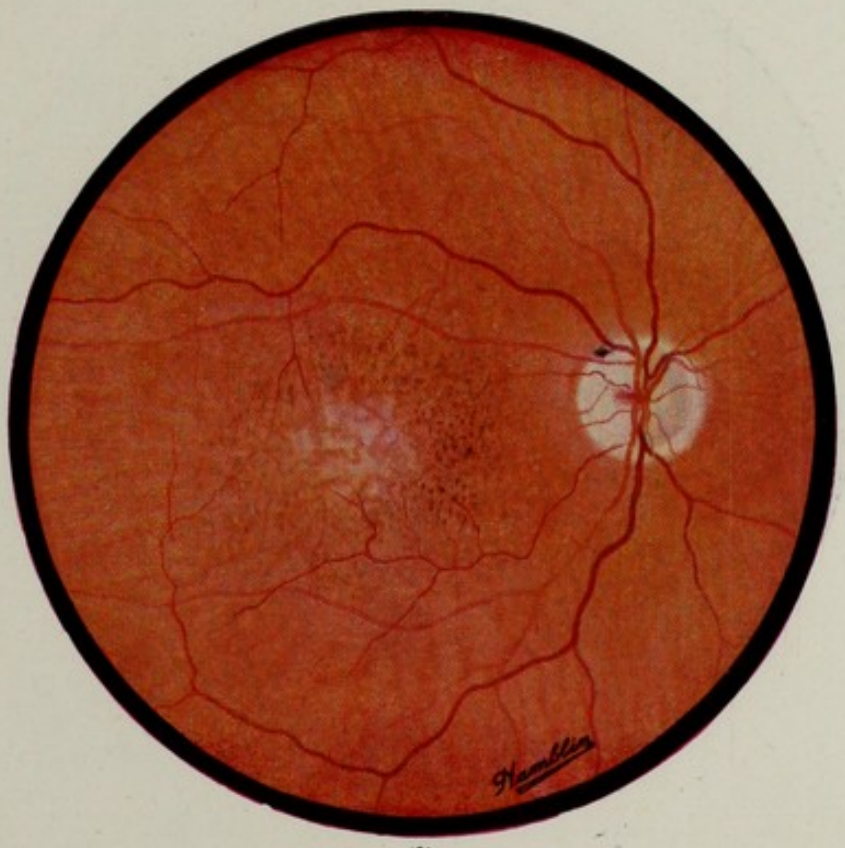
Dominant type.—Ophthalmoscopic appearances would not appear to be substantially different from those seen in the recessive type (Fig. 159 *c* and *d*). Dominant inheritance is suggested by Fig. 160 *b*.

Adult forms

Doyne's "familial choroiditis".—It is not unlikely that Doyne's choroiditis represents the early stages of the affection described below as generalized dystrophy of the fundus. The honeycomb reaction, which Doyne stressed in his early cases,



(*a*)



(*b*)

FIG. 157.—Macular dystrophies with atrophic reaction. Ophthalmoscopic appearances.
Juvenile recessive type.
(*a*) The right and left eyes of a girl aged 10 years. Her identical twin showed exactly similar lesions. (*Personal observation, Royal Eye Hospital, No.* 49/7561–2.)
Juvenile dominant type. (*After A. Sorsby* (1940). *Brit. J. Ophthal.*, **24,** 473.)
(*b*) The right eye of a woman, aged 43 years. The left eye was affected similarly.

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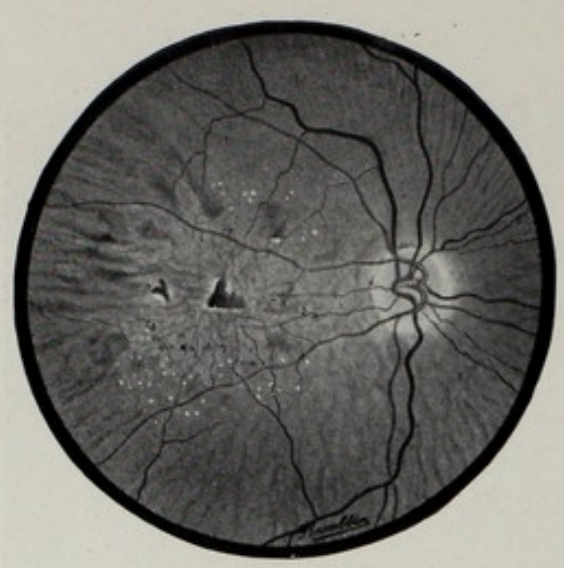
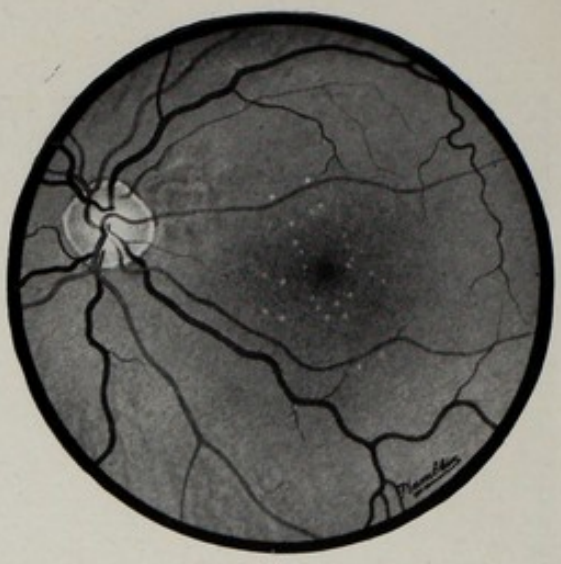


(*c*)



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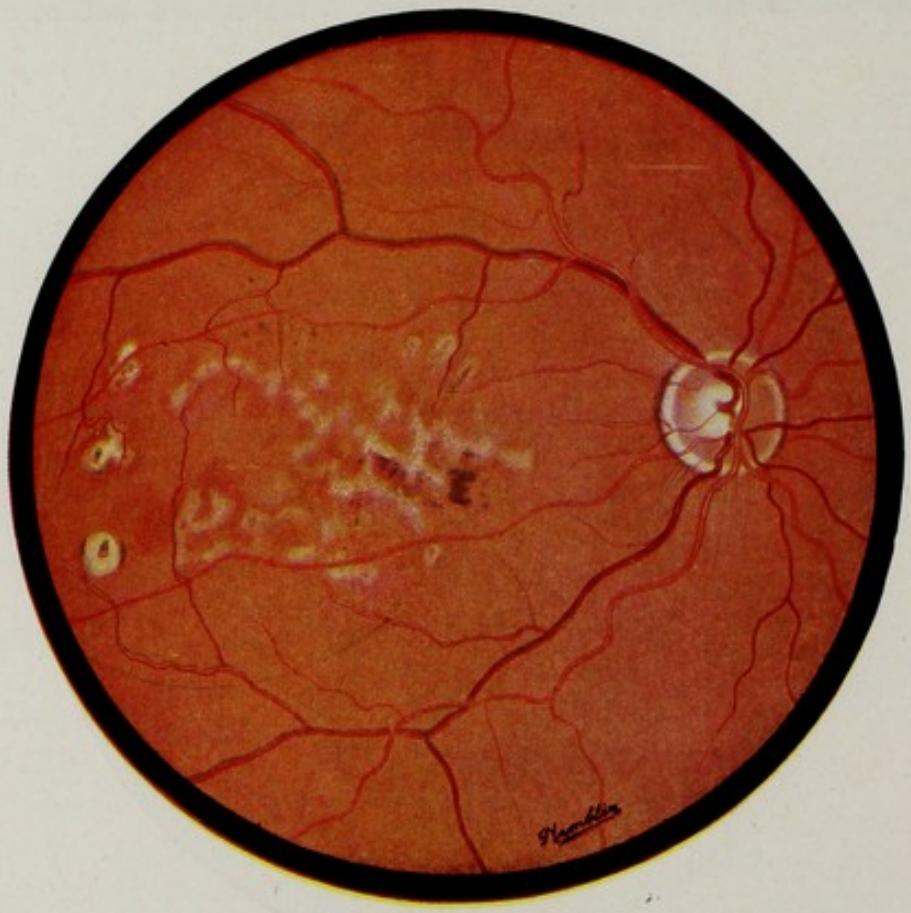

(*e*)

FIG. 157 (*cont.*)—Juvenile dominant type (*cont.*).

(*c*) Her sister 4 years younger was rather more severely affected.

(*d*) The earliest stages of the affection were observed in a niece, aged 5 years. It consisted of little more than heightened pigmentation over the central area with a few surrounding white dots. This child's brother, 3 years older, showed a well-established pigmentary lesion at the maculae.

Adult recessive type.

(*e*) The right fundus of a man aged 43 years. The left eye showed a similar lesion. Visual defect had existed for only a few years. A brother, aged 40 years, had a milder lesion with full vision. (*Personal observation. Royal Eye Hospital No.* 50/7584.)

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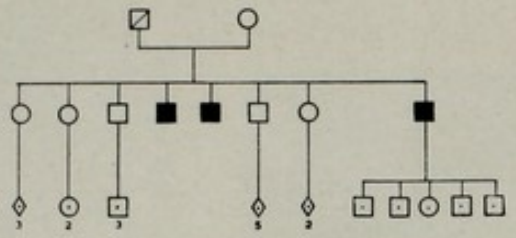


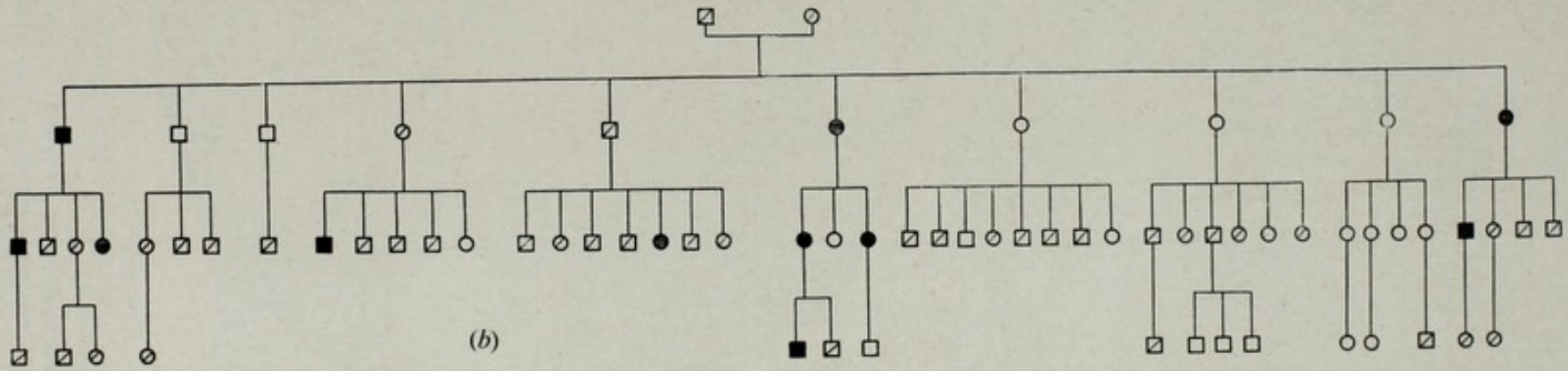
■ Affected.
▨ Reputed normal, deceased.
□ ○ Normal, seen.
□ ○ ◊ Children or young adults, ages ranging between 5 and 26 years.

(*a*)

FIG. 158.—Macular dystrophies with atrophic reactions. Adult forms. Pedigrees.

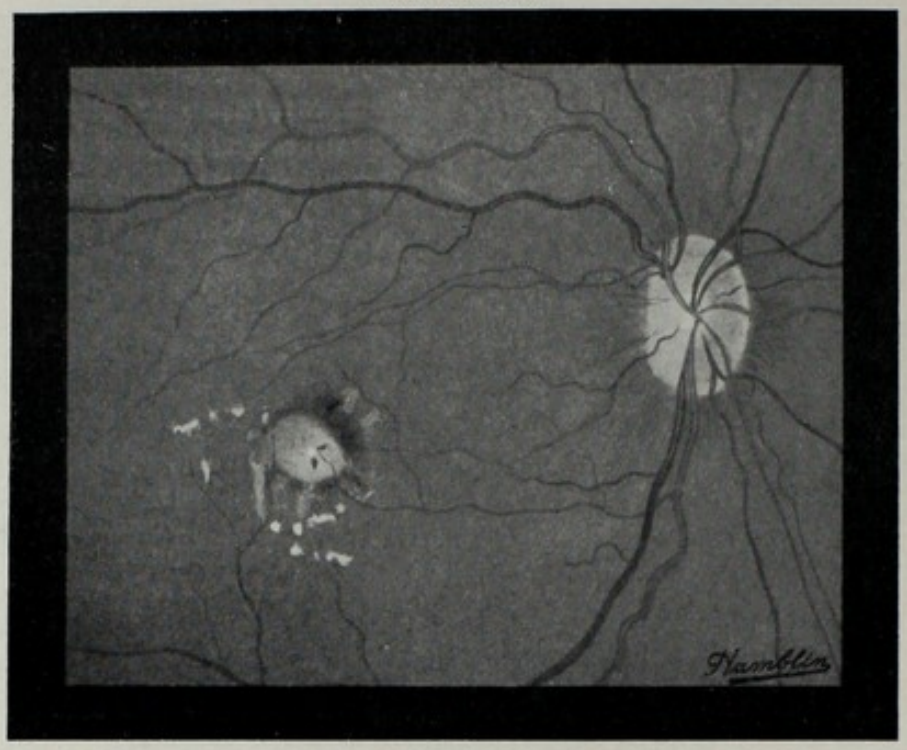
(*a*) Pedigree suggesting recessive inheritance. (*Personal observation on case shown in Fig.* 157*e*, *Royal Eye Hospital No.* 50/7584.)

(*b*) Pedigree showing dominant inheritance. (*After Gasteiger* (1936). *Ber. dtsch. oph. Ges.*, **51**, 86.)

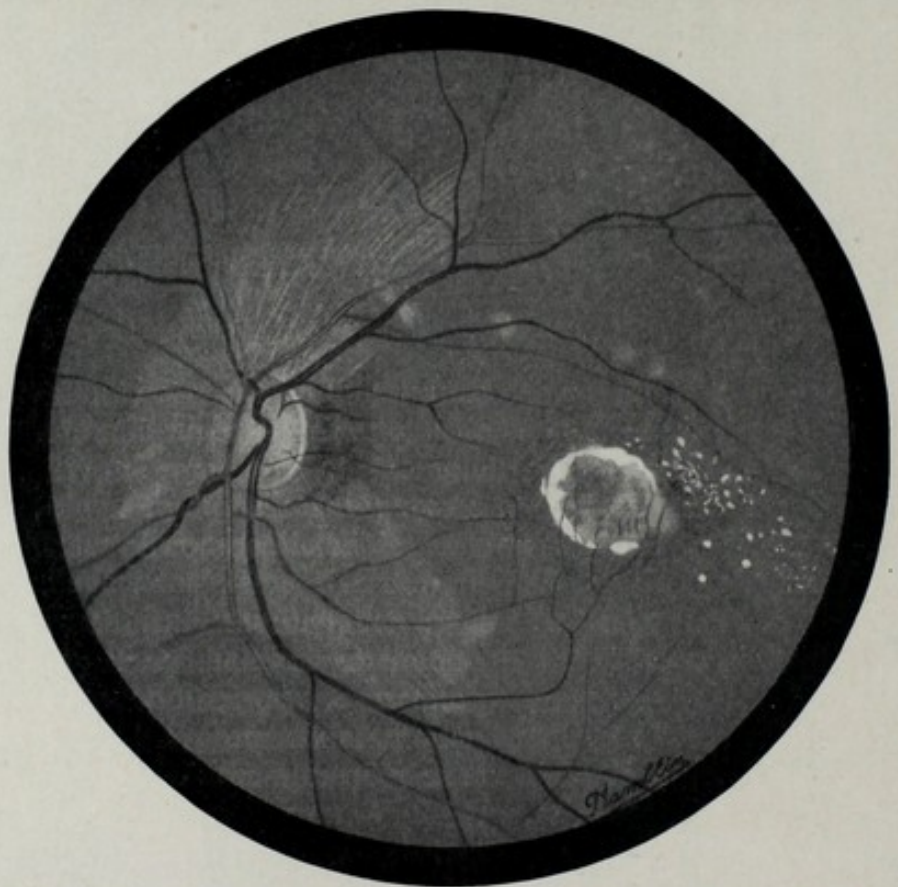


(*b*)

■ ● Affected.
▨ ⊘ Reputed normal.
□ ○ Normal, seen.



(*a*)

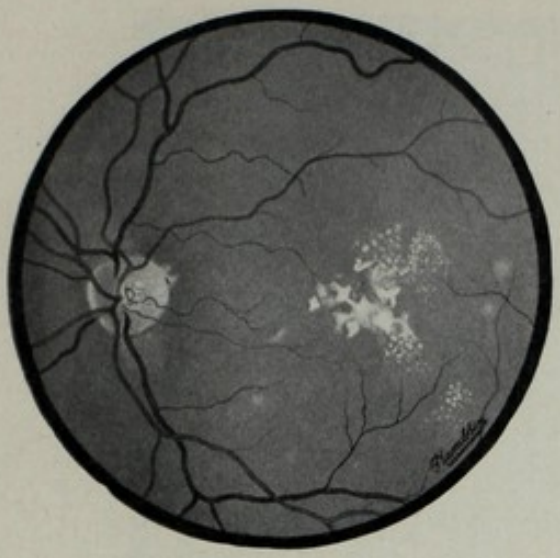


(*b*)

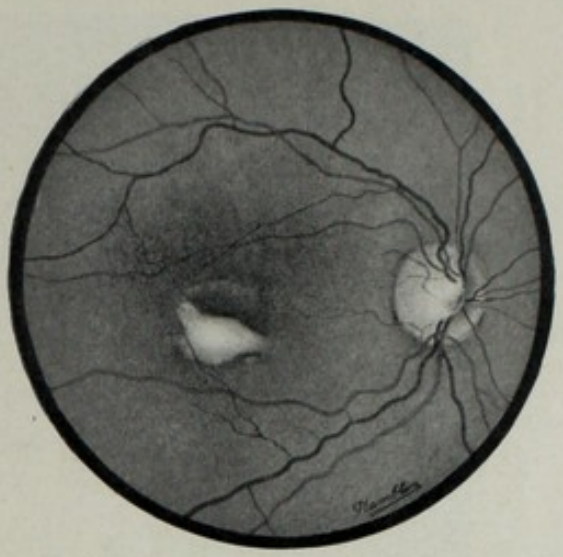
FIG. 159.—Macular dystrophies with exudative reactions. Ophthalmoscopic appearances. Recessive juvenile type. (*Cases of H. Grimsdale in A. Sorsby* (1940). *Brit. J. Ophthal.*, **24,** 477 (*Figs.* 14 *and* 16).)

(*a*) Fundus appearances in the right eye of a woman aged 25 years. Vision first failed at the age of 12 years when there was no ophthalmoscopically visible abnormality. Two years later white dots were present at both maculae. Central exudative reactions were present in the left eye.

(*b*) Her brother 3 years younger showed similar lesions. The parents were first cousins.



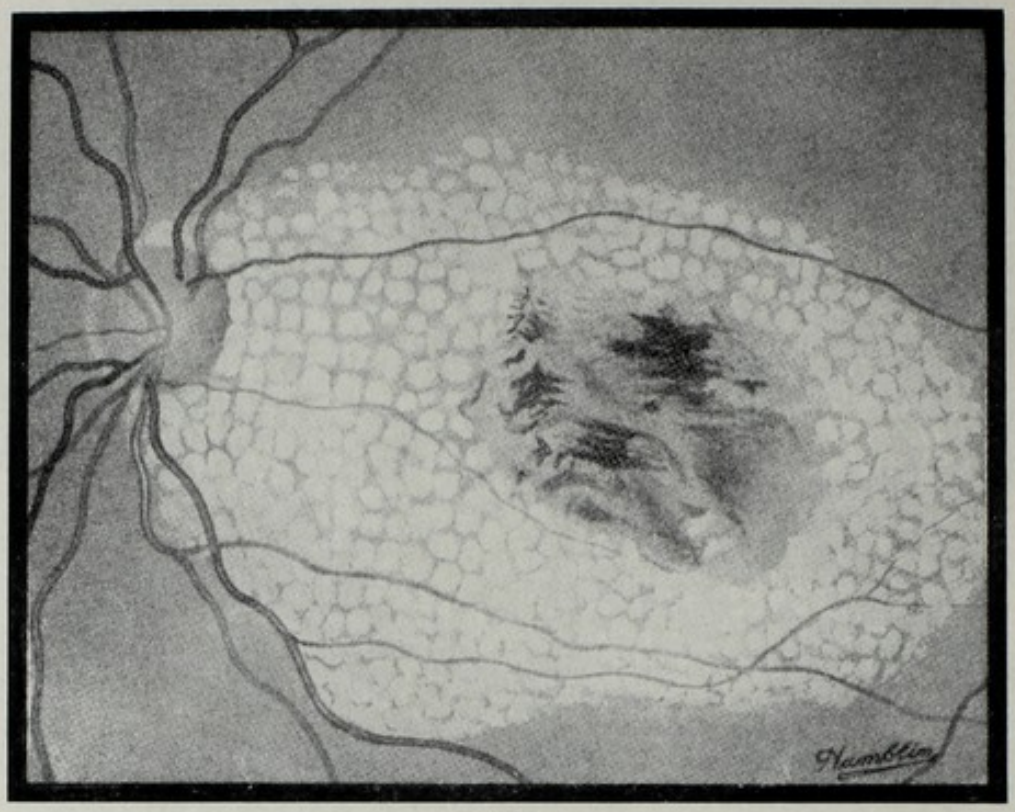
(*c*)



(*d*)

(*e*)

FIG. 159 (*cont.*).—Dominant juvenile type (*After A. Sorsby* (1940). *Brit. J. Ophthal.*, **24,** 475.)
(*c*) The left eye of a woman, aged 39 years, whose vision failed at about the age of 20 years.
(*d*) Her son, aged 11 years, already shows similar changes, with vision still 6/9.
Dominant adult type. (*After M. Tree* (1937). *Brit. J. Ophthal.*, **21,** 65.)
(*e*) Doyne's choroiditis.



(*f*)

FIG. 159 (*cont.*).—(*f*) Dominant adult type. (Doyne's choroiditis). (*After M. Tree* (1937). *Brit. J. Ophthal.*, **21**, 65.)

does not appear to have been a constant feature (Fig. 159 *e* and *f*). The one histological record available appears to incriminate the elastic membrane of Bruch as the starting point. Dominant inheritance is shown in the pedigree (Fig. 161).

For the present it may be best to regard "Doyne's choroiditis" as the adult form of exudative macular dystrophy, though the exudates are rather hard, and differ in this respect from the juvenile forms and the senile form.

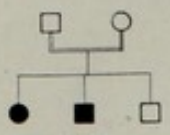
Senile forms

To what extent the exudative senile reactions seen in the elderly are genetic in origin is as yet undetermined. There are two case records of the occurrence of the affection in sibs.

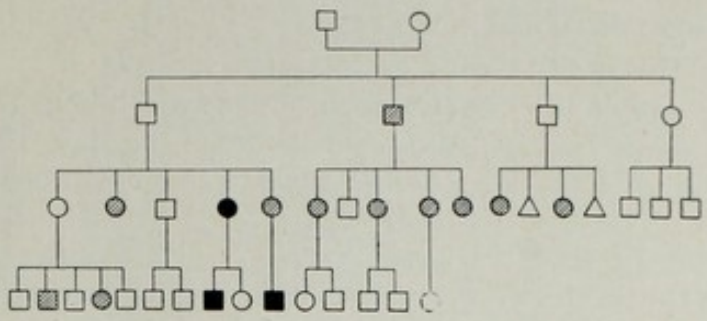
FUNDUS LESIONS, POSSIBLY RETINAL OR POSSIBLY CHOROIDAL IN ORIGIN

Gyrate atrophy

It is unlikely that gyrate atrophy is a stage in the development of choroideremia, as has been repeatedly suggested. Though many cases of gyrate atrophy have been followed up, in no case is there a record of choroideremia as the end-result. Ophthalmoscopically, a plexus of blood vessels at the macula is common in choroideremia, but is not seen in gyrate atrophy. Moreover, the two affections have a different mode of inheritance: gyrate atrophy is probably recessive in most cases (Fig. 162 *a*); choroideremia on the other hand is clearly sex-linked. A possible relationship to retinitis pigmentosa is suggested by Fig. 162 *b*.



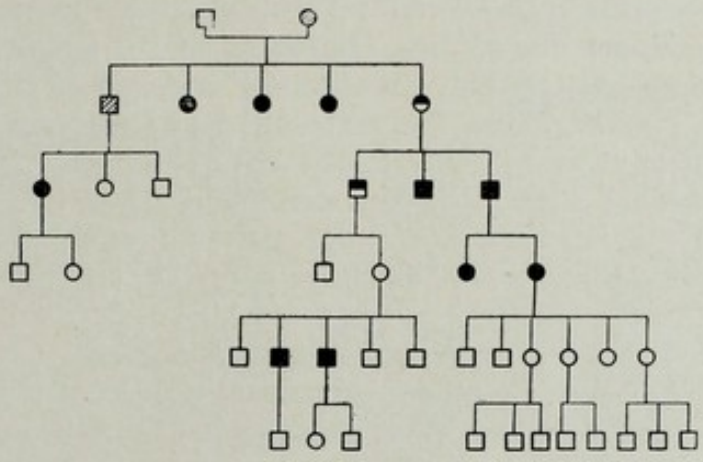
(*a*)



■ ● Affected.
▨ ◎ Reputed affected.

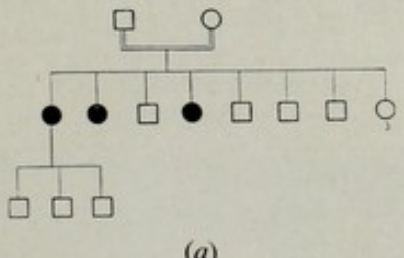
(*b*)

FIG. 160.—Macular dystrophies with exudative reactions. Juvenile forms. Pedigrees.
(*a*) Pedigree suggestive of recessive inheritance. (*Cases of H. Grimsdale. In A. Sorsby* (1940). *Brit. J. Ophthal.*, **24,** 477.
(*b*) Pedigree suggestive of dominant inheritance. (*After A. Sorsby* (1940). *Brit. J. Ophthal.*, **24,** 475.

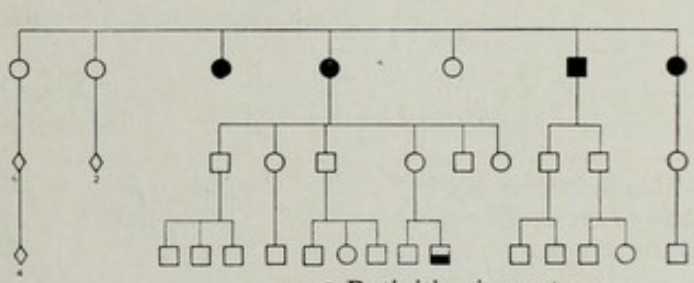


■ ● Affected.
◓ ◒ Known to have had "bad sight."
▨ ◎ Nothing definite known.

FIG. 161.—Adult (dominant) exudative macular dystrophy (Doyne's choroiditis). Pedigree chart. (*After M. Tree* (1937). *Brit. J. Ophthal.*, **21,** 65.)



(*a*)



■ ● Retinitis pigmentosa.
◓ Gyrate atrophy of choroid and retina.

(*b*)

FIG. 162.—Gyrate atrophy of the retina and choroid.
(*a*) Pedigree suggestive of recessive inheritance. (*After C. W. Cutler* (1895). *Arch. Ophthal.*, **24,** 334.)
(*b*) Pedigree of a family with retinitis pigmentosa in which a case of gyrate atrophy occurred. (*After J. Bourquin and J. B. Bourquin* (1949). *Ophthalmologica*, **118,** 848.)

Generalized fundus dystrophy

This entity shows the following features:

Age at onset.—The affection begins at about the age of 40 years.

Subjective symptoms.—The first subjective symptoms are blurring of central vision in one eye followed by the same symptoms in the other eye within a matter of months, or perhaps within a few years. It is not known whether the two eyes may be affected simultaneously. Central vision rapidly declines, but there is no involvement of peripheral vision or colour vision at this stage. There are no symptoms of night-blindness early on or during the course of the affection.

Objective signs.—Objectively the first signs are oedema, haemorrhages, and exudates in the central area. This progresses to scar formation with a varying amount of pigment proliferation, which may be exceedingly massive. The choroidal vessels become exposed and show some sclerosis. Over the course of years the process extends peripherally, choroidal sclerosis generally becomes more manifest and sometimes dominates the picture. During its spread peripherally, exudates—sometimes patterned—may appear. Occasionally, widespread glistening "colloid" bodies may be a pointing sign. The end-stage is widespread disappearance of the choroidal vessels exposing the sclerotic covered irregularly by proliferating pigment. The terminal stage produces practically total blindness. The polymorphism of the fundus reactions is such that any stage of oedematous and inflammatory fundus lesions as well as diffuse choroidal sclerosis can be simulated (Fig. 163).

Course.—The full course of the affection spreads normally over about 35 years. The process may, however, be milder or more severe in individual cases.

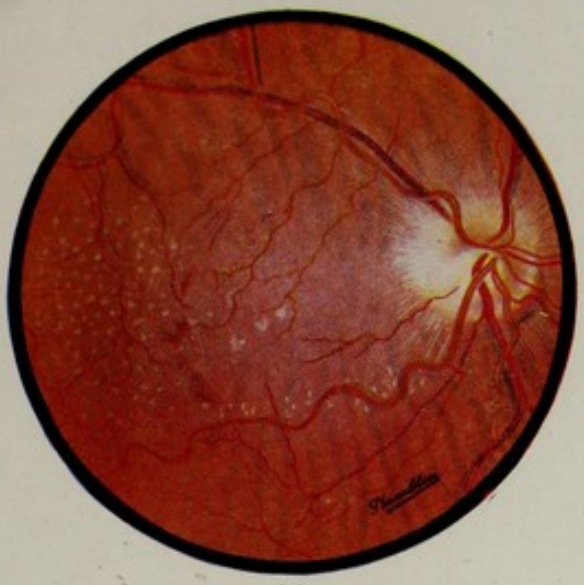
Heredity.—Genetically the condition is probably a simple autosomal dominant (Fig. 164).

This affection, which begins as a central lesion, presents a sharp contrast to the recessive macular dystrophy of the Stargardt type, as shown in the following table.

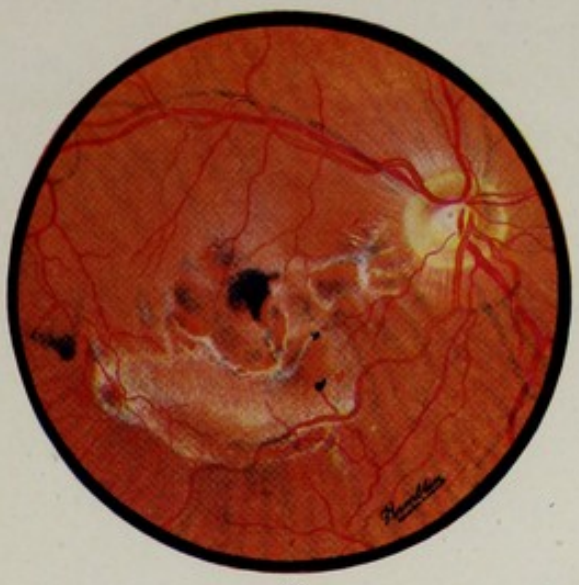
TABLE VIII

CLINICAL FEATURES OF STARGARDT'S MACULAR DYSTROPHY CONTRASTED TO THOSE OF GENERALIZED FUNDUS DYSTROPHY

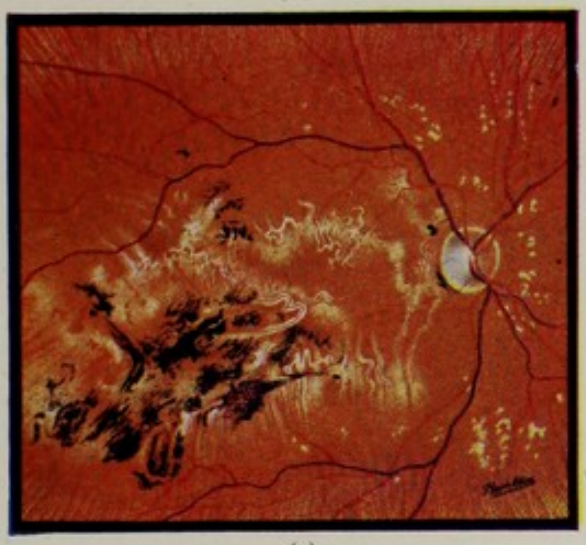
Features	Macular dystrophy (Stargardt)	Generalized fundus dystrophy
Mode of inheritance	Recessive	Dominant
Age of onset of symptoms	Adolescence	About 40 years
Ophthalmoscopic appearances :		
Site	Central	Central at first ; then generalized
Reaction	Mottling, fine pigment changes and atrophy	Oedema, haemorrhages, exudates, colloid bodies, gross pigment changes
End-result	Central lesion	Generalized chorio-retinal atrophy
Symptoms	Loss of central vision; retained peripheral fields	Loss of central vision; progresses to total blindness



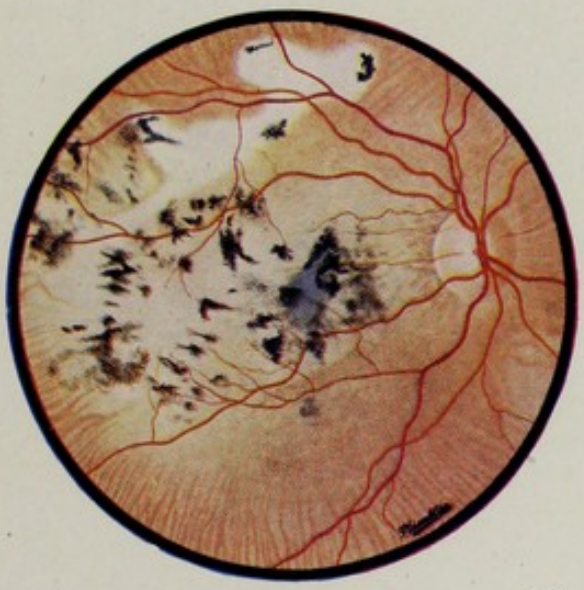
(*a*)



(*b*)



(*c*)



(*d*)

(*e*)

FIG. 163.—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 neuroretinal 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.

To face page 178

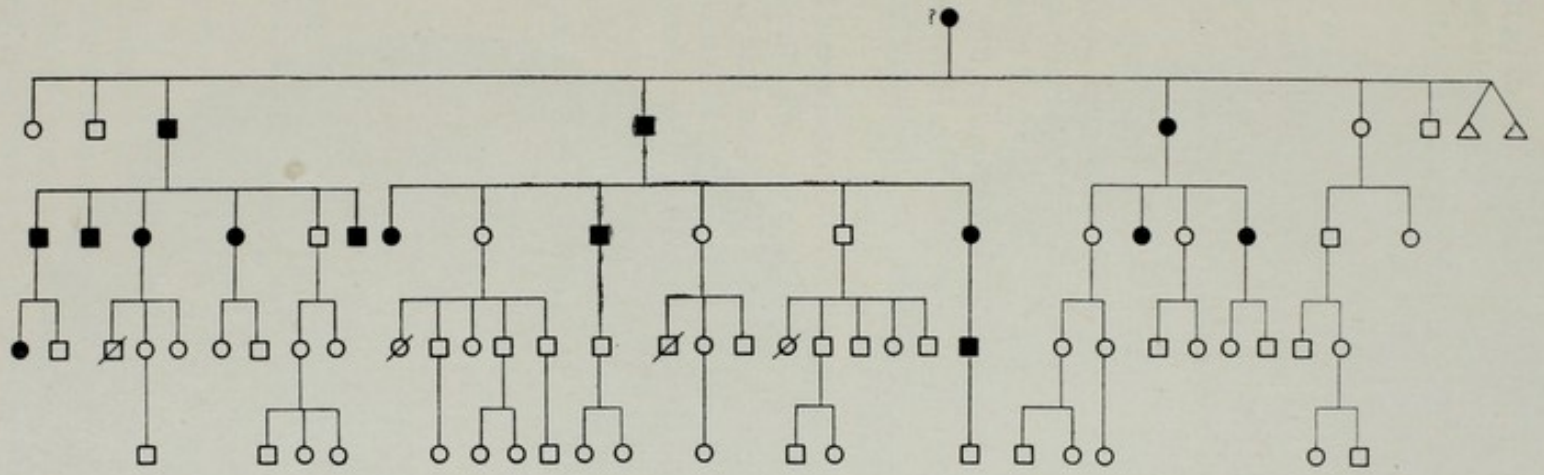
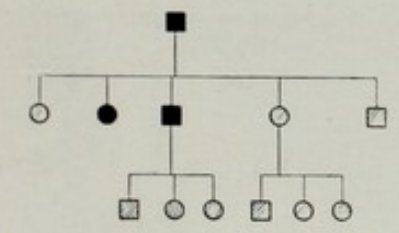


FIG. 164.—Generalized dominant fundus dystrophy. Pedigree showing dominant inheritance. (Most of the members of the fourth and fifth generations have not yet reached the age of manifestation of the affection.) (*After A. Sorsby and M. E. Joll Mason* (1949). *Brit. J. Ophthal.*, **33**, 67.)



■ ● Myopia and detachment of retina.
▨ ○ Myopia.

FIG. 165.—Detachment of the retina in a family of high myopia. (*After M. S. Zimmer* (1937). *Contribution à l'étude du caractère familiale du décollement rétinien idiopathique. Lausanne; Thesis.*)

OTHER AFFECTIONS OF THE RETINA

Detachment of the Retina

There are a number of pedigrees on retinal detachment suggestive of both dominant and recessive inheritance. Myopia is generally but not invariably present, and in most cases the genetic basis for these detachments is probably the inherited myopia of a type leading to detachment (Fig. 165). The possibility of a hereditary basis for detachment in general has still to be assessed.

Three special forms of detachment have a definite genetic basis:

Congenital falciform detachment (Figs. 166 *a* and *b*).—Most of the recorded cases have occurred in boys. Weve holds that there is a high rate of consanguinity; recessive inheritance cannot, however, be taken as proved and the possibility of sex-linkage arises.

Congenital total detachment (*pseudoglioma*).—Congenital total detachment (Fig. 166 *c* and *d*) is also more frequent in males. Evidence for sex-linkage—at any rate for some forms—is more conclusive (Figs. 167 *a* and *b*). That congenital total detachment is a variant of congenital falciform detachment has been suggested by Weve, and is supported by such pedigrees as those shown in Fig. 168.

Presumed congenital cystic detachment.—This affection (Fig. 166 *e* and *f*) is also noted almost exclusively in males, and it is not known definitely whether it is congenital. Fig. 169 suggests that the affection is sex-linked.

It is not unlikely that not only is congenital falciform detachment a variant of congenital total detachment of the retina, but that these two affections themselves link up with cystic detachment. The occurrence of a falciform fold in a member of a family with cystic detachment shown in pedigree Fig. 169 lends support to that reading, apart from the fact that most cases of these three affections appear to be confined largely to males, and possibly inherited in a recessive sex-linked manner.

Congenital vascular veils in the vitreous, as described by Mann and Macrae (1938) appear to be aspects of congenital cystic detachment.

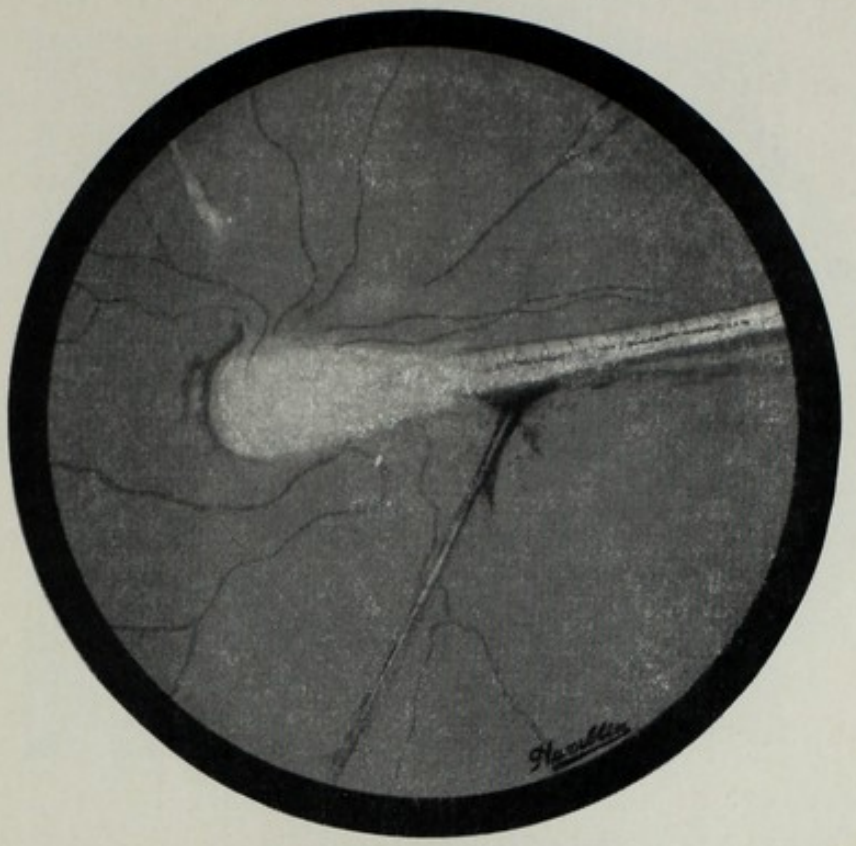
Retinoblastoma

A hereditary factor in retinoblastoma is well recognized. The earliest records gave affected sibships, and the suggestion emerged that retinoblastoma was recessive. Consanguinity was, however, exceptional. A clearer picture emerged when records of affected children of survivors began to appear. That glioma is, in fact, a dominant affection is shown by Fig. 170 *a*. Presumably it can also appear as an irregular dominant (Fig. 170 *b*).

Whether these pedigrees are exceptional can only be established if the fate of children in a successive series of glioma survivors is known. Such evidence as is available suggests that survivors from glioma tend to pass the affection on to their children (Fig. 170 *a*). Of 8 children born to 5 survivors from glioma, Reese found 7 affected.

Glioma generally occurs as isolated—"sporadic"—cases in a family the history of which is clear. In a series of 60 cases with 103 sibs, Reese found only 1 affected

(*a*)



(*b*)

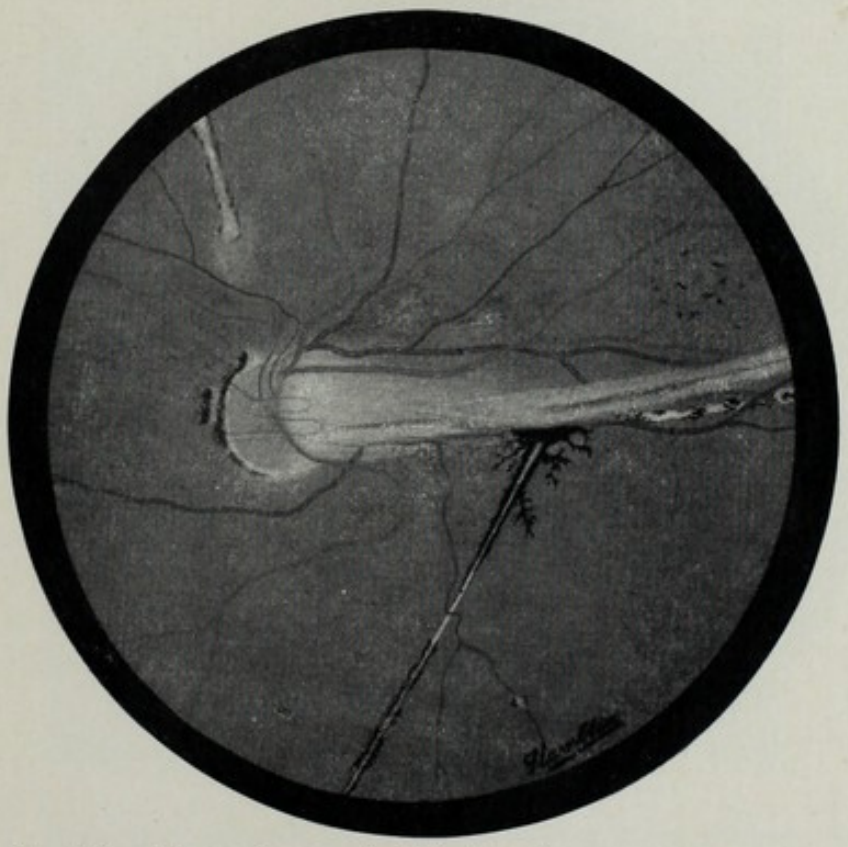
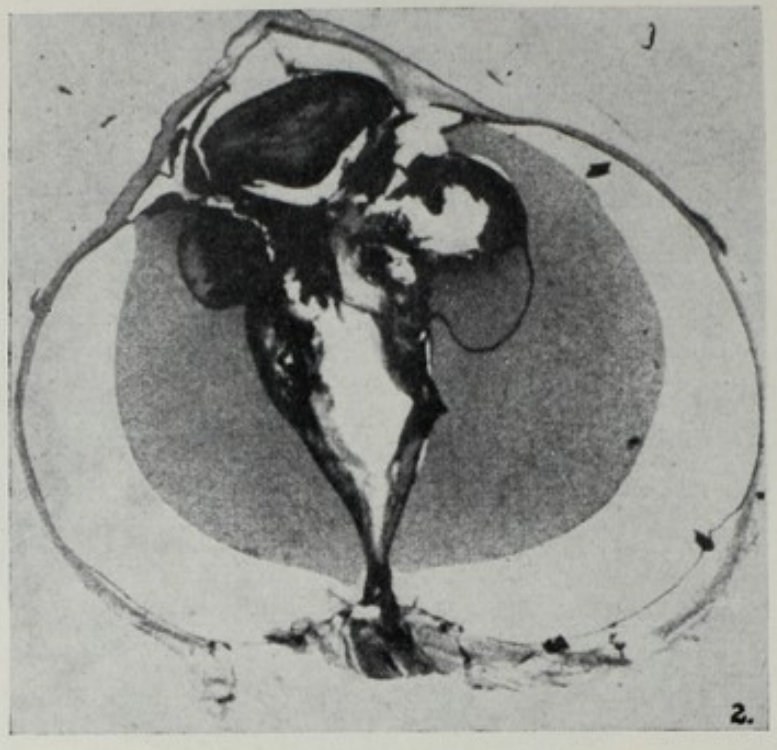
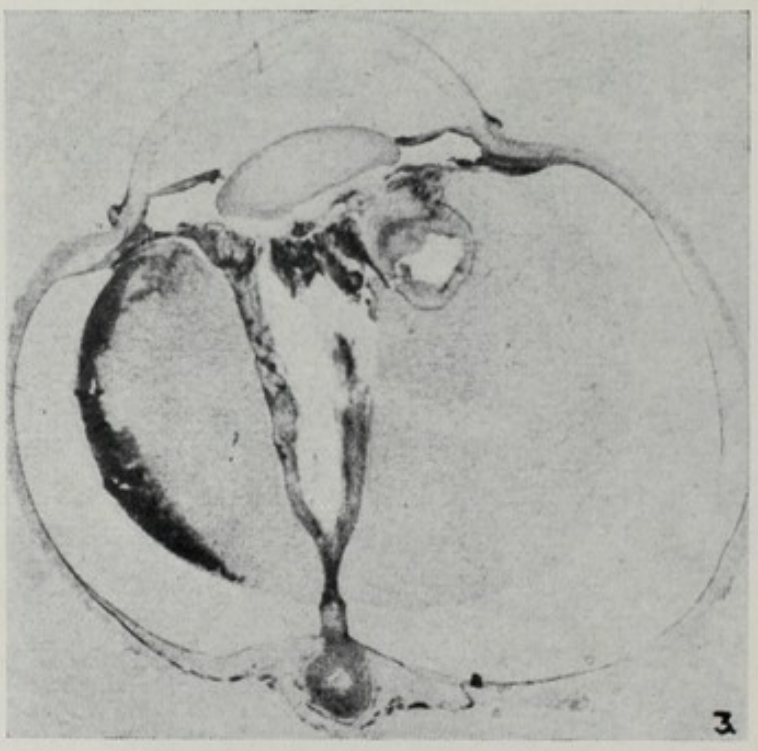


FIG. 166.—Forms of congenital detachment.
(*a*) and (*b*) Falciform detachment in a boy aged 12 years. Right and left eyes. (*Drawings made in* 1928 *of a patient seen by the late A. D. Griffith.*)



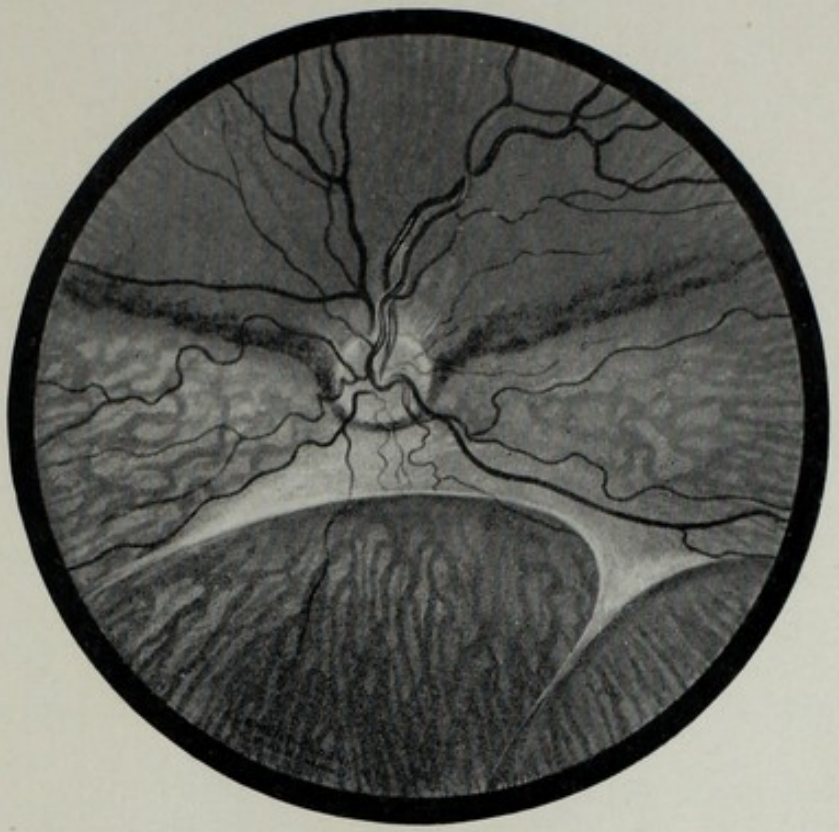
(*c*)



(*d*)

FIG. 166 (*cont.*).—(*c*) and (*d*) Total detachment of the retina (pseudoglioma). Two eyes of members of the family shown in pedigree chart Fig. 167 (*a*). (*After W. M. G. Wilson* (1949). *Canad. med. Ass. J.*, **60**, 580.)

(*e*)



(*f*)

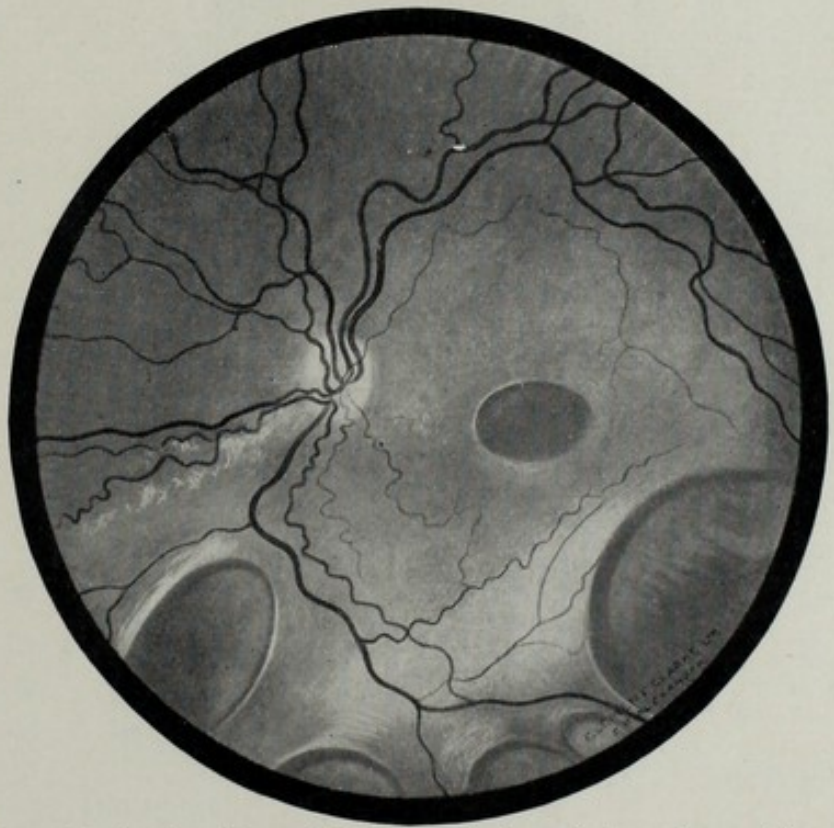
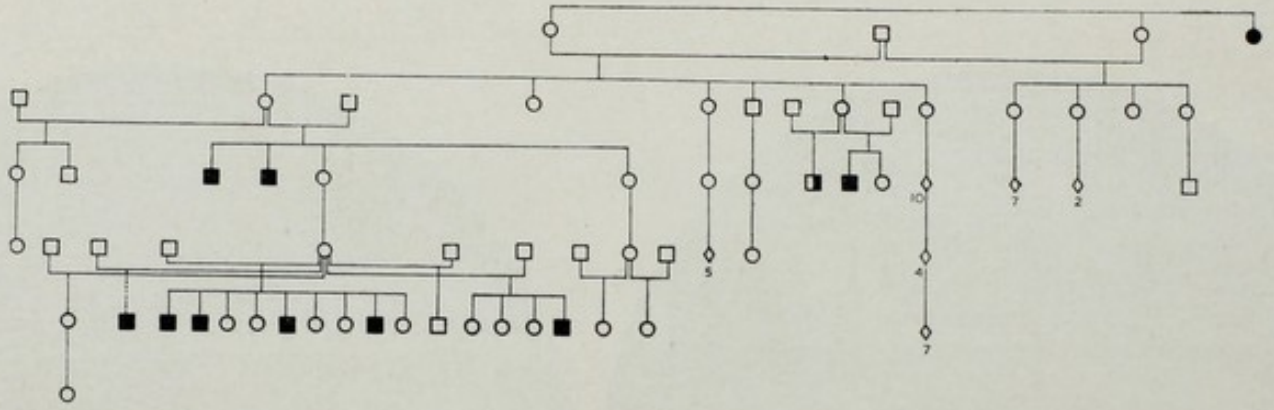


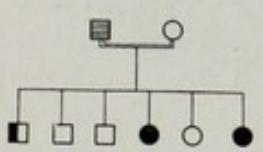
FIG. 166 (*cont.*).—(*e*) and (*f*) Congenital cystic detachment. The left fundus of a boy aged 13 years and the left fundus of his eldest maternal uncle, aged 36 years, members of the family shown in pedigree chart Fig. 169. (*After A. Sorsby, M. Klein, J. H. Gann and G. Siggins. In the press.*)



■ ● Affected, bilateral.
◨ Affected, left.

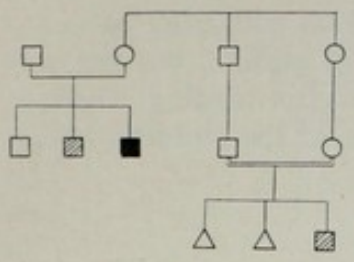
(*a*)

FIG. 167.—Congenital total detachment (pseudoglioma). Pedigrees suggestive of sex-linkage.
(*a*) (*After W. M. G. Wilson* (1949). *Canad. med. Ass. J.*, **60,** 580.)
(*b*) (*After E. Clarke* (1898). *Trans. Ophthal. Soc. U.K.*, **18,** 136.)



● Affected, bilateral.
◧ Affected, right.
▨ Unsuccessful operations in childhood, reputedly for "cataract."

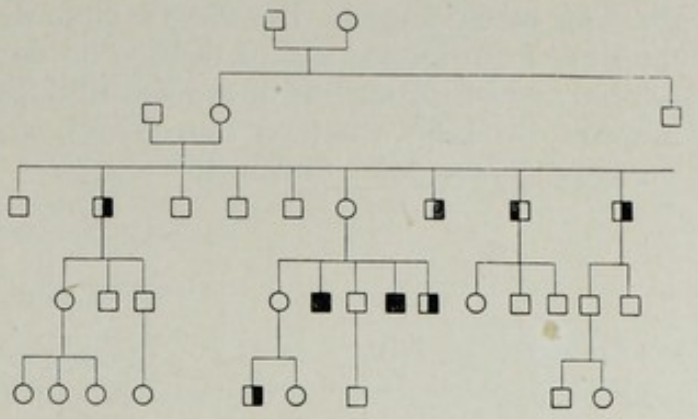
(*b*)



■ Falciform detachment.

▨ Pseudo-glioma.

FIG. 168.—Occurrence of falciform detachment and pseudoglioma within the same family. Recessive inheritance, but also sex-linked inheritance come into question. (*After H. M. Weve* (1935). *Arch. Augenheilk*, **109,** 370.)

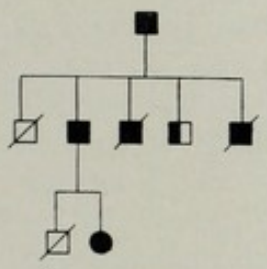


■ Affected, bilateral.

◨ Affected, left.

◧ Affected, right.

FIG. 169.—Congenital cystic detachment. A pedigree suggestive of sex-linkage. (*After A. Sorsby, M. Klein, J. H. Gann and G. Siggins. Brit. J. Ophthal, in the Press.*)



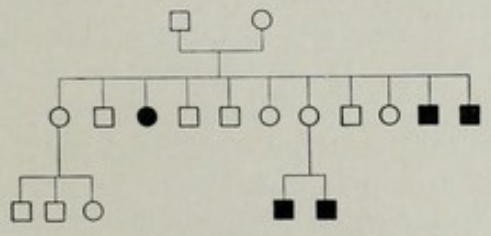
(*a*)

■ ● Bilateral retinoblastoma.

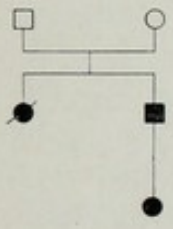
◧ Right retinoblastoma.

⊠ { II, 1 Died at 8 days after premature birth.
III, 1 died at 5 weeks from "congenital heart disease".

■ Died from retinoblastoma.



(*b*)



(*c*)

FIG. 170.—Retinoblastoma.

(*a*) Pedigree showing dominant inheritance. (*After A. D. Griffith and A. Sorsby* (1944). *Brit. J. Ophthal.*, **28,** 279.)

(*b*) Pedigree showing irregular dominance. (*After O. Purtscher* (1915) *Zbl. prakt. Augenheilk.*, **39,** 193.)

(*c*) Occurrence of bilateral retinoblastoma in the only child of a man who, like his sister, had bilateral tumours. (*After S. Snell* (1905). *Trans. Ophthal. Soc. U.K.*, **25,** 261, *and personal observation* (1948).)

sib. This would suggest that there is little danger of glioma occurring amongst the sibs of an isolated case if there is no family history of glioma, but the substantial number of records of affected sibships is against such a reading. There is, however, no doubt whatever that there is a great danger of the children of any surviving glioma patient being affected.

CHAPTER 6

THE OPTIC NERVE

OPTIC ATROPHY

Leber's Disease

Leber's disease with its abrupt onset, rapid evolution, and essentially stationary course subsequently (with a not infrequent tendency towards some improvement) presents a clinical picture that differs from the abiotrophies in many of the essential features. These clinical incongruities are as puzzling as the difficulties in interpreting the genetic behaviour of the affection.

There is an exceptionally large number of pedigrees on Leber's disease. Some features stand out beyond dispute (Figs. 171 *a* and *b*).

(1) The affection is very much more common in men than in women. The incidence of affected women in pedigrees of Leber's disease varies considerably in pooled pedigrees for different countries. In all probability this arises from the inclusion of a variable number of pedigrees of autosomal dominant optic atrophy—an affection that differs from Leber's disease in both clinical and genetic aspects.

(2) In most sibships there is a tendency for most of the men to be affected.

(3) Likewise, in sibships of affected men there is a tendency for most of their sisters to be carriers.

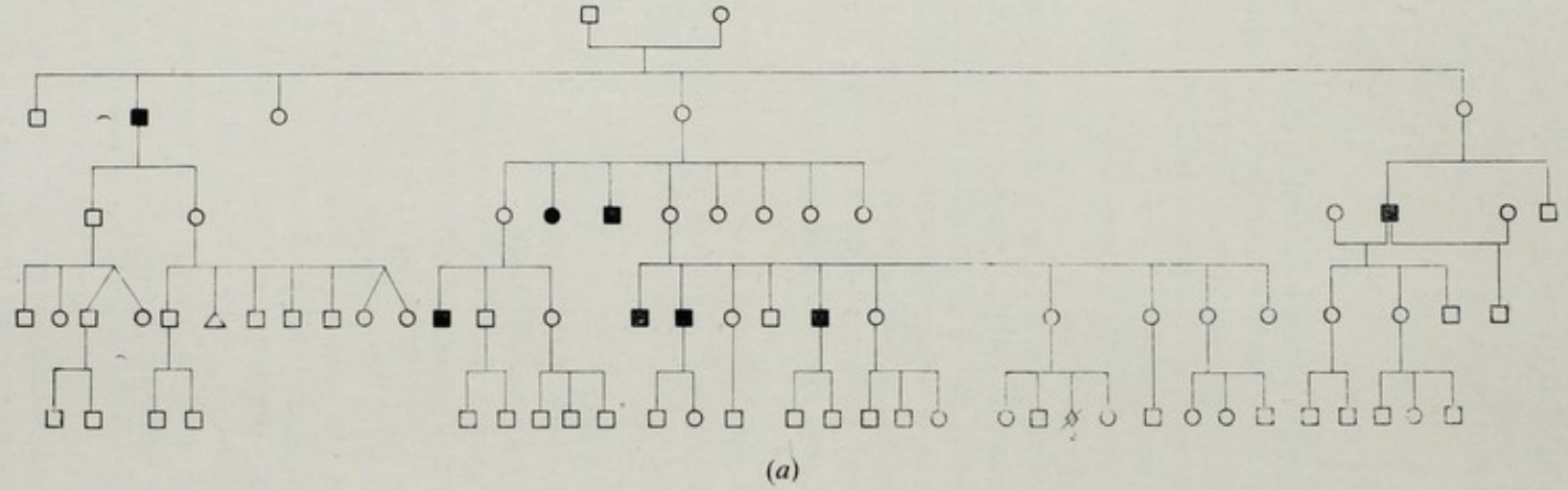
(4) It is now accepted that there is no evidence that a female carrier has an affected father. It appears that transmission is through continuous descent by women, so that the female carrier derives her carrier state from her mother and not her father.

(5) Likewise, and as a corollary, it is accepted that an affected man does not transmit the carrier state to his daughters, nor the affection to his sons. In other words an affected man marks the end of a line of descent.

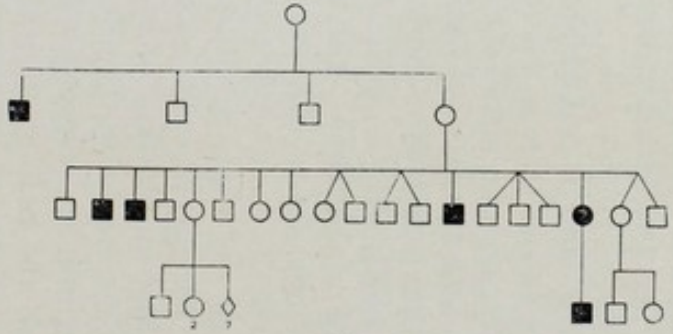
The fact that the sons of carrier women are affected suggests a simple sex-linked recessive mode of inheritance, and this mode of inheritance has been assumed and is still widely held as applicable to Leber's disease. It is obvious that no such simple mode of inheritance can explain the transmission of Leber's disease, for such an assumption would mean that the grandsons of affected men would be affected—and this is not the case. Transmission by women carriers also fails to explain both the high proportion of affected sons and of carrier daughters (instead of the theoretically expected 50 per cent), nor would it explain readily the fairly high proportion of affected women, unless it is assumed that heterozygous women manifest the affection fairly frequently.

From the practical aspect the significant thing is that it is not the affected man who spreads the pathogenic gene in the population, but his unaffected sister—obviously a matter of importance in advising such patients and their relatives.

The mode of inheritance of Leber's disease fits in with an old pre-mendelian observation which was summed up in the so-called Lössen's law. This stated—in contrast to Nasse's law or Horner's law—that transmission is not by affected



(*a*)



(*b*)

FIG. 171.—Leber's disease.

(*a*) Pedigree showing affected sons of unaffected women whose brothers are affected. An affected woman is also seen. (*After C. H. Usher* (1927). *Brit. J. Ophthal.*, **11**, 417.)

(*b*) Pedigree showing transmission by an affected woman to her son. The son was, however, affected before the mother manifested the disease. (*After E. Godtfredsen* (1949). *Acta Ophthal.*, **27**, 429.)

men but exclusively through women. Lössen's law was elaborated on findings in haemophilia and it appears that it is not applicable in this affection. In Leber's disease it does, however, apply.

The mode of inheritance seen in Leber's disease cannot be explained on the mechanism of sex chromosomes as understood today, and various attempts have been made to fit the transmission of Leber's disease with present-day genetic theory. The most significant explanation is the one which regards Leber's disease not as a sex-linked affection, but an autosomal dominant with special features. This view, advocated by Komai in 1934, is based on several assumptions —unproven and very largely unprovable.

(1) It is held that the disease is transmitted autosomally, but that the expression is different in the two sexes. It is completely, or almost completely, dominant in men, and completely, or almost completely, recessive in women. Such an assumption, consistent with experimental findings, presents no theoretical difficulties.

But this assumption does not explain the manifestation of the affection in succeeding generations. A recessive gene in women should become manifest in 50 per cent of their sons, whilst a dominant gene in men should produce 50 per cent of sons affected and 50 per cent of daughters with an unexpressed gene. These carrier daughters would in turn have 50 per cent of affected sons, that is, an affected man would have affected grandsons. None of these expectations is actually observed.

(2) To overcome these difficulties, Komai postulated that spermatozoa carrying pathogenic genes are less viable than normal spermatozoa. This would explain why affected men do not transmit the affection. Women carriers would remain the only possible source of transmitting the affection, and, as the condition is dominant in men, 50 per cent of the sons should be affected. The considerably greater incidence than 50 per cent observed in pedigrees would, therefore, seem to require yet a further hypothesis.

Other and less probable explanations have also been advanced. Waardenburg holds that, if it is assumed that cytoplasmic changes are produced in the ovum by a spermatozoon carrying an abnormal gene, the X chromosal theory can be upheld. This view has been further elaborated by Imai and Moriwaki.

The possibility that the sudden onset of Leber's disease conditions a chemical change in the affected man which causes the pathogenic gene to mutate back to normal does not seem to have been considered.

Japanese cases

The complexities of Leber's disease are made still more difficult by the pedigrees recorded from Japan. Here the incidence of affected women is very much higher than in the European cases, and it is possible that the clinical course is also different. It is, therefore, not unlikely that the Japanese cases may represent a different clinical entity.

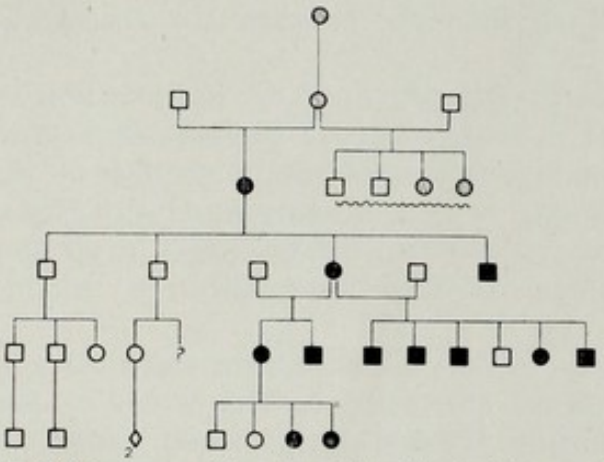
Congenital Optic Atrophy

In the past, pedigrees of congenital optic atrophy, and of optic atrophy setting in early in life, were recorded in the literature as examples of Leber's optic atrophy with anticipation. These cases are, however, a distinct clinical entity with a

clear-cut mode of inheritance of their own. Some of the confusion in the interpretation of pedigrees of Leber's disease has arisen from failure to isolate these cases into separate categories.

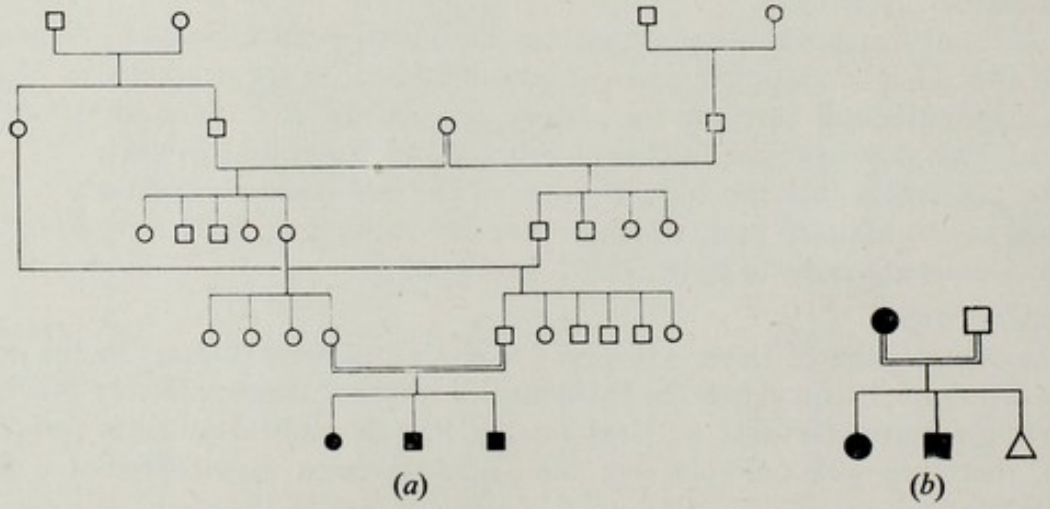
Dominant congenital optic atrophy

Fig. 172 shows a pedigree of inheritance over four generations of actually observed cases with two antecedent generations also reputed affected. Clinically this group differs from Leber's disease not only in its early onset, but also in ophthalmoscopic appearances and in the type of field defect it produces. Ophthalmoscopically, atrophy involving the whole of the disc with atrophic excavation is seen, dead white in colour. The field defect is a peripheral shrinking instead of the characteristic central scotoma of Leber's disease. Nystagmus is common. An outstanding



■ ● Known as affected to either Nettleship or to Dorrell and to Thompson and Cashell.
◎ Reputed affected.

FIG. 172.—Dominant congenital optic atrophy. Pedigree chart combining the findings of Nettleship with those of Dorrell and of Thompson and Cashell. (*After E. Nettleship* (1909). *Trans. Ophthal. Soc. U.K.*, **29,** *cxvi and cxlix; E. A. Dorrell* (1932). *Roy. Berks. Hosp. Rep.*, 122, *A. H. Thompson and W. G. T. Cashell* (1935). *Proc. R. Soc. Med.*, **28,** 1415.)



(*a*) (*b*)

FIG. 173.—Congenital or infantile recessive optic atrophy.

(*a*) An affected sibship whose parents were related. (*After P. J. Waardenburg* (1932). *Das menschliche Auge und seine Erbanlagen, p.* 459. *The Hague; Nijhoff.*)

(*b*) An affected sibship, the offspring of an affected mother and a normal father who was her first cousin. (*After M. Gunn.* (1907). *Trans. Ophthal. Soc. U.K.*, **27,** 221.)

feature is that the affected members are "born with the sight as it is now" and that "none of the affected get either worse or better". Objective evidence of optic atrophy is recorded as early as at the age of 6 months.

Another possible variety of dominant optic atrophy is suggested by an isolated record. Handmann observed in a father and son a congenital anomaly of the disc in which there was apparently glial degeneration filling an atrophic cup. Vision was grossly affected.

Recessive optic atrophy

A number of sibships have been recorded with optic atrophy either of the congenital type, or developing in infancy. The incidence of consanguinity in the more fully worked-out records is high. Figs. 173 *a* and *b* are illustrative pedigrees. In all probability this type is actually congenital, and perhaps not particularly uncommon.

Postnatal Optic Atrophy Other than Leber's Disease

Whilst there is strong presumptive evidence that many of the cases now recorded as of the dominant or recessive types of congenital optic atrophy are indeed congenital in origin, there is a possibility that some of them may be optic atrophies acquired early in life. There would appear to be little doubt that some of the recorded pedigrees of Leber's disease illustrate a dominant—possibly irregularly dominant—hereditary optic atrophy with onset late in childhood, or early adult life.

Vogt has observed, on two occasions, two elderly sibs with optic atrophy without any other disturbances, and these may well be examples of an abiotrophic optic atrophy with onset late in life.

It would appear that excessive attention has been paid to the Leber type of optic atrophy and its difficult mode of inheritance as the one and only possible variety of abiotrophic optic atrophy. Judging by established data on the retinal abiotrophies, it is not unlikely that several modes of inheritance, and several clinical types of hereditary optic atrophy exist, and little is to be gained by forcing them into one unifying but untenable conception.

OTHER ANOMALIES

Pseudo-papilloedema

At least three distinct types have to be recognized. The commonest is that congenital form of disc in which the physiological cup is absent or minimal and the nerve fibres are crowded together so that they become prominent ("swelling of the disc") and produce an indistinct disc margin, occasionally exaggerated by partially myelinated nerve fibres. Papilloedema may also be simulated by drusen bodies on the disc, whilst veils of epipapillary membrane constitute yet a third variety of pseudo-papilloedema.

Apparent swelling of the disc.—Familial cases have been recorded by a number of observers. Families thus affected appear to have inherited high hypermetropia,

but not all hypermetropes within the family show pseudo-papilloedema. Inheritance over two generations is shown in Fig. 174.

Pseudo-papilloedema has also been observed in father and daughter, the latter showing 1·5 D of myopia, and also in a mother and three children.

Drusen.—Drusen on the disc have been recorded over two generations. It is not certain whether drusen are minimal manifestations of tuberose sclerosis, or an independent entity.

Epipapillary membrane.—This has been observed over two generations.

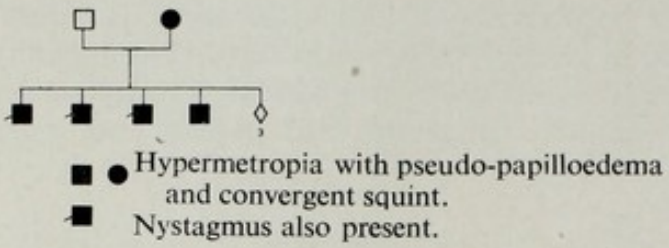


FIG. 174.—Pseudo-papilloedema. Inheritance over two generations. (*After R. K. Lambert and C. E. McDannald* (1931). *Amer. J. Ophthal.*, **14**, 46.)

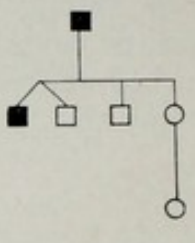


FIG. 175.—Megalopapilla. Inheritance over two generations. (*After A. Franceschetti and R. H. Bock* (1950). *Amer. J. Ophthal.*, **33**, 227.)

CRATER-LIKE HOLE IN THE DISC

There do not appear to be any records suggestive of either dominant or recessive inheritance. Crater-like holes have been observed repeatedly in association with coloboma of the optic nerve, typical and heterotopic crescents, and typical choroidal coloboma. It has also been observed in individuals of families affected with dominant typical colobomatous defects. The exact status of crater-like pits is therefore still undetermined. It is possible that they have nothing to do with typical coloboma.

MEGALOPAPILLA

A disc substantially larger than normal, has been observed over two generations (Fig. 175).

ABSENCE OF DISC AND RETINAL VESSELS

This rare anomaly appears to have been seen in two sisters by Newman in 1864.

COLOBOMA OF OPTIC NERVE AND HETEROTOPIC CONUS

These anomalies fall into the group of typical colobomatous defects and have already been discussed.

CHAPTER 7

OTHER TISSUES

LIDS

Epicanthus

The line of demarcation between the physiological epicanthus of infancy and epicanthus as an abnormal feature is fine. That there is a genetic basis for the marked type of epicanthus is shown by the following observation.

(1) Several observers have recorded concordance as to epicanthus in uniovular twins, and discordance in binovular twins.

(2) Many sibships with epicanthus are on record, with occasional occurrence of consanguinity in the parents.

(3) There are many more pedigrees traced over two or more generations, and in at least one family the possibility of sex-linkage, as opposed to regular or irregular autosomal dominance, emerges (Fig. 176 *a* and *b*).

Epicanthus may be part of the syndrome of embryonic fixation (Waardenburg). This is essentially dominant.

Blepharochalasis

Here, too, the line of demarcation between a mild bagginess of the upper lid (epiblepharon) and blepharochalasis is fine. Fig. 177 *a* represents a pedigree for the dominant inheritance of these conditions. Blepharochalasis associated with spasm of the lids and unusual changes in the skin of the lids in some of the patients has been observed as a dominant affection (Fig. 177 *b*); corneal ulceration from inturning lashes was a troublesome complication in some patients.

Hernia of the orbital fat and conjunctiva through the upper lid has been observed in a mother and daughter.

Elephantiasis

Elephantiasis of the lids may be part of von Recklinghausen's neurofibromatosis. As such it may be irregularly dominant and the possibility of other tumours elsewhere in the body has to be considered. In different families the same distribution tends to recur.

Spasm of lids—absence of tarsal plates

Spasm of the upper lid producing lagophthalmos has been observed as a dominant affection. In contrast, spasm of the lower lid producing entropion has been recorded only in sibships.

Lagophthalmos and entropion may be produced by absence of the tarsus in the upper or lower lid respectively. The first of these conditions has been observed in a sibship, and the second in a mother and two children.

Coloboma of the upper lid

This is generally associated with other anomalies, both of the globe and of the body as a whole. The condition has been observed in a mother and child, and also in the offspring of a consanguineous marriage.

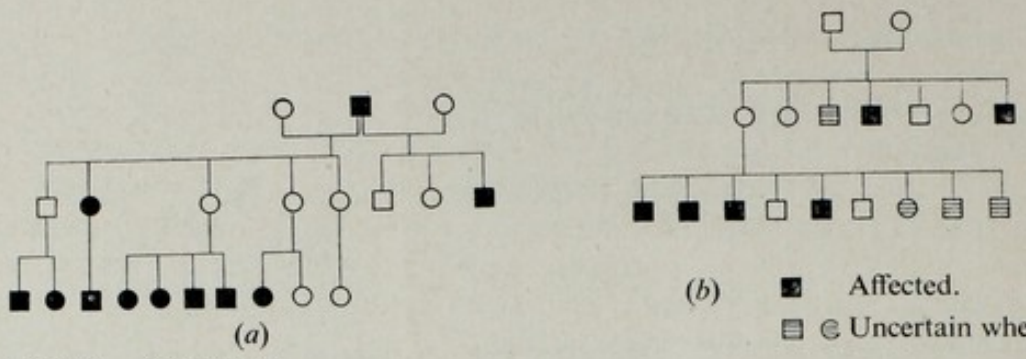


FIG. 176.—Epicanthus.
(*a*) Dominant inheritance. (*After C. H. Usher* (1935). *Biometrica*, **27**, 5.)
(*b*) Pedigree suggestive of sex-linkage. (*After A. Brückner* (1906). *Arch. Augenheilk.*, **55**, 23.)

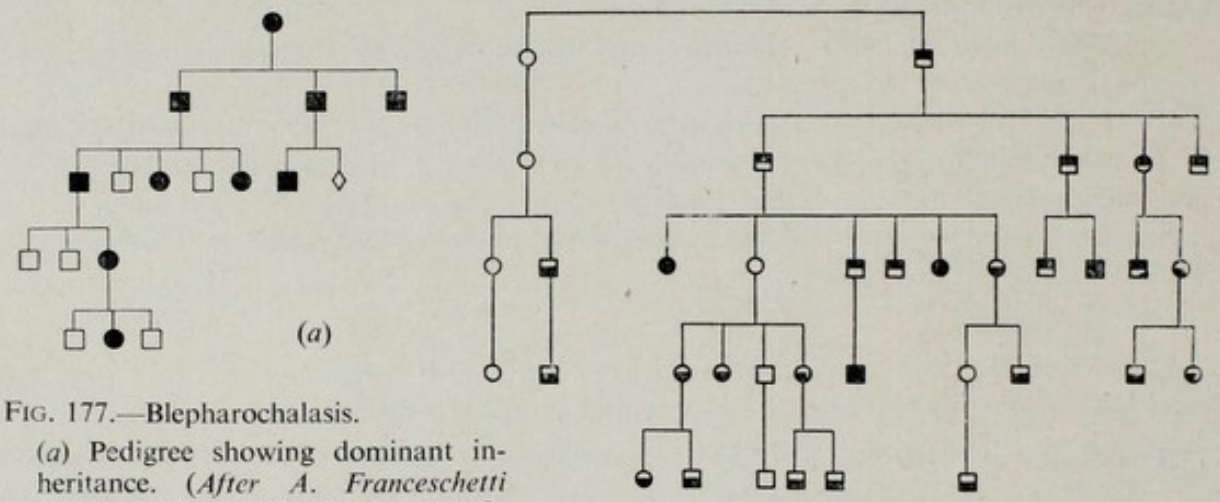


FIG. 177.—Blepharochalasis.
(*a*) Pedigree showing dominant inheritance. (*After A. Franceschetti* (1930). *In Kurzes Handbuch der Ophthalmologie, Ed. by F. Schieck and A. Brückner. Vol. I., p. 679. Berlin; Springer.*)
(*b*) Pedigree showing dominant inheritance of blepharochalasis in a family in which associated spastic entropion, possibly due to unusual changes in the skin of the lids, was observed in some members. (*After C. H. Usher* (1932). *Biometrica*, **24**, 1.)

Ankyloblepharon

Partial ankyloblepharon generally affecting the lateral parts of the lids has been observed in one family over four generations. Ankyloblepharon of the medial parts of the lids has been recorded in a pair of twins, and also in a father and six children; in these cases there were abnormally long lower canalculi. Total ankyloblepharon is, of course, seen in cryptophthalmos.

Anomalies of the skin of the lids

Apart from involvement of the skin and lid in generalized hereditary skin affections, some relatively localized hereditary anomalies have been observed.

(a) Dark coloration of the lids with the veins standing out markedly has been observed as a dominant affection over five generations.

(b) Xanthelasmas of the lids have been recorded over two successive generations.

(c) Of the more important generalized skin diseases with a great tendency

to involvement of the lids, ichthyosis and xeroderma pigmentosum are both dominant.

Anomalies of lashes

Distichiasis.—Congenital distichiasis has been observed repeatedly as a simple dominant affection (Fig. 178). In one family it is reported to have been inherited by women only over four generations.

Trichiasis.—There is a record of one family in which three rows of lashes were inherited over two generations.

Congenital deficiency of lashes and intermarginal area.—In one family this abnormality appears to have occurred dominantly.

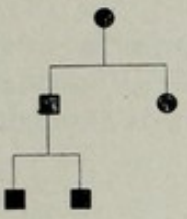


FIG. 178.—Distichiasis. Pedigree showing dominant inheritance. (*After N. Blatt* (1924). *Z. Augenheilk.*, **53**, 325.)

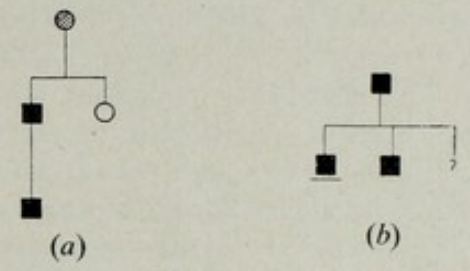


FIG. 179.—Congenital absence of all four puncta.
(*a*) Pedigree showing inheritance over three generations. (*After A. Sorsby* (1931). *Proc. R. Soc. Med.*, **25**, 692.)
(*b*) Pedigree showing inheritance over two generations. The underlined case showed fistulae at the sac. (*After A. E. Town* (1943). *Arch. Ophthal.*, **29**, 767.)

LACRIMAL APPARATUS

Genetic studies might well help to clarify the relationship of the different clinical types of disturbances in the lacrimal apparatus. Detailed studies are, however, lacking. As yet there is little more than tentative evidence of a genetic basis in some of them.

Lack of tears

This has been observed in three sibs, and is also a dominant affection.

Congenital absence of all four puncta

Total absence of all four puncta with rudimentary indication of the presence of some of them, has been recorded over three generations. A record over two generations with fistula from the sac in the second generation is also available (Fig. 179 *a* and *b*).

Atresia of the nasal openings

Atresia of the nasal openings has been recorded in several sibships, and held responsible for some cases of chronic dacryocystitis.

Elongation of canalculi

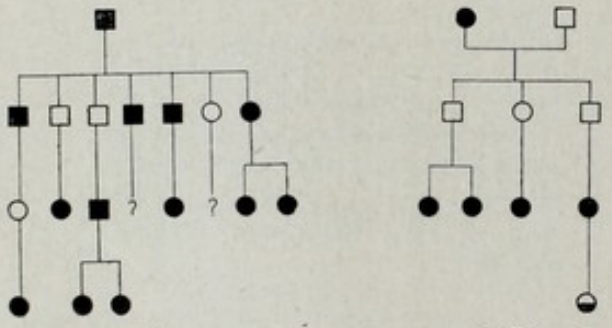
This may occur as part of the syndrome of embryonic fixation.

Congenital lacrimal obstruction and adult dacryocystitis

A striking clinical difference between these two affections is the sex distribution. Congenital lacrimal obstruction shows no marked sex difference, whereas chronic dacryocystitis in adults is largely an affection falling on women. A genetic basis for congenital lacrimal obstruction is suggested by several pedigrees in which the affection was observed in sibships, and in one pedigree in which it was observed over two generations.

The evidence for the genetic basis of chronic dacryocystitis in adults is more broadly based. Fig. 180 shows inheritance over four generations. Traquair found that in 11 per cent of his patients admitted for operation a hereditary factor was present. The possibility of congenital lacrimal obstruction—or at any rate some varieties—linking up with chronic dacryocystitis is suggested by Figs. 180 *b* and 181.

It is possible, as Traquair points out, that excessive importance has been attached to infection in the aetiology of dacryocystitis, whether of the congenital or adult type. The infection is secondary to stasis, and the underlying condition is presumably some structural anomaly.



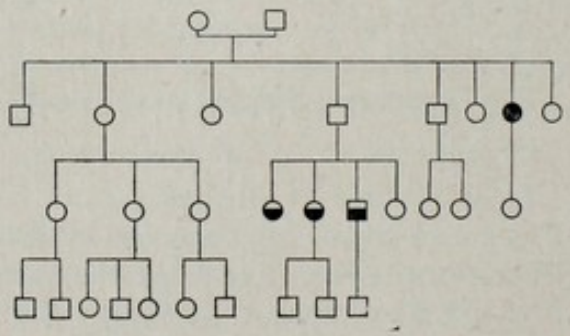
(*a*)

● Chronic dacryocystitis.

◒ Congenital lacrimal obstructions in an infant.

(*b*)

FIG. 180.—Chronic dacryocystitis.
(*a*) Inheritance of chronic dacryocystitis over four generations. (*After H. M. Traquair* (1941). *Arch. Ophthal.*, **26,** 165.)
(*b*) Occurrence of a case of congenita lacrimal obstruction in a family with chronic dacryocystitis. (*After H. M. Traquair* (1941). *Arch. Ophthal.*, **26,** 165.)



● Dacryocystitis at the age of 16 years.

⬓ ◒ Congenital lacrimal obstruction in newborn infants.

FIG. 181.—Congenital lacrimal obstruction. Occurrence in a sibship whose maternal aunt suffered from chronic dacryocystitis. (*After H. M. Traquair* (1941). *Arch. Ophthal.*, **26,** 165.)

There is, as yet, no evidence as to whether infants who have been cured of congenital dacryocystitis have the adult form in later life, or themselves have affected children, or children who are unaffected at birth but become affected in adult life.

CONJUNCTIVA

Dermo-lipoma

This has been observed over three generations (Fig. 182).

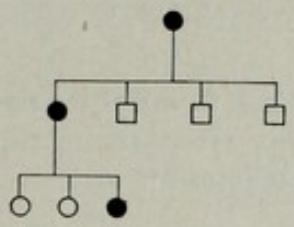


FIG. 182.—Dermolipoma. Inheritance over three generations. (*After J. Saebø* (1948). *Acta Ophthal.*, **26**, 447.)

Pinguecula

It is possible that cases of pinguecula are genetically determined, as they have been observed repeatedly in the same sibships late in life.

Pterygium

The possibility that there is at any rate a hereditary disposition to pterygium is suggested by a number of observations on pterygia in sibships and over two generations. Whether such pterygia are merely a similar reaction to similar environmental exciting factors is, however, not known. It has been observed, obviously as an independent feature, in a family with sex-linked night-blindness and myopia.

Pigmented naevus

There is a record of a mother and daughter with pigmented naevus; in the daughter malignant changes supervened.

Epibulbar carcinoma

This has been observed once in a father and son.

Telangiectasis of the upper fornix and essential shrinking of the conjunctiva

Both these conditions may be part of generalized hereditary disturbances. (*See* page 227.)

SCLERA

Episcleritis fugax

Episcleritis fugax has been observed over three generations (Fig. 183).

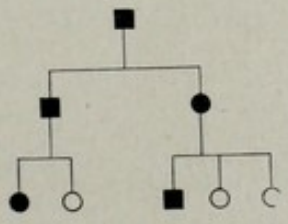


FIG. 183.—Episcleritis fugax. Pedigree showing inheritance over three generations. (*After O. Heinonen* (1927). *Acta Ophthal.*, **4**, 278.)

VITREOUS

As yet only two clearly defined anomalies of the vitreous are recognized as having a genetic basis.

Persistent hyaloid artery

Generally this would appear to be a developmental rather than a hereditary affection and is confined to one eye, which is frequently highly amblyopic. The occurrence of bilateral persistent hyaloid artery in a father, two sons, and two daughters, and a unilateral lesion in one further daughter, has been recorded.

" *Degeneratio hyaloideo-retinalis* "

Under this designation Wagner has recorded a family showing over three generations an optically empty vitreous except for a few floating threads, associated with anomalies of the internal limiting membrane and the retina (Fig. 184).

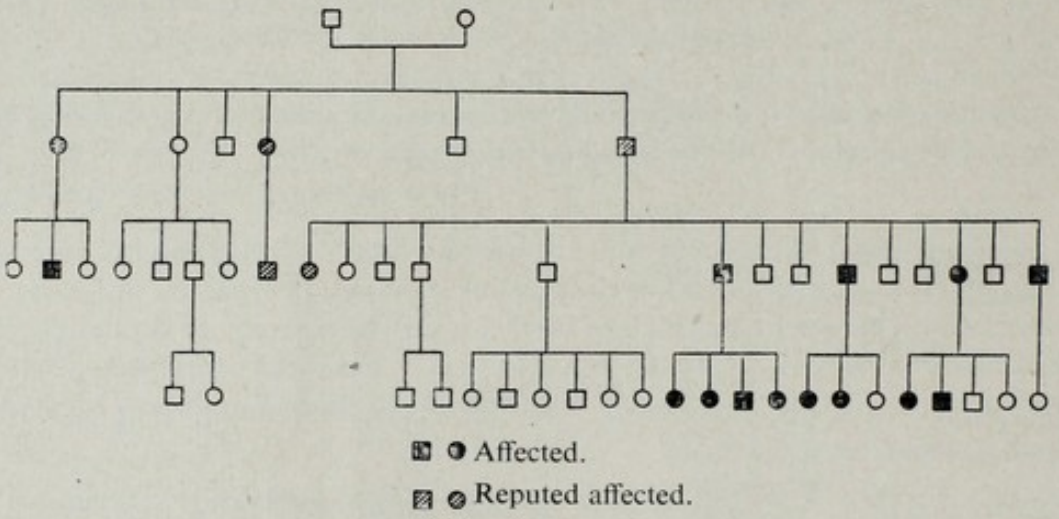


FIG. 184.—"Degeneratio hyaloideo-retinalis". (*After H. Wagner* (1938). *Klin. Mbl. Augenheilk.*, **100**, 840.)

SECTION III

GENERALIZED DISORDERS WITH OCULAR ASPECTS

CHAPTER 1

METABOLIC DISORDERS

CLASSIFICATION

METABOLIC DISORDERS fall roughly 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.

AFFECTIONS CHARACTERIZED BY ABNORMAL PRODUCTS IN THE URINE

Affections present at birth or in early infancy

Alkaptonuria.—In early cases there are no clinical signs apart from the presence of homogentisic acid in the urine, imparting to the urine the characteristic property of darkening on standing. In long-standing cases ochronosis—a bluish-black discoloration of the cartilages—develops, clinically most marked in the ear and nose; chronic arthritis of the osteoarthritic type also supervenes. The bluish-black discoloration occurs occasionally on the sclerotic, producing wedge-shaped areas with the base towards the cornea (Fig. 187).

The affection is generally recessive. The rate of consanguinity in parents is as high as 44 per cent—conforming to the rarity of the gene in the population. Dominant inheritance has been observed.

Cystinuria.—Apart from the excretion of cystin in the urine, deposition of crystals may occur throughout the body. In some families there is renal dwarfism associated with cystic kidneys. Deposition of cystin in the cornea leads to one of the forms of corneal thesaurismoses (Fig. 185). The whole of the parenchyma may become involved. Cystinuria is generally recessive, but may occasionally be dominant.

In one sibship of six, retinitis pigmentosa and cystinuria were seen in association. The available evidence is not sufficient to decide between the possible alternatives, of one gene being responsible for the two affections, or two separate genes either linked or not linked (Fig. 186).

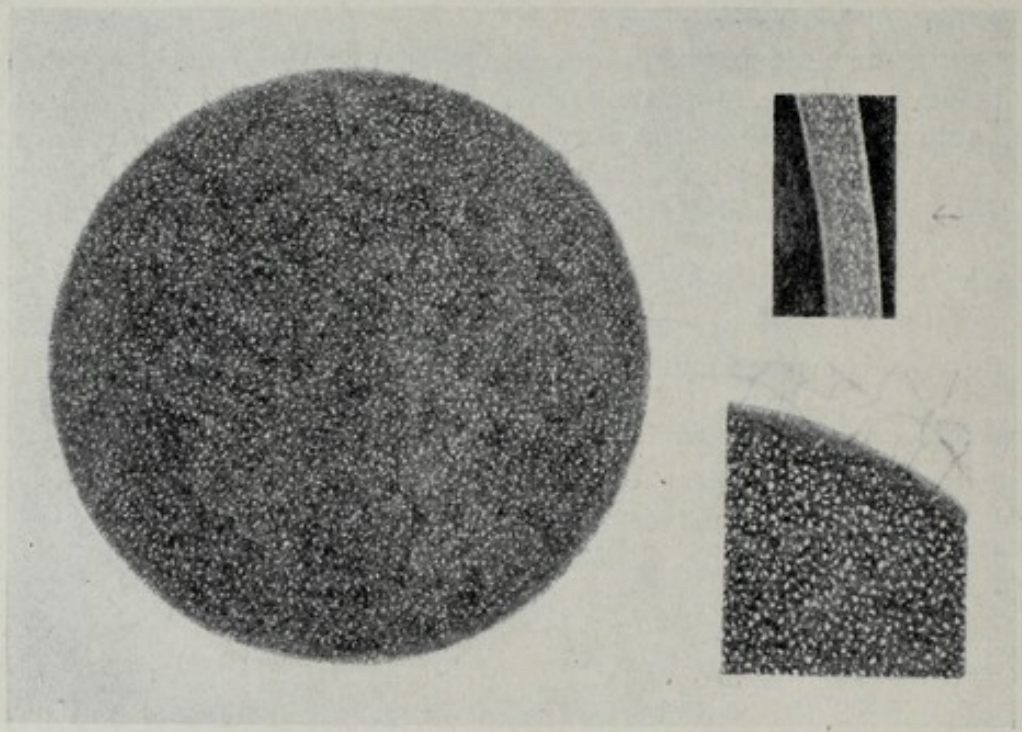


FIG. 185.—Cystinuria. Deposition in cornea. (*After E. Burki* (1941). *Ophthalmologica*, **101**, 257.)

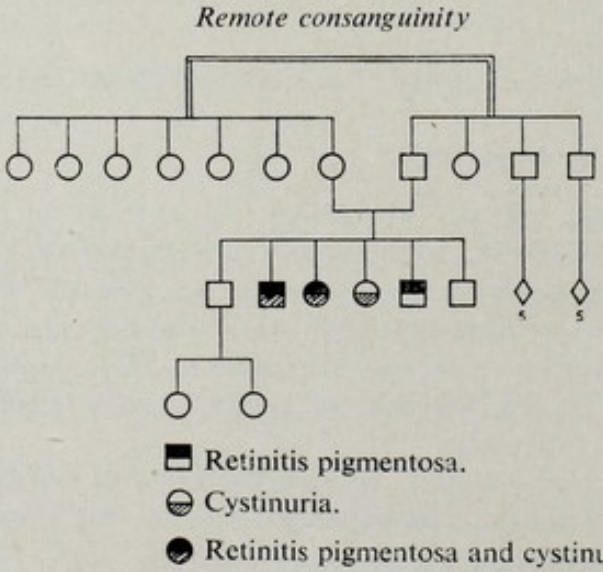


FIG. 186.—Occurrence of cystinuria and retinitis pigmentosa in the same family. Pedigree. (*After W. D. W. Brooks, M. A. Heasman, and R. R. H. Lovell* (1949). *Lancet*, **1**, 1096.)

FIG. 187.—Alkaptonuria. Clinical appearances. Note discoloration of cartilages of ear and nose and pigmentation of the sclera. (*After J. van der Hoeve* (1948). *Lipoidosis and Scleromalacia Perforans. Kon. Ned. Ak. Wet., Verh. Afd. Nat.* (*Tweede Sectie*), *Dl. XLV. No.* 5, 1948.)

To face page 202

Porphyrinuria.—As distinct from the appearance in the urine of porphyrin as the result of toxic factors like sulphonal poisoning, there is a hereditary form, generally recessive, but occasionally irregularly dominant. The cornea shares the extreme sensitivity to light, so that in addition to extensive blister formation of the skin leading to disfiguring deformities, blindness may supervene from dense corneal scarring.

Pentosuria.—Pentosuria is generally recessive, but may also be dominant. Migraine is fairly frequent.

Affections with late onset

Diabetes mellitus and gout.—Apart from those metabolic disturbances with abnormal urinary products present at birth, or early in infancy, there are the metabolic disorders coming on later in life, such as diabetes mellitus and gout. Diabetes has both recessive and dominant modes of inheritance, and it is possible that different genes are concerned in the diabetes of early onset, and the diabetes of late onset. Whether the ocular complications of diabetes mellitus are genetically determined, or are secondary to the somatic changes produced by the metabolic disorder, is not known. The growing evidence that all diabetics of long standing tend to develop retinal complications, whilst suggestive, is not conclusive of the possibility that these changes are genetically determined. It is also not known whether the ocular changes in gout are genetically determined, or secondary effects.

ABNORMAL CELLULAR METABOLISM

Albinism

The outstanding anomaly of this form of abnormal metabolism is albinism, though it is possible that many other affections fall into this group.

In albinism, as already indicated, there is failure to build up pigment from phenylalanine. In the production of melanin, phenylalanine is oxydized to tyrosine, and this to 3,4 dihydroxyphenylalanine (" dopa ") and by successive steps is ultimately converted to melanin. Each of these steps requires the presence of a specific enzyme. In albinism there is inability to convert " dopa " to the next stage in the building up of melanin.

Clinical types

Clinically five types of albinism are recognized.

(1) At the one extreme there is the fully developed generalized albinism with its characteristic picture of total lack of pigment throughout the body. Even in this type, however, some pigment is present, as has been shown histologically in the examination of the eyes of such individuals.

(2) Not infrequently this generalized albinism is not quite complete: the hair is straw-coloured rather than white, and there is a yellowish greenish coloration of the iris which, however, transmits light, so that the eye is red. Whether these two types are distinct entities is not certain. Not infrequently the typical albino tends to develop some colour later in life; there is thus some link between these two forms.

(3) There is also the condition known as albinoidism, or leucism. Here, the hair and skin are only slightly darker than those of albinos, but sight is good, there is generally no photophobia, no nystagmus, and the iris does not transmit light. Moreover, in some individuals the condition is present only early in life.

In contrast to these three varieties of generalized albinism—complete or incomplete—there is albinism confined to the globe:

(4) The whole of the globe may be involved, so that the picture, as far as the eye is concerned, is that seen in complete albinism.

(5) More commonly the albinism is still more limited; the lack of pigment is confined to the fundus only—the albinotic fundus of clinical practice.

It is possible that the albinotic fundus can in turn be subdivided into two varieties, dependent upon whether the macula is developed or not. It is also possible that some of the cases in which the macula is not developed are cases of total colour-blindness in which this symptom has been missed; cases diagnosed as congenital nystagmus may perhaps also be instances of this type of localized albinism.

The complexity of clinical classification is reflected in the considerable complexity concerning the mode of inheritance of albinism.

Generalized albinism

Albinism has been seen repeatedly in the two partners of a uniovular twin and there is good evidence that generalized albinism—whether complete or incomplete—is recessive in character. This is shown by a number of well established pedigrees (Fig. 188).

Several difficulties arise in the interpretation of the extensive pedigrees that are available.

(a) The rate of consanguinity is high (approximately from 20 per cent to 33 per cent). This argues in favour of an exceptionally rare condition. Albinism, however, is not so rare as this high rate of consanguinity suggests, though certainly not so common as the extensive literature on the subject implies. The high rate of consanguinity has been explained on the supposition that there are several different genes which are capable of producing albinism.

(b) The number of affected individuals in pooled pedigrees shows a higher proportion than the theoretical 25 per cent expected. According to Seyfarth, when this pooled material is recalculated after the Weinberg method the theoretically expected percentage is obtained. It would, however, seem that the expected ratio is not obtained in substantial series of unselected cases.

(c) In the antecedents of albino patients there are frequently partial manifestations suggestive of albinism—such as a great frequency of light-coloured hair, and skin. It has been suggested that the recessive gene is not altogether recessive, but shows partial expression in the simplex state.

(d) This suggestion of intermediate behaviour is strengthened by the fact that in at least one pedigree an apparently dominant behaviour was observed (Fig. 189).

Detection of heterozygotes.—Waardenburg holds that it is possible to detect the heterozygote for generalized albinism, as also the female carrier of sex-linked ocular albinism. Such individuals show abnormal translucency of the iris on transillumination of the sclera. This constitutes further evidence that the genes are not entirely recessive but intermediate.

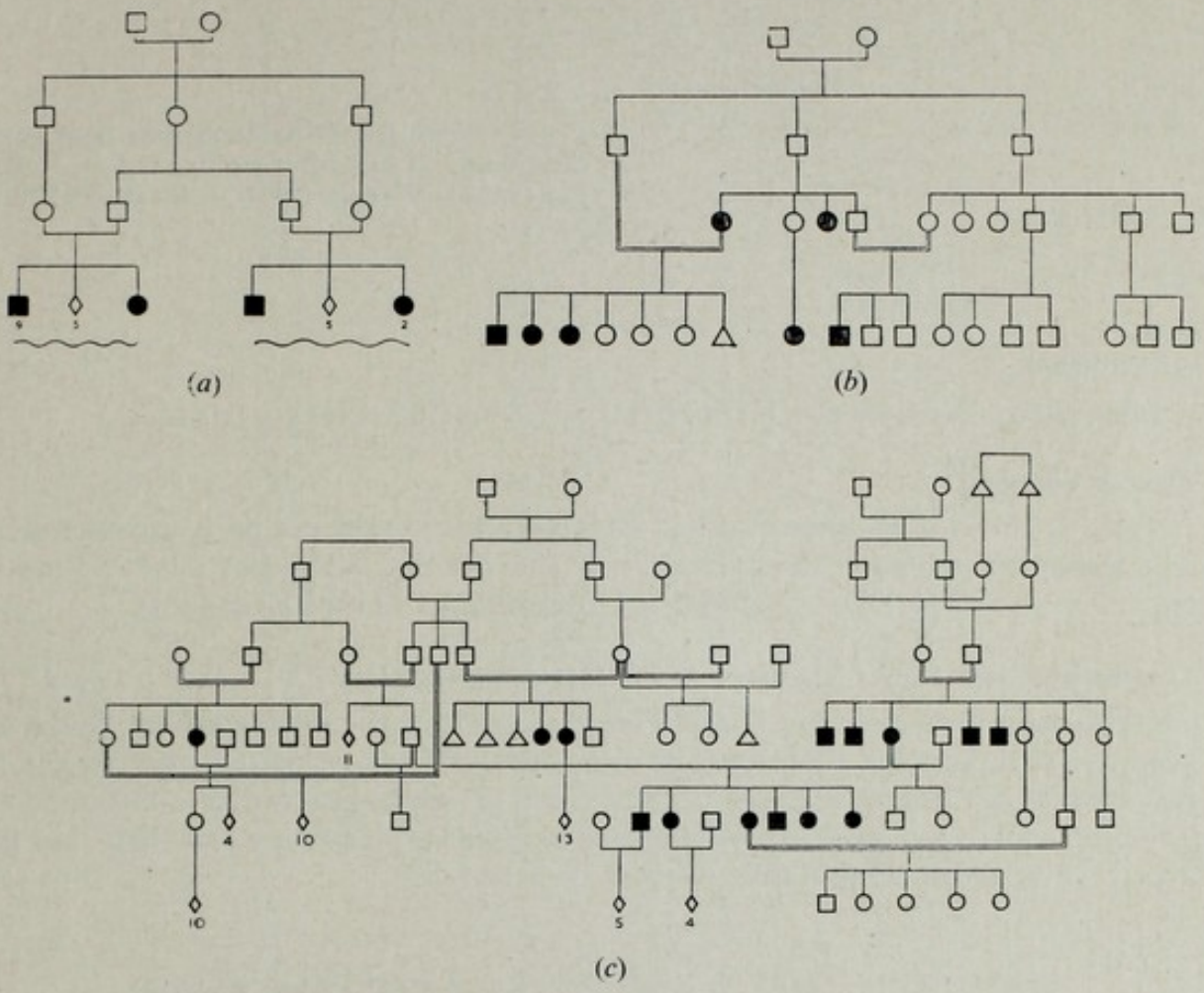


FIG. 188.—Albinism. Pedigrees suggestive of recessive inheritance.

(*a*) Albinism in two collateral branches of a family. The parents were all derived from common ancestors. (*After E. Stainer, in K. Pearson, E. Nettleship and C. H. Usher* (1913), *A Monograph on Albinism in Man. Pt. IV, Fig.* 206. *London, Cambridge University Press.*

(*b*) Albinism in collateral branches. The offspring of parents related in the first and second degree. The assumption of recessive inheritance would explain IV, 9 and also IV, 1–3. To explain IV, 8, one must assume not only that their mother was a carrier, but that she married a carrier. Likewise it is necessary to assume that the same circumstances applied in the case of II, 2. The assumption of irregular dominance would fit this pedigree almost as readily. (*After H. Tertsch. Ibid. Fig.* 4, *Plate IV.*)

(*c*) The evidence for recessive inheritance is stronger in this pedigree. (*After F. W. Marlow and W. L. Faxon. Ibid. Fig.* 412.)

(*d*) This extract from the fourth and fifth generation of the preceding pedigree is particularly convincing in view of the fact that it is known there is evidence that the unaffected father had affected cousins on both sides of his family. (*After F. W. Marlow and W. L. Faxon. Ibid.*)

(*e*) This pedigree is best explained on the assumption that a man and his two cousins, whom he married successively, were carriers. (*After J. Heidenreich. Ibid. Fig.* 444.)

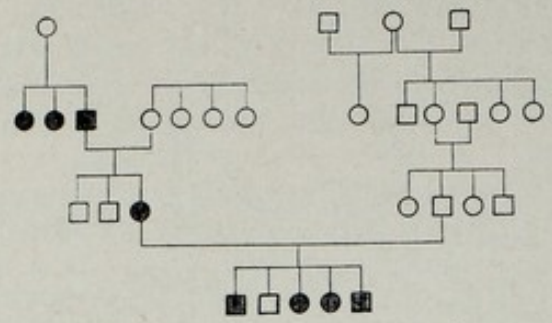


FIG. 189.—Albinism. Pedigree showing dominant inheritance in a Negro family. (*After A. C. Pipkin and S. B. Pipkin* (1942). *J. Hered.*, **33**, 419.)

Albinoidism

Inheritance is strictly dominant in this affection (Fig. 190).

Ocular albinism

Fig. 191 shows a pedigree in which albinism affecting the eye only was inherited as a sex-linked recessive. As nystagmus is also present such cases might perhaps equally well be regarded as instances of congenital sex-linked nystagmus.

Generalized and ocular albinism as distinct affections

On genetic grounds there is therefore good reason for distinguishing between generalized and ocular albinism. The one is probably an autosomal recessive and the other a sex-linked affection. Many cases of sex-linked ocular albinism do, however, show some evidence of generalized albinism: they may have hair that is nearly white and their skin may likewise be very fair.

AFFECTIONS CHARACTERIZED BY ABNORMAL BLOOD AND TISSUE CHEMISTRY

Whether such carbohydrate disturbances as glycogen disease have any ocular associations is not established. Ocular associations are prominent in the group of diseases associated with abnormal metabolism of fats—the lipoid dystrophies.

These dystrophies present complex clinical, biochemical, and genetic problems. Clinical criteria determine the arrangement into distinct clinical types, but different clinical types appear to have a fundamentally similar chemical basis. Genetically the mode of inheritance is not clearly established in many of the affections. Dependent upon the predominant type of chemical disturbance these anomalies may be classified as phosphatide, cholesterol and cerebroside disturbances respectively.

PHOSPHATIDE DISTURBANCES

The amaurotic idiocy group

Infantile amaurotic idiocy (*Tay-Sachs disease*).—This affection, which is clinically a clear-cut entity, was at one time regarded as exclusively confined to Jews. This is not the case, and the issue at present is whether there is, in fact, any racial predilection in this affection at all. Histologically the ganglion cells throughout the central nervous system are immensely distended, the nucleus is displaced

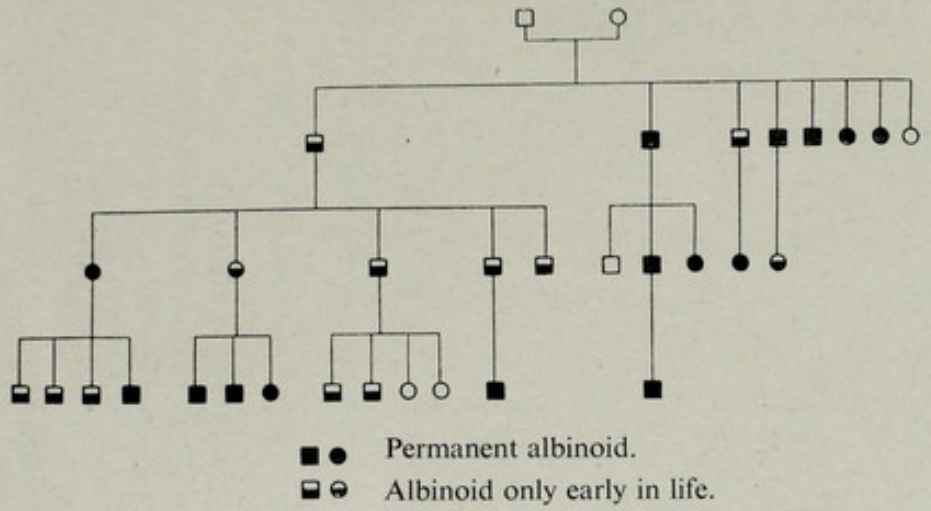
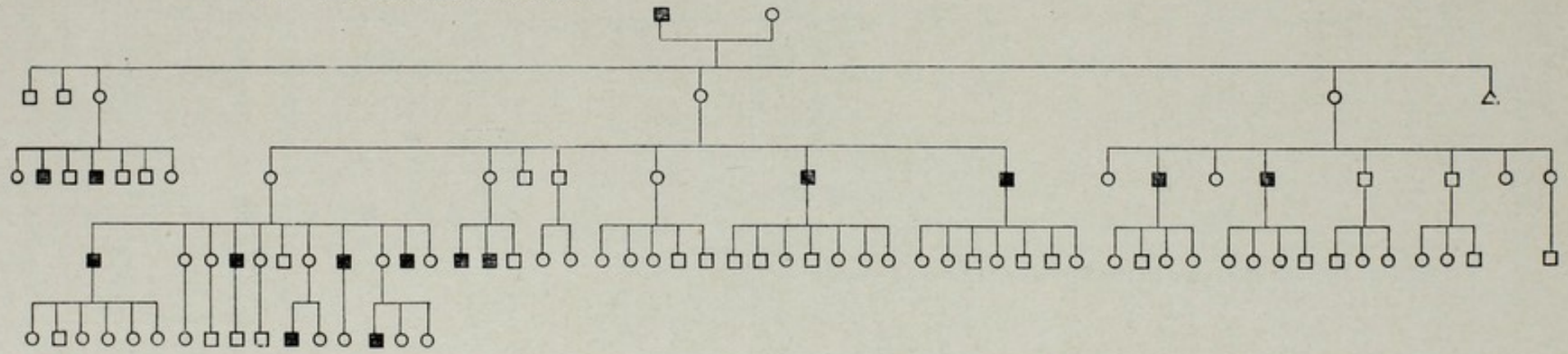


FIG. 190.—Albinoidism. Pedigree showing dominant inheritance. (*After W. Jablonski* (1920). *Dtsch. med. Wschr.*, **46,** 708.)

FIG. 191.—Ocular albinism. Pedigree showing sex-linked inheritance. (*After A. Vogt* (1925). *In Handbuch der ges. Augenheilk* (*Graefe-Saemisch*) 3*te Aufe Vol. III, p.* 56. *Berlin; Springer.*)



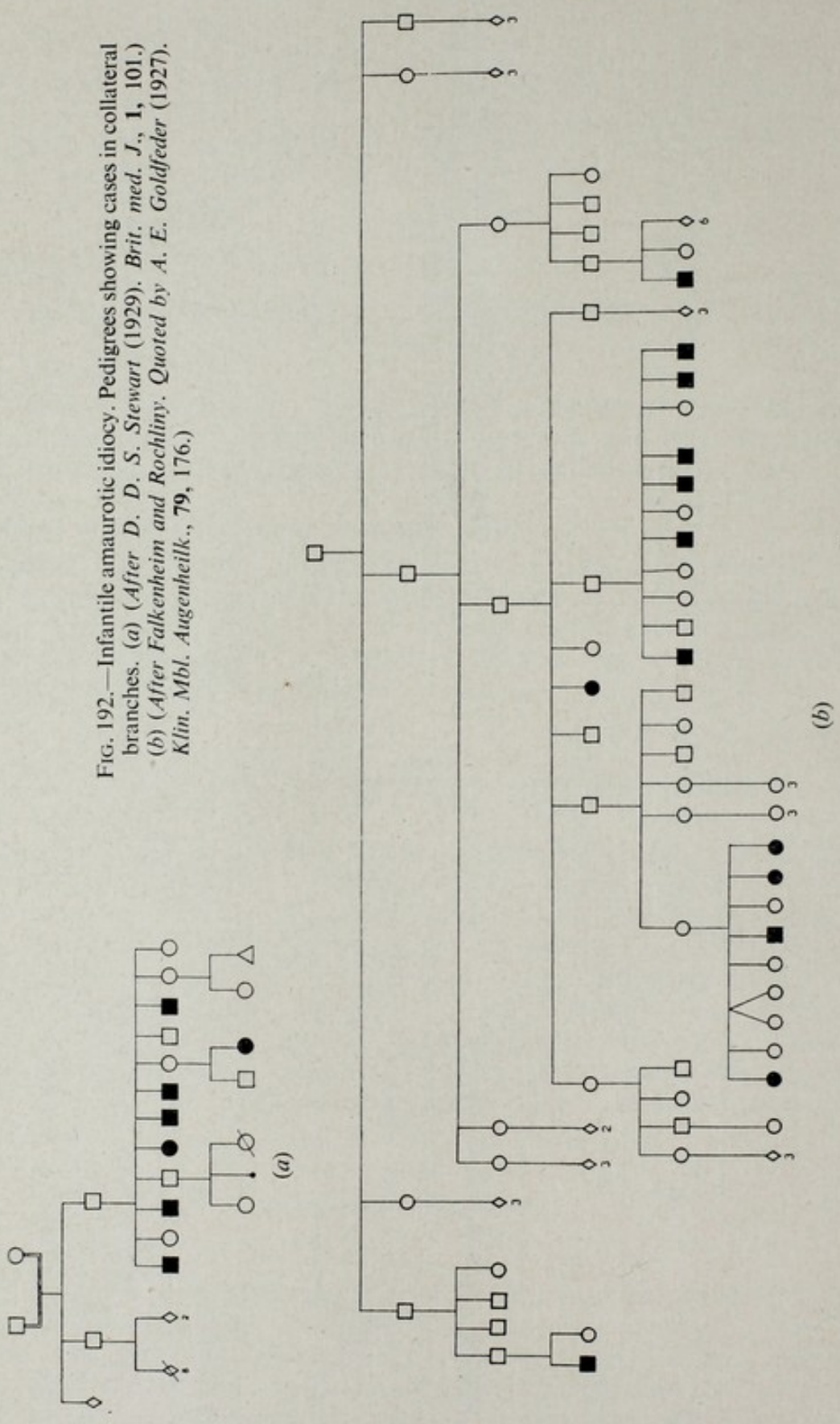


FIG. 192.—Infantile amaurotic idiocy. Pedigrees showing cases in collateral branches. (*a*) (*After D. D. S. Stewart* (1929). *Brit. med. J.*, **1**, 101.) (*b*) (*After Falkenheim and Rochliny. Quoted by A. E. Goldfeder* (1927). *Klin. Mbl. Augenheilk.*, **79**, 176.)

towards the periphery, stains poorly, and ultimately disappears together with the rest of the cell contents. Fat stains show the granules in the cells to be in the nature of a pre-lipoid lecithin-like material. These fatty changes are the result of infiltration and not of degeneration.

The affection has been recorded frequently in several sibs, and there is a high rate of consanguinity in the parents. This would suggest recessive inheritance. There are, however, pedigrees in which the affection has occurred in collateral branches of the family—an unexpected event with rare genes (Fig. 192 *a* and *b*). Direct dominant inheritance does not, of course, arise, as the affection is lethal, generally by the end of the second year of life. The possibility of intermediate inheritance, with the affection as the expression of the homozygous state, cannot be excluded in view of the fact that in families in which Tay-Sachs disease occurs, neurological stigmata are not uncommon. An alternative, and possibly more likely, reading, is that the affection is indeed recessive, with the recessive gene occasionally manifesting itself in the simplex state.

Juvenile amaurotic idiocy.—This affection, coming on at about the age of 6 years, and running a slower lethal course, differs clinically from the infantile type in lacking the characteristic cherry-red spot at the macula, which in these cases shows pigmentary changes. The pigmentary changes are, however, not confined to the macula, but are seen throughout the whole of the retina, which is highly atrophic histologically. Chemically the widespread changes in the central nervous system are rather different from those seen in Tay-Sachs disease, for the fats are of a simpler form, approaching the constitution of neutral fats. The histological picture is, however, fundamentally similar in the two affections.

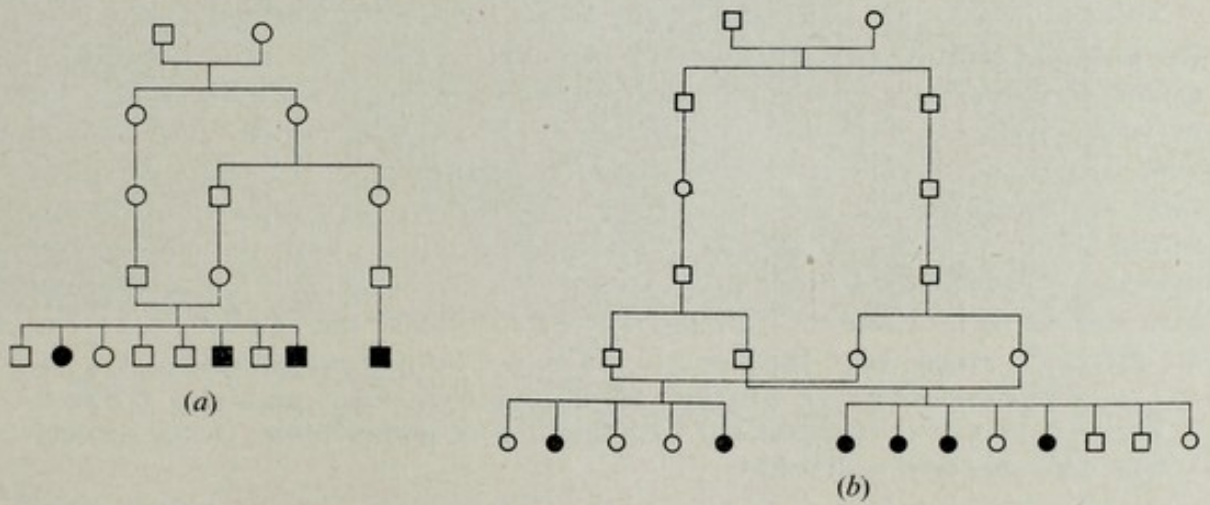


FIG. 193.—Juvenile amaurotic idiocy. Recessive inheritance. (*After T. Sjögren* (1931). *Hereditas*, **14**, 197.)
(*a*) and (*b*) Pedigrees showing cases in two collateral branches with common ancestry.

The mode of inheritance in this group appears to be a simple recessive, as shown by the systematic survey of Sjögren (Fig. 193 *a* and *b*). As in Tay-Sachs disease, there appears to be an increased incidence of mental disorders in heterozygotes.

Late infantile amaurotic idiocy.—This type, established on both clinical and histological evidence, seems to form an intermediate group between the infantile

and juvenile diseases. The affection is rare and the literature rather confused from the admission of only doubtfully relevant cases. The mode of inheritance is presumed to be recessive.

Late juvenile and adult amaurotic idiocy.—These groups, too, are based on histological as well as clinical observations. They are rare, and appear to run a milder course than juvenile amaurotic idiocy. The eye changes in particular may be lacking. The mode of inheritance again is not clearly known, but is presumed to be recessive.

Senile amaurotic idiocy.—It would appear that there is a senile variant of these affections, as confirmed histologically. Little definite is known of the condition.

Infantile dementia (Heller).—This ill-defined entity is characterized by the onset of profound dementia in the third or fourth year of life in children who had developed normally up to that time. It is a slowly progressive affection, and death generally supervenes from intercurrent disease. Ocular changes are lacking, but histologically the appearances of amaurotic idiocy are present in the cerebral cortex.

To what extent these affections—which have in common a strikingly similar histological reaction with somewhat different chemical staining reactions of the affected cells in the central nervous system—are variants of one and the same clinical entity, is difficult to decide, and the available genetic information does not help much. There is at the present time not enough evidence to justify regarding these different affections as expressions of the same gene—possibly with allelomorphic forms—under different conditions.

Relationship of Tay-Sachs disease to Niemann-Pick disease

These difficulties are not eased to any extent by the considerable evidence that the infantile type of amaurotic idiocy may be part of a systemic lipoid disease extending to the whole of the reticuloendothelial system in addition to the central nervous system—Niemann-Pick disease. The association of this affection with Tay-Sachs disease has been observed repeatedly in the same infant, and there are records of the appearance of either of these affections within the same sibship. The chemical changes in Niemann-Pick disease with or without ocular associations are fundamentally those seen in Tay-Sachs disease. In fact Niemann-Pick disease is the visceral form, and Tay-Sachs disease the neurological form of an affection, which when fully developed shows both these components.

A generalized recessive affection of mucous membranes and skin (Urbach-Wiethe's disease) is characterized by infiltration of phosphatides. Ocular associations have not been established.

Cholesterol Disturbances

Hypercholesteraemic disturbances

"*Arcus senilis.*"—Xanthoma of the skin is the simplest manifestation of a generalized cholesterol disturbance with hypercholesteraemia. The ocular aspects of the different forms of hypercholesteraemic disturbances are not clearly known, except that " arcus senilis " in youngish people may occur as part of dominantly inherited xanthomatosis of skin and tendons.

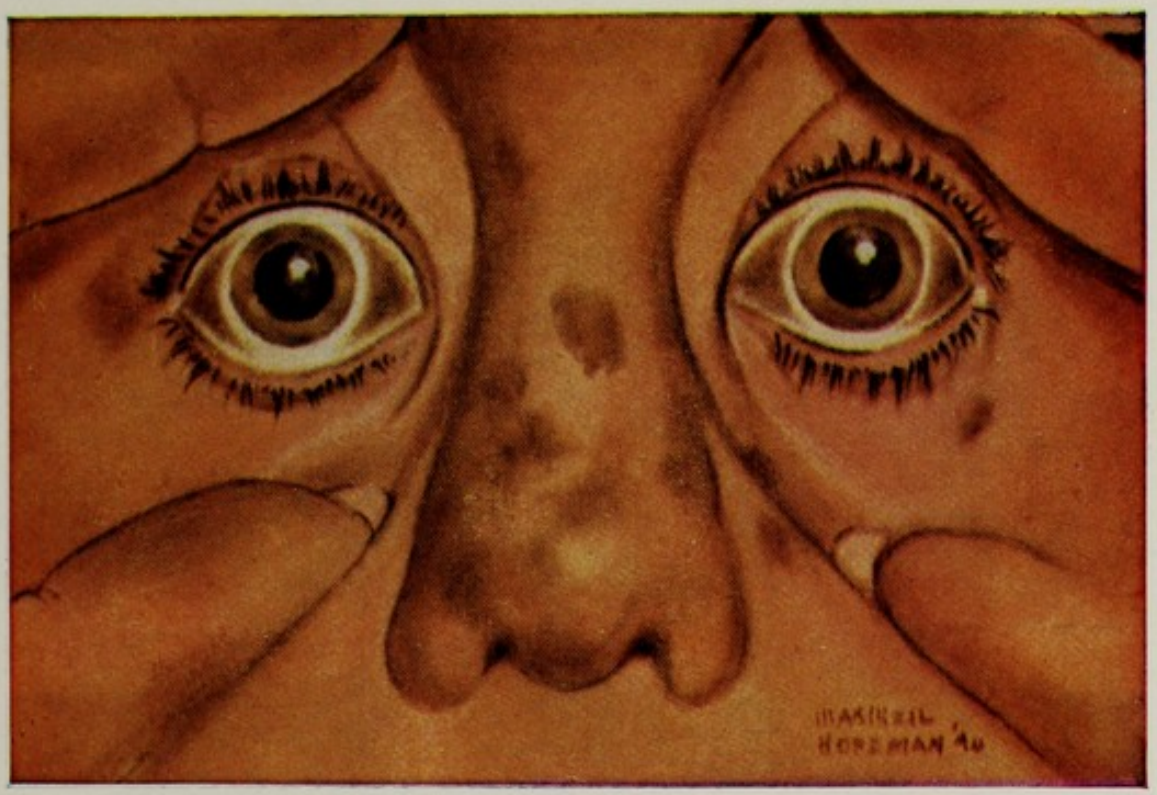


FIG. 194.—Gaucher's disease. Pigmentation of sclera and skin. (*After S. J. Thannhauser* (1940) *Lipoidoses. London; Oxford Medical Publications.*)

To face page 210

Normocholesteraemic disturbances

Of the cholesterol disturbances in metabolism with normal blood content of cholesterols, the outstanding example is the Schüller-Christian syndrome.

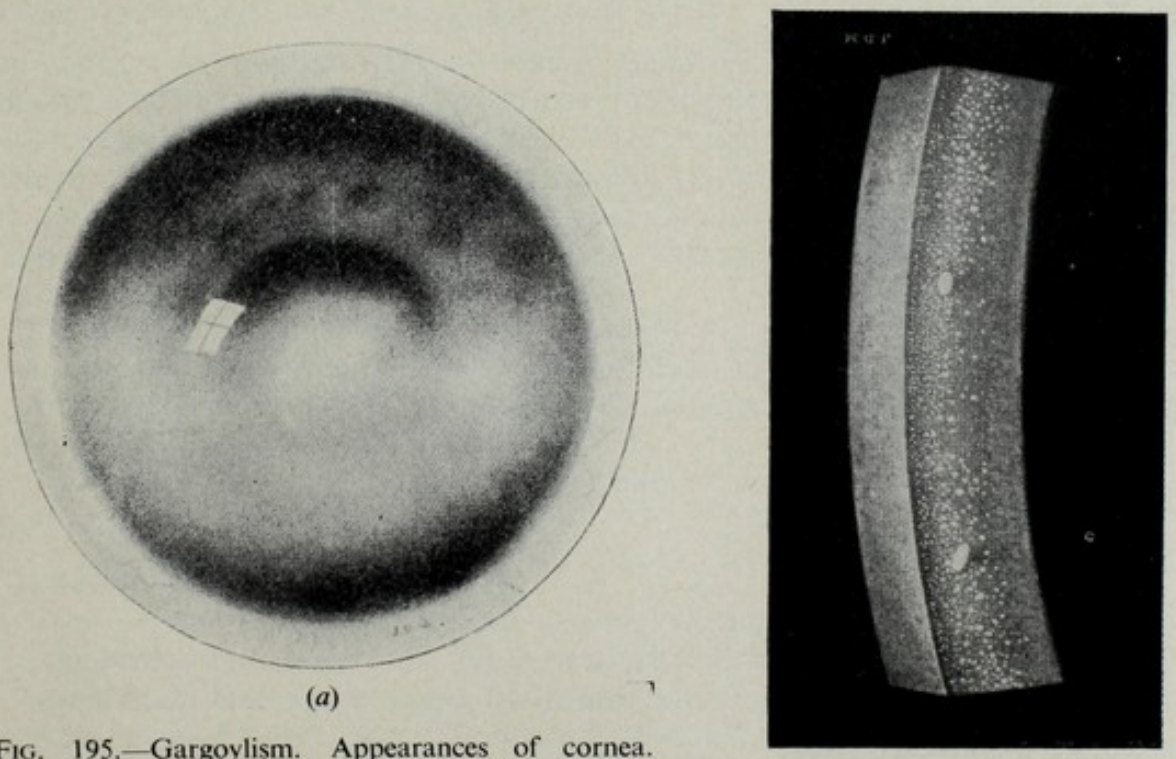
Schüller-Christian disease.—Here exophthalmos is a prominent feature. Xanthoma of the lids and fatty infiltration of the cornea have been recorded, as also papilloedema and optic atrophy. Nystagmus may develop from involvement of the pyramidal tracts; ataxia has been observed. Though essentially a fatal disease of infancy, a more chronic form appears to occur in adults. The affection has been observed in sibships, but most cases are sporadic and whether the affection is recessive is not established.

Scleromalacia perforans.—Van der Hoeve has advanced evidence that scleromalacia perforans, with its associated arthritis and nephrosis, is a cholesterol lipoidosis. In one of his cases, the young son of a patient had a macular lesion which might have been caused by scleromalacia perforans at the posterior pole.

Osteochondral dystrophy.—François has recorded the occurence in two sibs of an osteochondral dystrophy in fingers and toes, xanthoma of the skin, and subepithelial opacities in the corneae. Histologically xanthomatous foam cells were present, and chemically cholesterol was demonstrated.

Cerebroside Disturbances

Gaucher's disease.—This affection, with its infantile and adult forms, is the outstanding example of cerebroside disturbances. Histologically, characteristic foam cells are present. In the adult type, pigmentation of the sclera is not



(*a*) (*b*)

Fig. 195.—Gargoylism. Appearances of cornea. (*After M. L. Berliner* (1939). *Arch. Ophthal.*, **22**, 97) (*a*) Face view ; (*b*) optical section.

uncommon, and wedge-shaped thickening of the conjunctiva is seen (Fig. 194). In the infantile variety, the central nervous system may become involved, and the course is generally rapidly fatal; little is known of the ocular aspects. The affection has been recorded in sibships, though the possibility of dominant inheritance arises.

Gargoylism.—This is a generalized disturbance, which in the fully developed state gives characteristic skeletal and facial anomalies, and mental deficiency from

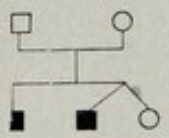


FIG. 196.—Gargoylism. Pedigree showing an affected sibship. There was no consanguinity. (*After F. C. Cordes and M. J. Hogan* (1942 *and* 1944). *Arch. Ophthal.*, **27**, 637; *Ibid.* **32**, 287.)

involvement of the central nervous system. The corneae show infiltration with the abnormal cerebroside, the corneal reaction being so severe as to have been mistaken for interstitial keratitis (Fig. 195). The affection has been recorded in sibships (Fig. 196).

CHAPTER 2

SOME SYSTEMIC DISORDERS

THE OCULAR aspects of systemic hereditary affections constitute a neglected chapter of genetics. In only a few of these affections are there any systematic studies on the frequency and variability of the ocular lesions.

SKELETAL SYSTEM

The frequent association of inherited abnormalities of the eye with those of the skeleton has led to various postulates as to the association of the two. The fact that next to the eye the bony system gives the largest number of readily recognized inherited abnormalities is perhaps in itself an adequate explanation.

There is a growing tendency to reduce the multitude of inherited skeletal abnormalities to a few fundamental lesions with a wide range of variation and expression. Some skeletal anomalies are secondary to changes in the bone marrow, others involve mainly the osseous tissue, yet others the periosteum or the epiphysis. For the present a classification into different clinical types is unavoidable.

GENERALIZED BONE DISTURBANCES

Osteopetrosis (*Albers-Schönberg disease*)

In contrast to fragilitas ossium, there is an excess of osseous tissue, throwing a dense shadow on radiography (hence the name marble bones). This excess encroaches on the cavity of the bone marrow, but consists of remarkably soft bone which tends to fracture (and cut) readily. Subsidiary features are abnormal deposits of calcium, dental anomalies, and osteomyelitis, particularly of the jaw. Secondary anaemia is frequently present with such compensatory reactions as enlargement of spleen and liver.

Optic atrophy may develop from bony changes at the optic foramina, not always readily detected by radiography. Hydrocephalus with its ocular concomitants has been observed. The aspects and course of the affection are generally remarkably uniform.

The affection has been noted repeatedly in several sibs, and the rate of consanguinity in parents is high.

Osteitis deformans (*Paget's disease*)

It is possible that Paget's disease develops early in life, though it does not lead to symptoms until middle life. The characteristic changes are in the skull, vertebral column and tibiae. Generalized arteriosclerosis is exemplified by skiagrams of the posterior tibial artery, which stands out as a calcified streak.

Retinal arteriosclerosis is frequent; central choroidal sclerosis in its early or late phases is not uncommon. Bilateral grey-brown, or chocolate coloured corneal

opacities have been recorded. Optic atrophy, exophthalmos and various palsies have also been noted.

The affection appears to be dominant. In one family van Bogaert observed an associated retinitis pigmentosa. Over four generations there were six cases of retinitis pigmentosa alone, and four cases of osteitis deformans, of which three also had retinitis pigmentosa, possibly inherited independently.

Of late, angioid streaks with and without pseudo-xanthoma elasticum has been reported repeatedly in Paget's disease. As these anomalies, together with widespread arterial changes, constitute the syndrome of elastosis dystrophica, it is possible that Paget's disease may be a variable and unrecognized part of the syndrome.

Leontiasis ossea.—This affection, in which there may be optic atrophy, various ocular palsies and exophthalmos, is generally regarded as a localized form of Paget's disease. It has been recorded over four generations, developing early in childhood.

Achondroplasia

The ocular interest of this affection is limited. Walsh reported optic atrophy in two unrelated cases. The affection is inherited in a simple dominant manner.

Morquio's disease

It is now generally accepted that the widespread skeletal abnormalities described by Morquio are part of the clinical picture of gargoylism.

Cranio-cleido dysostosis

In this widespread membrane-bone anomaly ocular lesions do not appear to have been recorded, except for the presence of exophthalmos in one case. This paucity of ocular features is rather unexpected.

The affection is inherited in a simple dominant manner.

Ankylosing spondylitis

Ankylosing spondylitis is inherited in a dominant manner in some families. It is not known whether the frequently occurring iritis in this affection is genetically determined.

Cranio-facial Anomalies

Oxycephaly (*acrocephaly, tower skull*)

This is a composite entity:

Oxycephaly proper.—The skull changes are an almost direct contrast to those seen in cranio-cleido dysostosis. There is a characteristic deformity, well shown on x-ray examination which also reveals digital impressions arising from intracranial pressure. Optic atrophy is a common occurrence, frequently preceded by papilloedema. The affection is said to be commoner in males. Most cases are sporadic, but there are records in twins, in sibships and over two and even three generations.

The frequent association with generalized bone disturbances, and the repeated observations that oxycephaly may occur in hereditary congenital acholuric jaundice,

and also perhaps in hereditary pernicious anaemia manifesting itself early in life, raises the question to what extent oxycephaly is part of a generalized bone marrow disorder with secondary features.

Acrocephalo-syndactyly (*Apert's anomaly*).—The deformity of the skull departs from the classical picture of oxycephaly in that the skull is foreshortened as well as showing the tower deformity. The term acrobrachycephaly is, therefore, more accurate. It is said that only the coronal suture is prematurely closed, allowing growth laterally and vertically, so that there are fewer signs of intracranial compression than in oxycephaly proper.

Apart from the deformity of the skull and the syndactyly at the extremities, other generalized bone defects are not uncommon. Exophthalmos and ophthalmoplegia have been reported repeatedly, and one observation speaks of ectopic lenses.

Genetically, some pedigrees suggest recessive inheritance and others dominance (Fig. 197), perhaps irregular dominance.

Cranio-facial dysostosis (*Crouzon's anomaly*).—Here the facial skeleton is also involved. The skull itself approaches the deformity seen in the Apert anomaly,

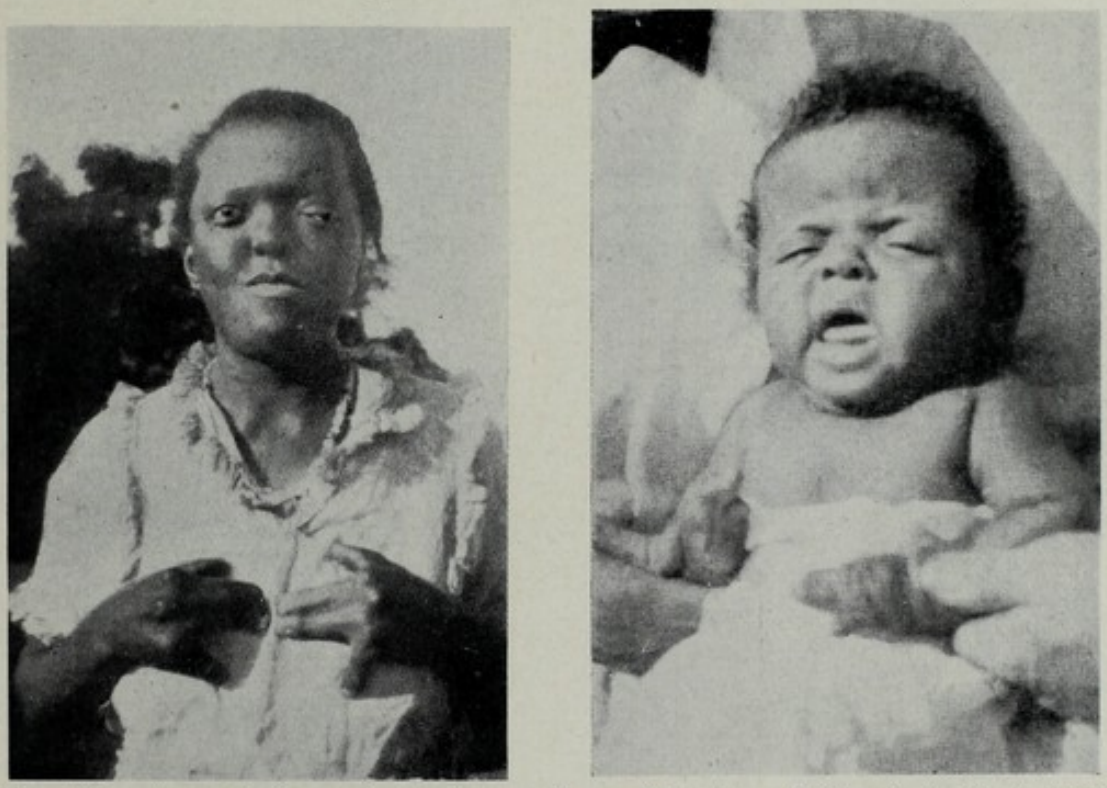


FIG. 197.—Acrocephalo-syndactyly in a mother and daughter. (*After A. A. Weech* (1927). *Bull. Johns Hopk. Hosp.*, **40**, 73.)

brachycephaly being marked; the facial skeleton shows under-development of the upper jaws, and there is marked prognathism of the lower jaw. Malformation of the nose gives it a hooked appearance suggestive of a parrot's beak. As in oxycephaly proper, divergent squint is frequently present, as also are optic atrophy and exophthalmos.

The dysostosis shows three stages of development: (1) owing to early synostosis the skull assumes its characteristic defect, while the face shows the earliest changes consequent on an undeveloped upper jaw; (2) further deformation of the skull

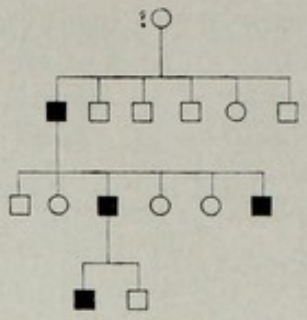


FIG. 198.—Crouzon's anomaly. Pedigree. (*After H. Günther* (1933). *Endokrinol.*, **13**, 255.)

occurs, where it yields at the unfused sutures to the growing brain; (3) compression changes of brain and optic nerve develop.

As with oxycephaly, minor skeletal anomalies elsewhere are not uncommon. Inheritance is more clearly dominant than in the Apert anomaly (Fig. 198).

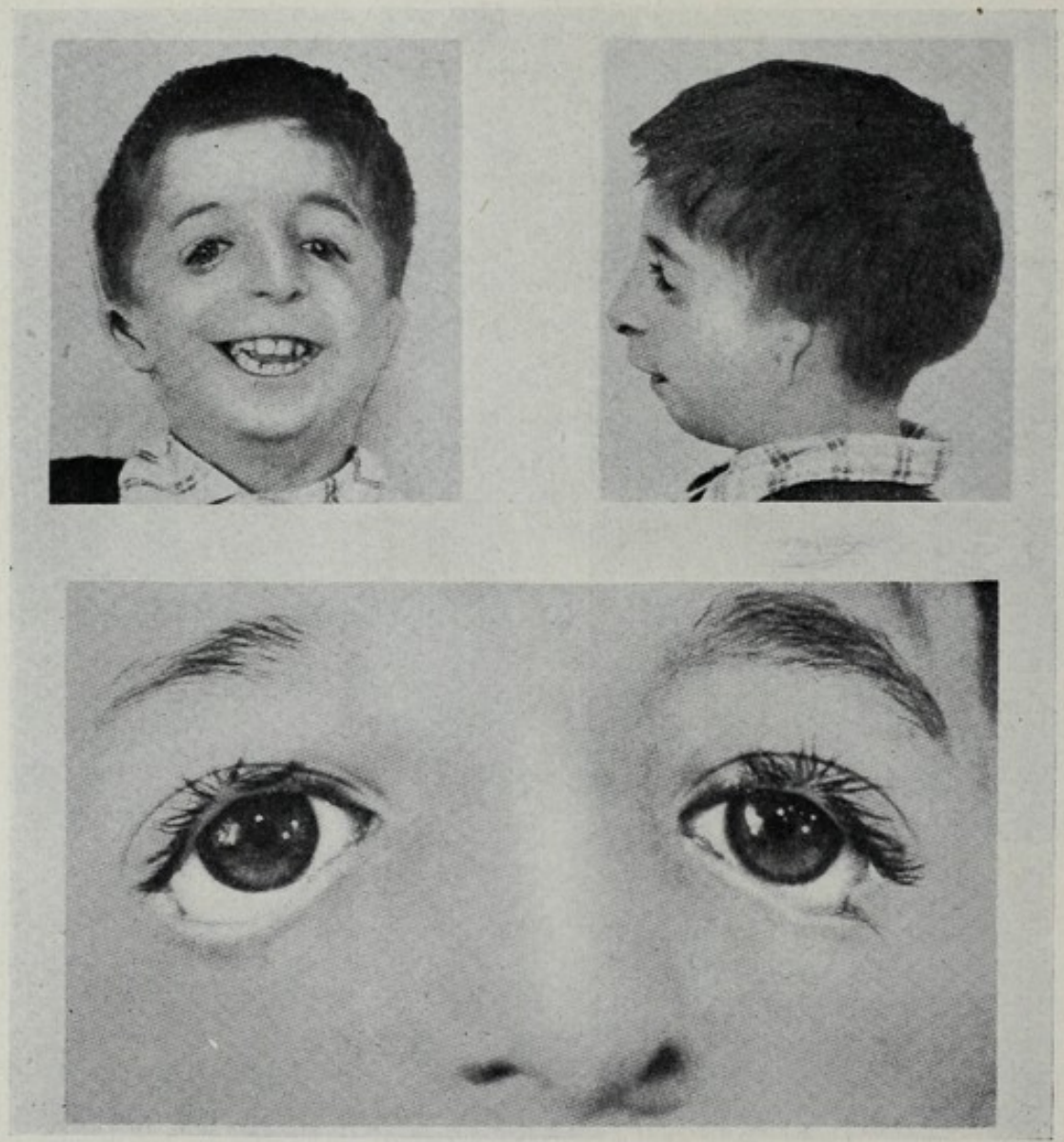


FIG. 199.—Mandibulo-facial dysostosis (Collins-Franceschetti-Zwahlen anomaly). (*After A. Franceschetti and P. Zwahlen* (1944). *Bull. Acad. suisse Sci. méd.*, **1**, 60.)

A transition between the Crouzon and Apert anomalies is shown by some cases reported by Vogt. The facial deformity was that seen in the Crouzon anomaly and the syndactyly was suggestive of the Apert anomaly.

Hypertelorism

In its minor degrees the condition is not uncommon. Fully marked, the striking appearance of a broad bridge of the nose and a wide interpupillary distance (as much as 85 millimetres) is unmistakable. The wide separation of the orbits is consequent on early ossification of the greater wings of the sphenoid, making them smaller than the lesser wings and so fixing the orbits in the lateral position normal in foetal life. Rarely, cleft face is present, shown minimally at the tip of the nose, and more extensively by cleft palate, or marked furrow in the forehead.

Apart from divergent squint, ocular lesions are uncommon, but optic atrophy has been observed, possibly associated with narrow optic foramina.

There are many records of inheritance over two generations.

Mandibulo-facial dysostosis (*Collins-Franceschetti-Zwahlen anomaly*)

Here there is a characteristic facial appearance consequent on an anti-mongoloid lateral downwards slope of the palpebral fissures with a temporal coloboma in the lower lid giving the fissure a triangular form; there is hypoplasia of the facial bones, especially the zygoma and the mandible. There are also malformation of the external and occasionally the middle and inner ears; macrostomia; high palate; blind fistulae between the angles of the mouth and ears; atypical hair growth with tongue-shaped processes towards the cheek; and a possible combination with other and lesser abnormalities. Those fully affected look very much alike, their appearance being somewhat fish-like or bird-like (Fig. 199). Anomalous development of the branchial clefts appears to be the underlying cause.

The affection is probably transmitted as an irregular dominant, the gene having occasionally a lethal effect. Expression is variable (Fig. 200).

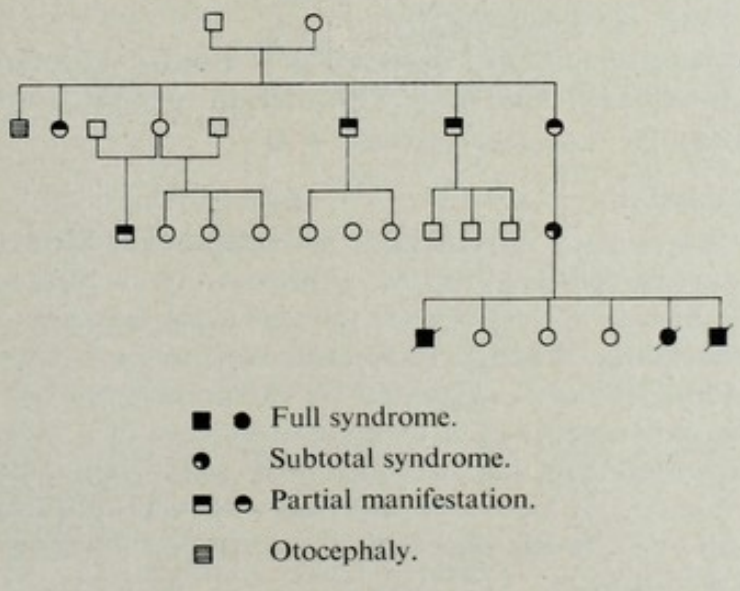


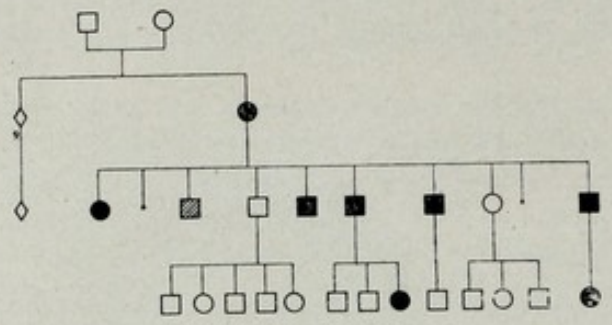
FIG. 200.—Mandibulo-facial dysostosis (Collins-Franceschetti-Zwahlen anomaly). Pedigree showing dominant inheritance with variable expression. (*After Debusmann. Quoted by A. Franceschetti and D. Klein* (1949). *Acta Ophthal.*, **27**, 143.)

Digital Anomalies

Apical dystrophy with coloboma of the macula

Apical dystrophy of hands and feet is a dominant affection. The terminal phalanges and the nails are rudimentary or lacking. The hands and feet are distinctly stump-like.

This anomaly, together with changes in the thumb, which in extreme cases leads to doubling of thumbs, has been observed as a dominant affection over three generations, all affected members also showing bilateral macular colobomas (Fig. 201).



■ ● Affected.
▨ Died in infancy, probably affected.

Fig. 201.—Apical dystrophy with macular coloboma. Pedigree showing dominant inheritance. (*After A. Sorsby* (1935). *Brit. J. Ophthal.*, **19**, 65. *And subsequent observation.*)

Brachydactyly

The many varieties of brachydactyly may arise from shortening of the metacarpals, of the middle phalanges, or of the terminal phalanges. In the more severe anomalies stature is generally shortened. Most of these anomalies are probably inherited dominantly.

Microcornea has been observed in a father and son, both of brachydactylous and short stature. The association may have been fortuitous.

Lobster hand and aniridia

Aniridia has been observed in a member of a family with dominantly inherited lobster hand and foot. The aniridic patient himself did not have the skeletal anomaly.

Syndactyly

No clear-cut associations are established. Syndactyly has been observed in the Laurence-Biedl syndrome, alternative or in association with polydactyly. In two families on record, syndactyly and night-blindness with fundus albi-punctatus has been noted. Whether these cases represent a fortuitous association of two distinct anomalies—as is suggested by the dissociation of the two affections in some of the individuals—or a variable expression of a pleiotropic gene, which when fully expressed gives the Laurence-Biedl syndrome, is not known.

Syndactyly has been observed with microphthalmos. Syndactyly in association with aniridia has also been noted. In one family it has been observed with ptosis (Fig. 202.)

Polydactyly

The association of polydactyly with retinitis pigmentosa, frequently noted in the literature, probably represents incomplete observations of the Laurence-Biedl syndrome.

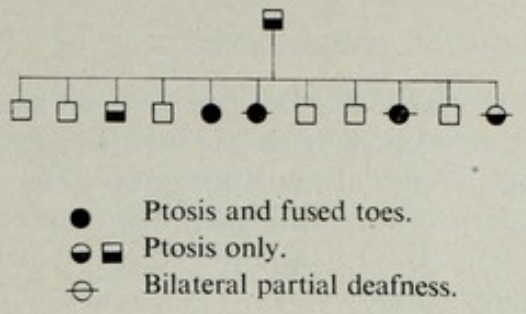


FIG. 202.—Ptosis with fused toes Pedigree suggestive of dominant inheritance. (*After F. B. Walsh* (1947). *Clinical Neuro-Ophthalmology*, *p.* 240. *Baltimore; Williams & Wilkins.*)

Crooked little finger

In one of Nettleship's pedigrees of retinitis pigmentosa a crooked little finger seems to have been inherited independently from the retinal affection.

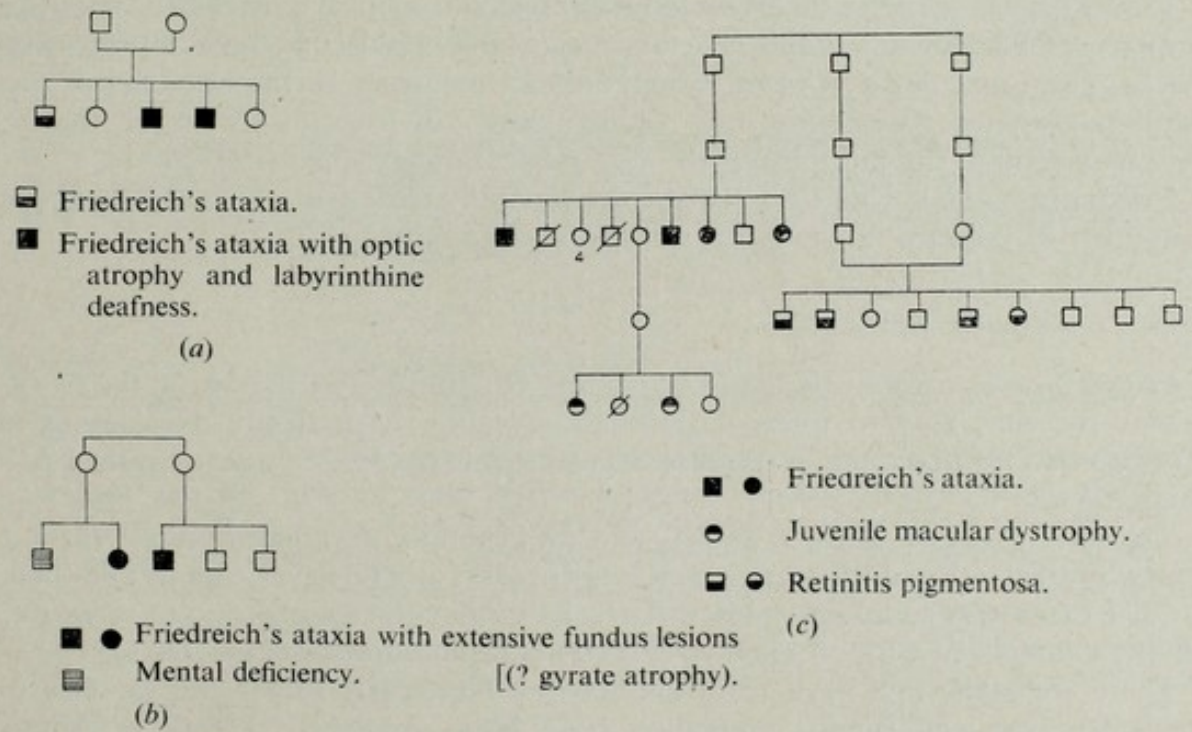


FIG. 203.—Friedreich's ataxia with ocular lesions.
(*a*) Pedigree showing optic atrophy and labyrinthine deafness. (*After L. van Bogaert* (1948). *In Modern Trends in Ophthalmology, Ed. by A. Sorsby. Vol. II, p.* 329. *London; Butterworth.*)
(*b*) Pedigree showing two affected members with extensive fundus lesions (? gyrate atrophy). (*After A. R. de Mello. Quoted by A. Franceschetti and D. Klein* (1948). *Rev. Oto-Neuro-Ophthal.*, **20**, 134.)
(*c*) Extract from the "Glaser" pedigree showing the occurrence of either retinitis pigmentosa or juvenile macular dystrophy with Friedreich's ataxia. (*After A. Franceschetti and D. Klein (1947). Arch. Julius Klaus-Stift Vererb.*, **22**, 93.)

CENTRAL NERVOUS SYSTEM

The Hereditary Ataxias

Friedreich's ataxia and Marie's ataxia, though they have some features in common, are genetically distinct, and they differ greatly in their ocular complications.

Friedreich's spinal ataxia

The classical ocular feature in Friedreich's spinal ataxia is nystagmus. This may develop early or late and is generally only present when the eyes are deviated from the primary position. Abducens palsy, ptosis and the Argyll Robertson pupil are rare complications, whilst optic atrophy, though uncommon, is probably not particularly so in the late stages. It is possible that optic atrophy may occur only in some families (Fig. 203 *a*), whilst in a few families retinitis pigmentosa, generally atypical, has been recorded (Fig. 203 *b* and *c*). It has been suggested that Leber's disease, which so frequently carries minor neurological stigmata, is an intermediate form between the type of Friedreich's ataxia with optic atrophy and the Marie type of ataxia in which optic atrophy is common—a view difficult to maintain on genetic grounds.

Franceschetti, who has observed retinitis pigmentosa in a particularly extensive pedigree of Friedreich's ataxia (the Glaser pedigree) holds that both retinitis pigmentosa and macular dystrophy, which appeared in some of the branches of this family as isolated occurrences, are " equivalents " of Friedreich's ataxia, that is, they may replace the more extensive neurological disturbance (Fig. 203 *c*).

Friedreich's ataxia with its early onset is generally recessive. There are, however, a number of families in which the affection was dominant.

Marie's cerebellar ataxia

Primary optic atrophy is common in this condition, and palsies of the extra-ocular muscles, as also internal ophthalmoplegia, are frequent. Nystagmus is exceptional. In one family retinitis pigmentosa appeared as an "equivalent" (Fig. 204 *a*).

The later onset of Marie's ataxia, and its generally dominant course, form a sharp contrast to Friedreich's ataxia. Recessive cases are, however, known and there are also cases with an infantile onset in which the affection appeared to be recessive, and was associated with progressive external ophthalmoplegia (Fig. 204 *b*).

There are many intermediate forms between the clearly spinal and the clearly cerebellar type and fundus anomalies have been observed in these cases too (Fig. 204 *d*). The spino-cerebellar ataxia of Sanger Brown is dominant. A type resembling disseminated sclerosis with characteristic exacerbations of retrobulbar neuritis is also dominant, whilst the type in which there is transition from ataxia to spasticity appears to be recessive.

The "complicated optic atrophy" recorded by Behr in children, who showed optic atrophy in addition to cerebrospinal symptoms, has been regarded as a transition between Leber's optic atrophy and Marie's ataxia. Its clinical and genetic status is not clear (Fig. 204 *c*).

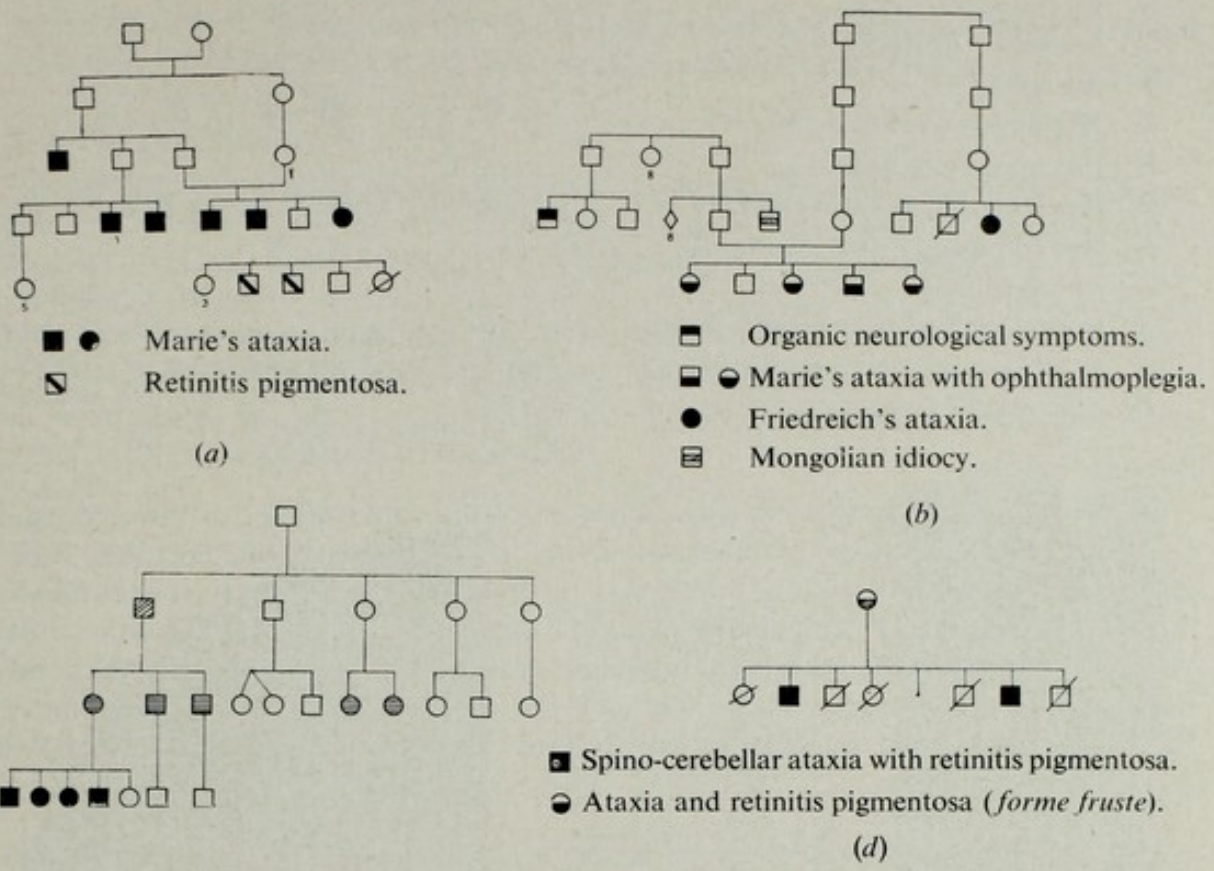


FIG. 204.—Marie's ataxia and allied conditions with ocular complications.
(*a*) Pedigree showing Marie's ataxia with retinitis pigmentosa. (*After A. Franceschetti and D. Klein* (1941). *Arch. Julius Klaus-Stift. Vererb.*, **16,** 469.)
(*b*) Pedigree showing the uncommon recessive form of Marie's ataxia which had two further unusual features, infantile onset and progressive external ophthalmoplegia. (*After A. Franceschetti, G. de Morsier and D. Klein* (1945). *Arch. Julius Klaus-Stift. Vererb.*, **20.** 60.)
(*c*) Complicated optic atrophy as recorded by Behr in children with cerebrospinal symptoms. Pedigree showing relationship to simple optic atrophy. (*After L. van Bogaert* (1948). *In Modern Trends in Ophthalmology, Ed. by A. Sorsby. Vol. II, p.* 319. *London; Butterworth.*)
(*d*) Pedigree showing occurrence of retinitis pigmentosa in a family with spino-cerebellar ataxia. (*After G. Zonca. Quoted by A. Franceschetti and D. Klein* (1948). *Rev. Oto-Neuro-Ophtal.*, **20,** 123.)

THE DEMYELINATING DISEASES

Disseminate sclerosis

The genetic status of disseminate sclerosis is still undetermined. The affection has been noted in sibs, as also in uniovular twins. Generally the family history is, however, negative, except that not infrequently there is a history of nervous or mental disease. Iridocyclitis, too, is probably not uncommon both in those affected and in their relatives (Fig. 205).

- Disseminate sclerosis.
- Trigeminal neuralgia.
- Migraine.
- Migraine and psychopathy.
- Hemiplegia and dementia.
- Imbecility and infantile paralysis.
- Dysarthria and hypotony of arms.
- Duodenal ulcer.
- Hemiplegia from endocarditis lenta.
- Keratoconjunctivitis and episcleritis.
- Iritis and polyarthritis.

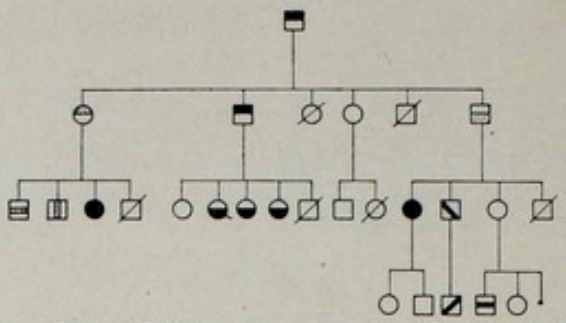


FIG. 205.—Disseminate sclerosis. Pedigree of two cases in collateral branches of a family. (*After F. Curtius*, (1933). *Multiple Sklerose und Erbanlage. Leipzig; G. Thieme.*)

Schilder's disease

In Schilder's disease there is demyelination of the white matter of the cerebrum. Cerebral blindness tends to come on from involvement of the occipital lobes, though no part of the optic tract itself may be involved. Optic neuritis is uncommon, but papilloedema may occur from increased intracranial pressure. The course may be acute, ending fatally within days, or may extend over years; generally the condition is fatal within a year. Although sporadic cases appear to be the commoner, the affection has been recorded in sibships and the affection is probably recessive.

Neuromyelitis optica

Here, too, most cases tend to be sporadic, but evidence of a genetic basis for the affection is derived from the fact that the disease has been observed in uniovular twins. One such pair developed neuromyelitis optica at 24 and 25 years of age respectively, and both died blind in the acute phase of the affection.

Pelizaeus-Merzbacher disease

This is generally regarded as a form of Schilder's disease. In the families followed up by these two observers the affection was clearly sex-linked (Fig. 206).

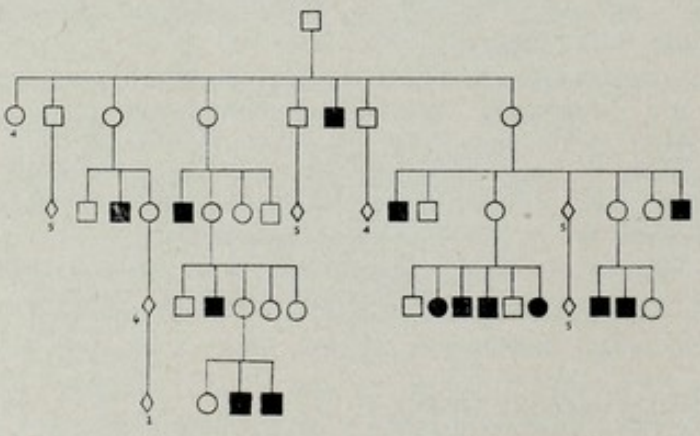


FIG. 206.—Pelizaeus-Merzbacher disease. Pedigree. (*After L. Merzbacher* (1910). *Z. ges. Neurol. Psychiat.*, **3**, 1.)

THE MUSCLE DYSTROPHIES

Of the many varieties of hereditary muscle disturbances only a few have ocular complications.

Myotonia congenita (*Thomsen's disease*)

In this clearly dominant affection the orbicularis muscle may be involved,

producing difficulty in closing the lids. Cataract is lacking in this affection, and this constitutes a striking point in the differential diagnosis from myotonia dystrophica.

Myotonia dystrophica

In myotonia dystrophica the extra-ocular muscles do not appear to be involved. Tonic pupils are common, but the outstanding ocular lesion is a characteristic punctate cortical cataract (Fig. 207). Minimal lens changes are almost constant, and fully developed cataract, which may come on very rapidly, is present in probably 30–40 per cent. of patients. The affection is dominant, though possibly irregularly so. Fleischer holds that the affection increases in severity with succeeding generations and that in a generation in which it appears fully developed further transmission becomes impossible.

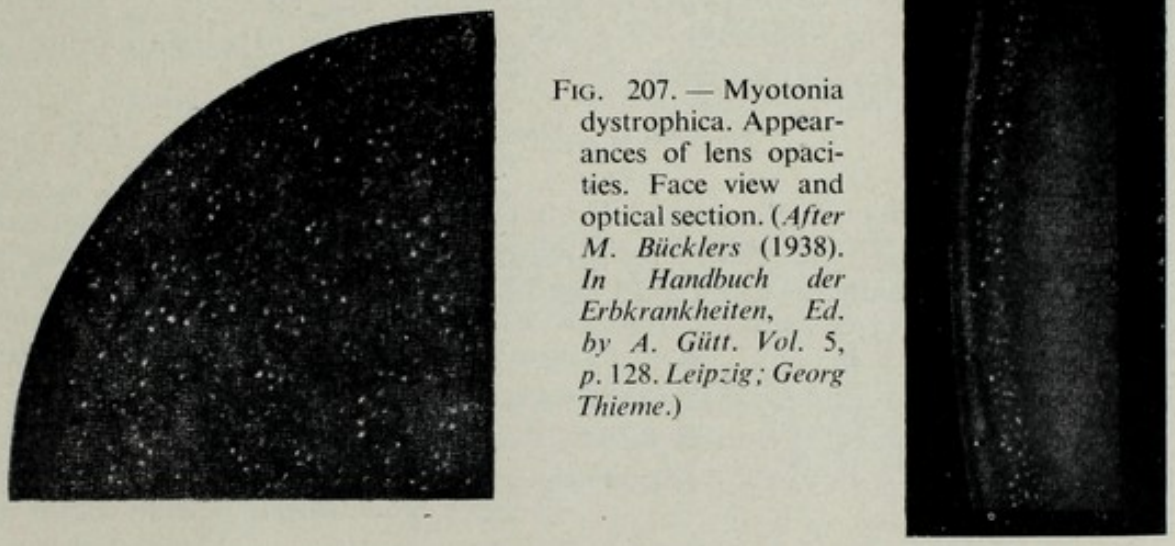


FIG. 207. — Myotonia dystrophica. Appearances of lens opacities. Face view and optical section. (*After M. Bücklers* (1938). *In Handbuch der Erbkrankheiten, Ed. by A. Gütt. Vol.* 5, *p.* 128. *Leipzig; Georg Thieme.*)

THE DYSKINESIAS

Hepato-lenticular degeneration (*Wilson's disease*)

In this recessive affection the Kayser-Fleischer ring may be a pointing sign.

Myoclonic epilepsy

In this rare affection, possibly sex-linked, nystagmus is frequent. Its relationship to sex-linked nystagmus is undetermined.

PARALYTIC AFFECTIONS

Diplegia

The older literature contained case reports of ocular lesions, especially optic atrophy and pigmentary fundus changes, in association with diplegias. It would appear that these older observations refer to ill-defined clinical entities classified by symptoms.

Hereditary spastic diplegia

Hereditary spastic diplegia is a definite entity and appears to be recessive. The ocular lesions are nystagmus, and, less frequently, optic atrophy and various ocular palsies including pupil anomalies.

Stationary congenital facial diplegia (Oculo-facial paralysis ; congenital paralysis of sixth and seventh nerves ; Moebius's syndrome)

The mask-like face, the inability to close the eyelids completely, the lack of lateral ocular movement, and the occasional atrophy of the tongue, constitute a characteristic picture. The affection has been observed in sibs.

Progressive bulbar palsy

Ocular lesions are uncommon, but are characteristic when present. The orbicularis palpebrarum is involved in the widespread paralysis of face, palate and pharynx, with consequent inability to close the lids fully. The affection has been observed in sibships, but also over two generations.

Progressive interstitial hypertrophic neuritis

Ocular signs are sluggish response of the pupil to light, frequently, and a fully developed Argyll Robertson pupil in many cases. The affection is generally recessive, but may be inherited in a dominant manner. Its relationship to neurofibromatosis is questionable.

Other Affections

Syringomyelia

If the concept of syringomyelia is extended to include status dysraphicus, dominant inheritance is obvious (Fig. 208). The concept of status dysraphicus is based on the reading that syringomyelia represents faulty closure at the midline of the

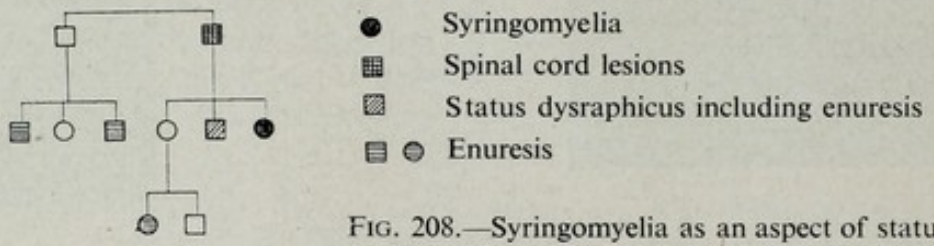


Fig. 208.—Syringomyelia as an aspect of status dysraphicus. Pedigree. (*After F. W. Bremer* (1926). *Dtsch. Z. Nervenheilk*, **95**, 1.)

neural canal, and that syringomyelia is the extreme form of a disturbance which minimally shows various other aberrations of midline development.

Tonic pupils

Most cases are sporadic, but Adie's pupil has been observed both in sibships and over two generations.

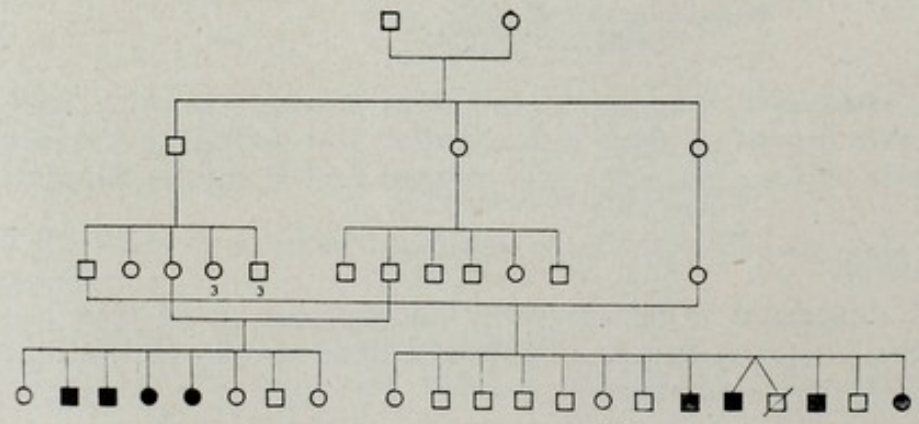


Fig. 209. — Retinitis pigmentosa and deafmutism. Pedigree showing the occurrence of the two affections together in two related sibships, both the offspring of first cousin marriages. (*After C. H. Usher* (1914). *Roy. Ophthal. Hosp. Rep.*, **19**, 130.)

Word blindness

Generally sporadic, there are several observations of the anomaly over two generations, and once over three generations. In his original account Hinshelwood had noted it in sibs.

Cerebral glioma

Isolated cases of cerebral glioma and retinoblastoma have been observed in two collateral branches of a family.

Retinitis pigmentosa and deaf-mutism

Retinitis pigmentosa is not infrequently observed at schools for deaf-mutes. In consecutive pedigrees of recessive autosomal retinitis pigmentosa deaf mutism, or deafness, figures with an incidence of about 10–22 per cent.

The fortuitous association of two recessive genes is a possible but unlikely explanation. The essentially parallel course of the two affections suggests a monofactorial basis. Though the two anomalies appear almost regularly together in certain families, there are families in which the two affections are dissociated (Fig. 209).

Mental deficiency (*oligophrenia*)

Mental deficiency is a component seen in many of the syndromes with ocular involvement. It is also seen in some apparently isolated ocular lesions, such as congenital optic atrophy, some cases of retinitis pigmentosa, anophthalmos, and possibly in other ocular anomalies.

Mental deficiency with retinitis pigmentosa.—According to Julia Bell, about 4 per cent of all cases of retinitis pigmentosa show mental deficiency. When this combination occurs other mental anomalies are likely to be seen in the remaining members of the family (Fig. 210).

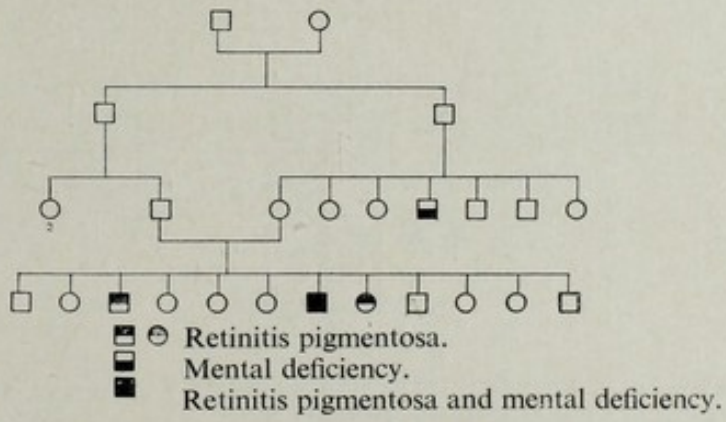


FIG. 210.—Retinitis pigmentosa with mental deficiency. Pedigree. (*After C. H. Usher* (1914). *Roy. Ophthal. Hosp. Rep.*, **19,** 130.)

Mental deficiency with microphthalmos.—Mental deficiency is present in about 50 per cent of cases of microphthalmos and anophthalmos. In a pedigree by Ash and Roberts recessive sex-linkage is suggested (Fig. 211). In a detailed field survey Sjögren found that most cases were sporadic. In seven families only males were affected, and in two families only females. He rejects Robert's reading that mental deficiency is sex-linked, and considers that partial sex-linkage would fit the available facts better.

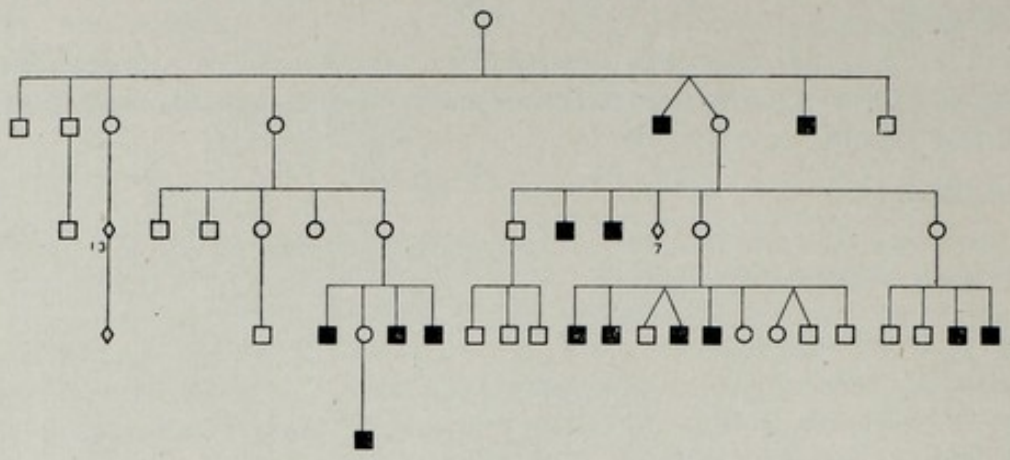


FIG. 211.—Microphthalmos with mental deficiency. Pedigree suggestive of sex-linkage. (*From J. A. F. Roberts* (1937). *Brit. med. J.*, **2**, 1213, *after W. M. Ash and J. A. F. Roberts.*)

THE GENETIC FACTOR IN NEUROLOGICAL AFFECTIONS OF ENVIRONMENTAL ORIGIN

In many of the genetically determined affections of the central nervous system there is ample evidence that environmental disturbances such as trauma or intercurrent disease may precipitate, or aggravate, the disease. This is, of course, an example of the interaction between genetic and environmental factors. Another aspect of fundamentally the same process is seen in affections generally regarded as exclusively environmental in origin; some of these affections occur more frequently in certain families than in others. Fig. 212 shows the frequent occurrence of syphilis of the central nervous system in one particular family. In such and similar. occurrences a genetic predisposition to environmental pathogens must be assumed.

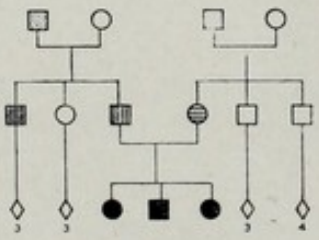


FIG. 212.—Occurrence of syphilis of central nervous system in a family. Pedigree. (*After F. Curtius and H. Schlotter* (1934). *Dtsch. Z. Nervenheilk.*, **134**, 44.)

- Cerebral syphilis.
- Paralysis; aortitis.
- Tabes.
- Juvenile tabes.
- Died, aged 57 years, from a stroke.

OTHER SYSTEMS

SKIN AND MUCOSA

Xeroderma pigmentosum.—In xeroderma pigmentosum conjunctival and corneal involvement are not uncommon, and photophobia may be intense. At

any particular point there may be a succession of erythema, pigmentation, atrophy and tumour formation, though the different stages need not develop successively.

The affection is recessive and carries a high mortality. Conforming to the rarity of the disease, consanguinity in parents is high. It has been suggested that in the heterozygous state the gene gives freckles.

Keratosis follicularis spinulosa cum ophiasi.—Genetical aspects of this condition are known from one family only, fully investigated by Siemens. The mode of inheritance was intermediate sex-linkage (Fig. 213).

In men there is keratosis follicularis followed by loss of hair; thickening of the skin of the eyelids with loss of eye lashes, ectropion, and corneal lesions. Women are only mildly affected.

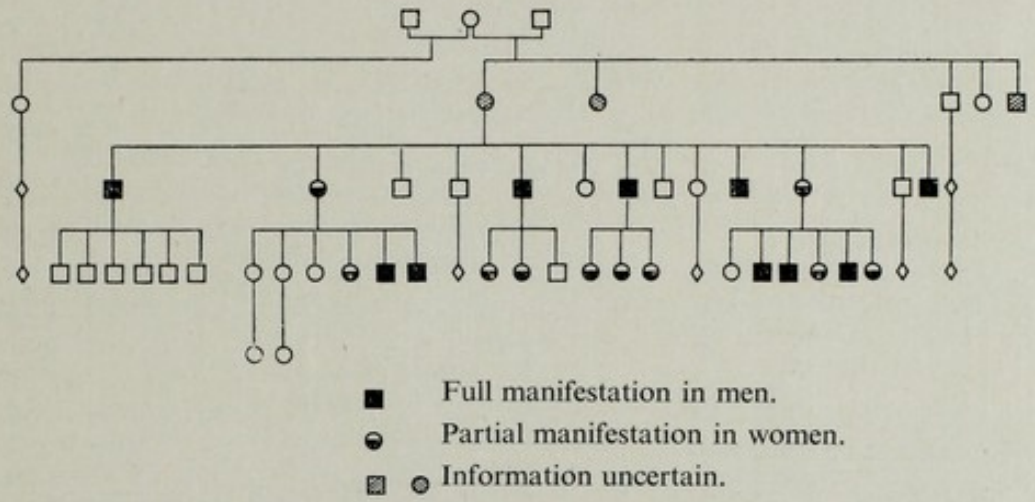


FIG. 213.—Keratosis follicularis spinulosa cum ophiasi. Pedigree showing intermediate sex-linkage. (*After H. W. Siemens* (1925). *Arch. Rass.-u. Ges.Biol.*, **17**, 47.)

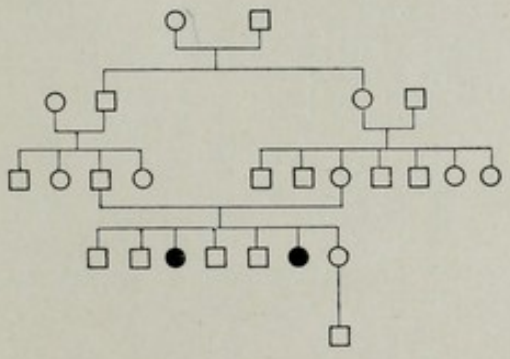


FIG. 214.—Epidermolysis bullosa. Pedigree suggestive of recessive sex-linkage. (*After A. Sorsby, J. A. Fraser Roberts and R. T. Brain. Documenta Ophthalmologica. In the press.*)

Ichthyosis.—In the different varieties of ichthyosis with their multiple modes of inheritance, ectropion from scarring and corneal damage from exposure are not uncommon. It is not known whether cases showing ocular involvement are genetically distinct types.

Epidermolysis bullosa with shrinking of the conjunctiva.—This has been observed once in two sisters, the offspring of consanguineous parents (Fig. 214). Corneal involvement led to blindness in one sister, and to grossly defective vision in the other. Both showed extensive deformities of the hands from scarring.

Multiple telangiectasia.—In this dominant affection cutaneous and mucosal

capillary angiomas develop in childhood and increase in severity and number. They give a characteristic appearance when situated at the upper conjunctival fornix.

Cyclical ulceration of the buccal and genital mucosa.—This has been observed in women over two generations. This affection is of interest in its possible relationship to Behcet's syndrome.

Dental Anomalies

Microphthalmos and dental anomalies.—Actual records are few. The anomalies were rather different in the families recorded by Brailey and by Wolff (Fig. 215).

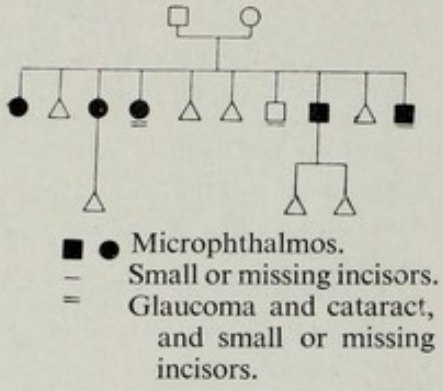


FIG. 215.—Microphthalmos with dental anomalies. Pedigree suggestive of recessive inheritance. (*After E. Wolff* (1929-30). *Proc. R. Soc. Med.*, **23**, 623.)

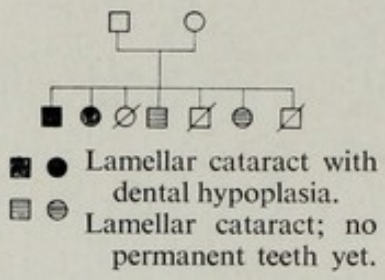


FIG. 216. — Lamellar cataract with hypoplasia of dental enamel. Pedigree showing an affected sibship. (*After N. B. Harman* (1910). *Trans. Ophthal. Soc. U.K.*, **30**, 264.)

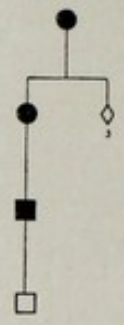


FIG. 217.—Hypertrophy of gums with dental defect and recurrent corneal lesions. Pedigree showing dominant inheritance. (*After M. E. Rutherford* (1931). *Brit. med. J.*, **2**, 9).

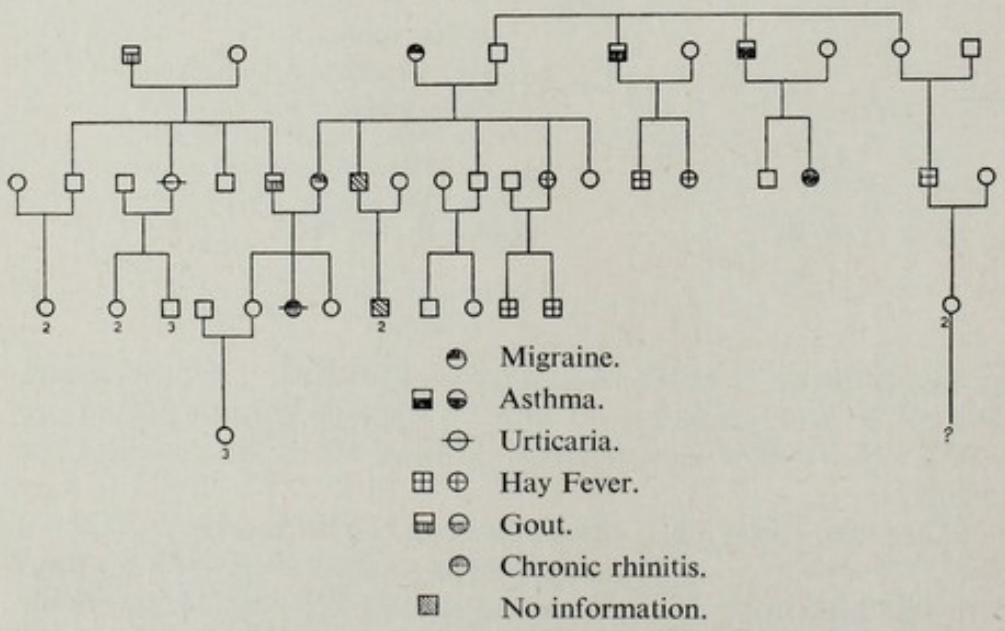


FIG. 218.—Allergy. Pedigree showing dominant inheritance and clinical range of manifestations. (*After Julia Bell* (1933). *Ann. Eugen.*, **5**, 311. *Fig.* 1.)

Lamellar cataract with hypoplasia of dental enamel.—This has been recorded as dominantly inherited by Nettleship and by Harman. Early deaths from fits are not uncommon (Fig. 216).

Pre-senile cataract with hypoplasia of dental enamel.—In two other pedigrees of Nettleship this was also observed as a dominant anomaly.

Hypertrophy of the gums with dental defect and recurrent corneal lesions.—In one family this was observed as a dominant affection (Fig. 217).

The Allergic Diseases

The dominant inheritance of allergic sensitivity is well established (Fig. 218). It is not known whether purely ocular allergy constitutes a distinct genetic type.

Angioneurotic oedema.—Dominant inheritance is the rule, and in different families selective localization, such as to the glottis—with fatal consequences—or in different viscera or areas of skin are frequently seen. An area once affected tends to show recurrent attacks. Almost any part of the body may be involved. Exclusively palpebral angioneurotic oedema does not appear to have been observed as a specific genetic type.

Angioneurotic oedema may be part of generalized allergic sensitivity, so that in some families angioneurotic oedema alternates with other forms of allergy.

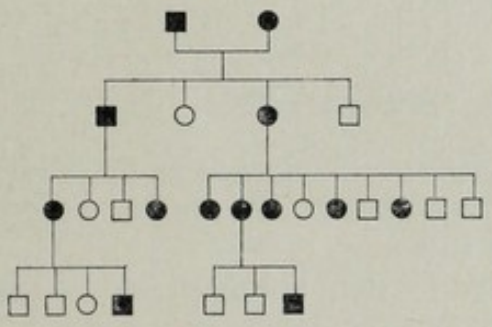
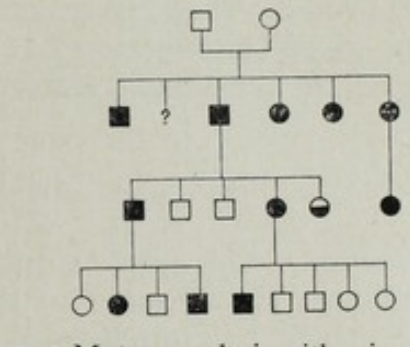


Fig. 219.—Migraine. Pedigree showing dominant inheritance. (*After Unger. Quoted by Julia Bell* (1933). *Ann. Eugen.*, **5**, 311. *Fig.* 14.)



Motor paralysis with migraine.
Hemiplegia after whooping-cough.

Fig. 220.—Ophthalmoplegic migraine. Pedigree showing dominant inheritance. (*After J. M. Clarke* (1910). *Brit. med. J.*, **1**, 150.)

Migraine.—Dominant inheritance in migraine is well established (Fig. 219). As women appear to be affected twice as frequently as men, the possibility of dominant sex-linked inheritance arises.

In one family with twelve affected members ophthalmoplegic migraine was inherited as a dominant (Fig. 220).

Blood Diseases

Haemophilia.—This sex-linked affection does not seem to carry any special ocular aspects. It has, however, considerable significance in ophthalmology as it has been

used for determining linkage with colour anomalies, also inherited as a sex-linked recessive.

Acholuric jaundice.—This irregularly dominant affection is of significance as bone anomalies are not uncommon, and there is the possibility that some cases of oxycephaly are secondary to acholuric jaundice.

Sickle-cell anaemia.— Sickle-cell anaemia too, is dominant, and bone anomalies are common. The skull, in particular, may show the characteristic appearance frequently seen in thalassaemia.

Thalassaemia (*Cooley's anaemia; Mediterranean anaemia*).—This severe affection with its typical osseus complications, which include skull anomalies and mongoloid features, is of uncertain genetic status. It has been observed in sibships and in identical twins. There is, however, not enough evidence to decide between irregular dominance and recessive inheritance.

Erythroblastosis neonatorum.—Optic atrophy in addition to widespread neurological disturbances is not uncommon in this severe affection. The recognition that this anomaly arises from iso-immunization to an Rh antigen has led to one of the most brilliant advances seen so far in the prevention of genetically determined disease.

Polycythaemia vera.—The violet discoloration of the conjunctiva, and the characteristic fundus appearance in polycythaemia vera give a special ophthalmological interest to this dominant affection.

The leukaemias.—The exact genetic status of this group, and its relationship to neoplasms, are still undetermined. It is also not known whether the ocular changes are incidental, or constitute a special genetic type.

Endocrines and Autonomic Nervous System

Hyperthyroidism.—The great excess in women and the occurrence in sibships is well established. The affection, appears to be dominant, and largely sex-limited, with environmental factors as precipitating causes.

In one series of 332 patients, 22 per cent had a family history of thyroid disease, including myxoedema or simple goitre.

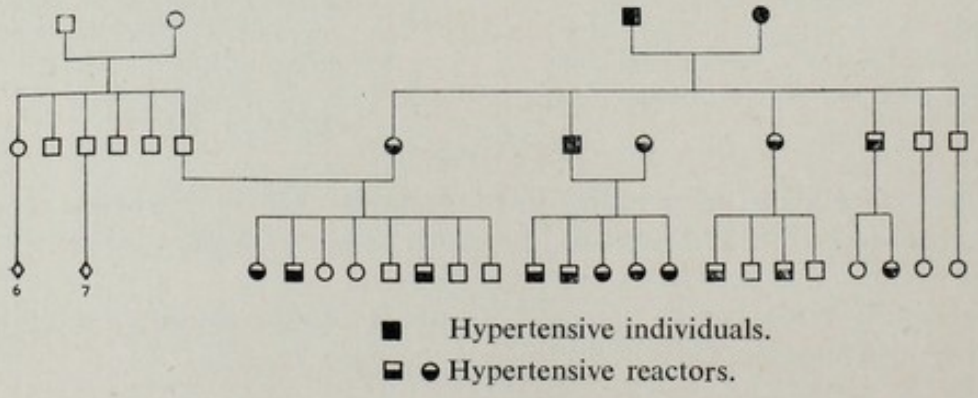


Fig. 221.—Vascular hypertension. Pedigree showing presumed dominant inheritance, expression being either clinical hypertension or induced hypertensive reaction. (*After E. A. Hines* (1937). *Ann. intern. Med.*, **11**, 593.)

Bartels holds that, genetically, hyperthyroidism is only one aspect of thyroid disturbances generally, for simple goitre and myxoedema often occur in families with hyperthyroidism.

Hypoparathyroidism.—Three of ten children, whose parents were first cousins, have been recorded as suffering from hypoparathyroidism. These three also had monilia infection; a possible susceptibility to such infection in this condition is also supported by isolated cases.

Vascular hypertension.—The possible inheritence of hypertension is complicated by the fact that the condition is excessively common. There is, however, good evidence that dominant inheritance is probably the rule (Fig. 221). This may apply to many of the arterial degenerative lesions including coronary atheroma. Whether ocular complications constitute a special genetic type or are incidental to all hypertensive patients is not known.

CHAPTER 3

SYNDROMES

STUDIES of disturbances confined to one organ, or to one system, are a characteristic reflection of the present-day attitude in medicine, for they fit in well with the findings by pathologists and physiologists. The syndromes—and these have been described in increasing numbers in recent years—run counter to these conceptions, for they bring together a mass of apparently disconnected anomalies. Attempts to explain syndromes as disturbances in relatively ill-defined systems—such as the reticulo-endothelial system—do not solve many difficulties, though they have helped to elucidate the syndromes with a metabolic basis. Nor is the embryological approach of attempting to explain syndromes in terms of disturbances in ectodermal or mesodermal tissues always successful, for more than one embryonic layer is generally involved. The conception of status dysraphicus with its postulate of a failure in midline development, is a refinement of the embryological approach and is at best only of limited application.

Genetics has provided another possible approach in stressing the pleitropic action of genes, so that a combination of bizarre anomalies becomes less unintelligible. The variable expression of such genes does, moreover, help to explain both incomplete syndromes—the *formes frustes*—and the frequent observation of apparently unrelated disturbances in collateral branches. Even so, it is not easy to see why club-foot, or cleft palate and such-like anomalies, should be recorded so frequently in relatives of patients with various syndromes, the components of which have apparently no obvious relationship to such anomalies. But this excess may be largely illusory, since comparative data from equally detailed searches in the general population are not available.

Since syndromes cannot, by definition, be classified by organs or systems, nor—except in a few cases—on the basis of a metabolic disorder, nor, as yet, as the result of anomalous effects of particular genes, the embryological approach, with all its limitations, has some value.

PREDOMINANTLY MESODERMAL SYNDROMES

The syndrome of fragilitas ossium, otosclerosis and blue sclerotics

A large number of proper names have been attached to this syndrome, such as Eddowes, Adair-Dighton, Lobstein, Van der Hoeve and others.

The bluish sclera is the most constant feature, and is always present; fragility of bone has been found in only 59·9 per cent in a series of 392 cases; whilst otosclerosis was present in 23·7 per cent of those over 25 years of age. The penetrance of the different components therefore varies considerably. Expression within the same family varies but slightly, but varies considerably as between different families. Subsidiary features of the syndrome are a somewhat characteristic deformity of the skull—there is a high occipital region, a markedly curved parietal region, and a rather broad base; dental defects; minor abnormalities of the

extremities; a slender bone system throughout the body, markedly transparent to x-rays; and laxity of joints. Defective calcification, possibly based on a disturbance of calcium and phosphorus metabolism, appears to be the underlying pathological condition.

The affection is transmitted in a dominant manner, with a variable distribution of the individual components (Fig. 222).

Arachnodactyly

Though the name suggests a merely localized abnormality of hands and feet, arachnodactyly is in fact a particularly generalized disturbance. Poor musculature and joint ligaments, poor development of subcutaneous fat, spinal anomalies, dolichocephaly, slender development of bones, particularly in the extremities, increased stature, congenital heart lesions, and malformation of the ears, are all seen in addition to the important ocular lesions. These, in turn, though most commonly in the nature of subluxation of the lens with tremulous iris, frequently show other features. Coloboma of the lens, opacities of the lens, buphthalmos, megalocornea, high myopia or high hypermetropia, miotic pupils, deep anterior chamber, macular coloboma and even colour-blindness have all been recorded. Amongst the rarer general disturbances are fissure of the face or of the palate, macroglossia, syndactyly, hypogenitalism or hypergenitalism, and spina bifida.

In a series of 60 cases poor development of fat was observed in 76·6 per cent of cases and congenital subluxation of the lens in 61·6 per cent. The other anomalies were seen less frequently: spinal anomalies in 58·3 per cent, contractions in 56·6 per cent, congenital heart disease in 36·6 per cent, malformations of the ear in 25 per cent, and poor muscular development in 20 per cent.

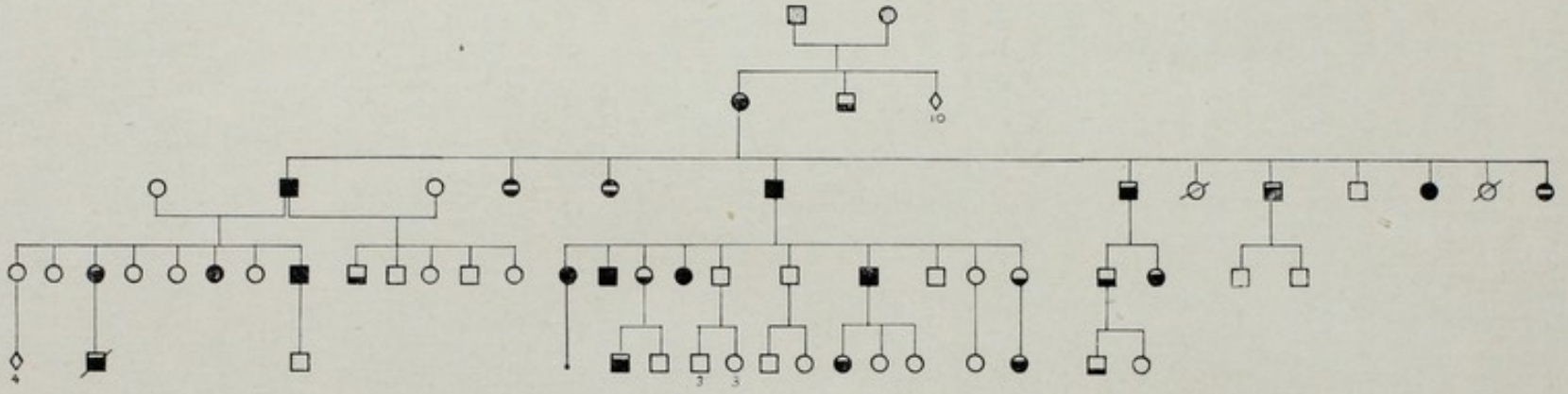
It is generally accepted that arachnodactyly is a mesodermal disturbance. The ocular lesions are regarded as secondary to embryonic changes in the fibrovascular tunic of the lens, or in the suspensory ligament which may, perhaps, be of mesodermal origin.

A patient affected with arachnodactyly is a frail individual. There is a heavy mortality in childhood, particularly in the more severely marked cases. In consequence the genetic aspects have not appeared obvious. There is some evidence that the condition might be recessive, but the rate of consanguinity is not high, and it is more likely that only dominant inheritance comes into consideration. Direct inheritance of the more severe defects is not likely to be frequently observed, owing to the high mortality of affected individuals. It becomes more obvious when the less marked cases are studied (Fig. 223).

Brachydactyly with spherophakia

This syndrome is less well established than arachnodactyly, of which it is the opposite in many respects. Stature is short; hands and feet are short and broad; the musculature and subcutaneous fat are well developed; and there is brachycephaly rather than dolichocephaly. The ocular abnormality is essentially spherophakia, which produces an index myopia; the lens is also small; ectopia and secondary glaucoma are not uncommon.

The condition has been observed in the offspring of first cousins, but the exact genetic status is still undetermined. In the original family, recorded by Marchesani, the possibility of dominant inheritance arose.



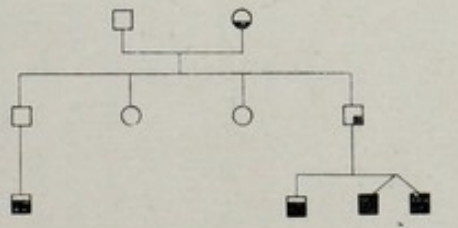
Deafness.

Brittle bones.

Blue sclerotics.

No, or uncertain, information.

FIG. 222.—Fragilitas ossium. Pedigree showing dominant inheritance and variable expression. (*After K. S. Seedorff* (1949). *Osteogenesis Imperfecta. Arhus Universitetsforlaget.*

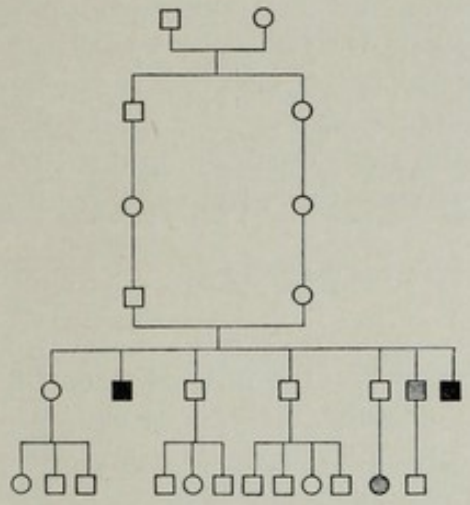


Long fingers and toes; little subcutaneous fat.
Slender; tremulous iris.
Slender; dislocated lens.
Complete syndrome.

FIG. 223.—Arachnodactyly. Pedigree showing dominant inheritance and variable expression. (*After Becker* (1935). *Klin. Mbl. Augenheilk*, **95**, 547.)

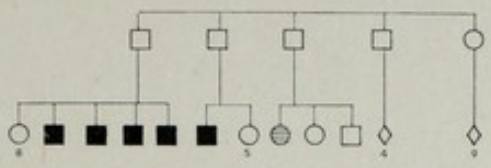
Elastosis dystrophica

The association of angioid streaks with pseudo-xanthoma elasticum was first recognized in 1929 by Grönblad. Subsequently Prick and also Urbach and his associates have shown that elastic tissue degeneration involves the systemic arteries with secondary hypertension. The term elastosis dystrophica was suggested by Böck. Calcinosis of the skin is not uncommon whilst central choroidal sclerosis appears to have replaced angioid streaks in one family (Fig. 224*b*).



■ Pseudo-xanthoma elasticum and angioid streaks.
□ ◎ Fundus coloration not uniform.

(*a*)



◎ Eye trouble.
■ Pseudo-xanthoma elasticum and choroidal sclerosis.

(*b*)

FIG. 224.—Elastosis dystrophica.
(*a*) Pedigree suggestive of recessive inheritance. (*After H. Hartung* (1932). *Klin. Mbl. Augenheilk*, **88**, 43.)
(*b*) Pedigree recording choroidal sclerosis instead of angioid streaks. (*After B. Anderson* (1948). *Trans. Amer. Ophthal. Soc.*, **46**, 326.)

The possibility that osteitis deformans also falls into this group has already been indicated, but angioid streaks appear to be relatively uncommon in osteitis deformans, whilst pseudo-xanthoma elasticum would appear to be exceptional.

The frequency with which the components of the syndrome are associated is not well known. In one series pseudo-xanthoma was found in 59 per cent of patients with angioid streaks, whilst in 100 cases of pseudo-xanthoma recorded in the literature, there were 87 in which angioid streaks were noted. The mode of inheritance is probably recessive (Fig. 224 *a*), though there is some evidence that there might be a dominant form.

In contrast to true xanthomatous changes of the skin, there is no evidence of any lipoid disturbance.

Chondrodystrophy with vascular hamartomas (*Maffucci's syndrome*)

In this rare affection there are associated a chondrodystrophy of the Ollier type with cavernous angiomas and phlebectasia. In one case there was papilloedema from cerebral glioma. The exact genetic status and ocular aspects of the syndrome are still undetermined.

PREDOMINANTLY ECTODERMAL SYNDROMES

Amongst a mass of skin affections in which cataract is occasionally seen, two hereditary syndromes stand out. Rothmund's syndrome and Werner's syndrome

were first regarded as one and the same affection, but they have a markedly different course.

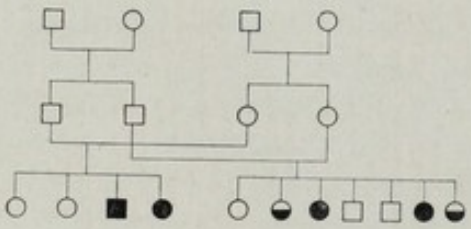
Rothmund's syndrome

Skin changes are observed early in infancy and may perhaps be present at birth. These changes do not readily fall into any definite category, and the usual names, poikilodermia and scleropoikilodermia do not fully, or correctly, describe them. The earliest changes are a reticulated appearance of the skin taking on a reddish hue. Subsequently telangiectases appear, and later on yellowish scars which tend to scale. Normal skin encircled by such yellowish scar tissue acquires a characteristic areolated appearance. The skin on the hands and feet is pliable and thin as tissue paper. Cataract develops early. General development is affected, but not always markedly so. Marked shortness of stature is common, and sexual under-development not infrequent. The affection is compatible with long life and reproduction.

The condition is uncommon, and appears to be recessive (Fig. 225).

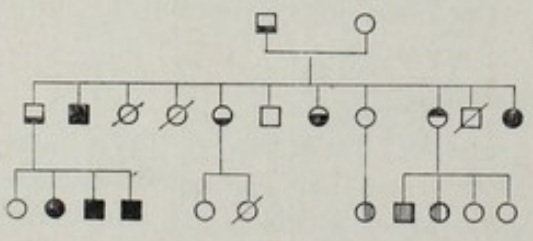
Werner's syndrome

This is a more widespread disturbance, but does not become fully obvious till at about the age of 20–30 years. Stature is markedly affected. Greying of hair sets in at about the age of 20 years, when cataract, atrophy of muscles and subcutaneous fat, huskiness of voice from characteristic and bizarre changes in the vocal cords, diffuse arteriosclerosis, osteoporosis, joint deformities, and ulcers on the feet, all begin to make their appearance, producing the characteristic picture of "progeria of adults". Hypogenitalism is present, and the skin changes are essentially in the nature of an atrophic and thin skin tightly drawn over the



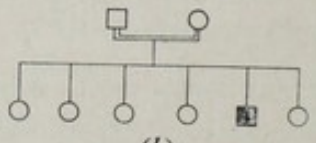
Skin disease and cataract.
Skin disease.

FIG. 225.—Rothmund's syndrome. Pedigree showing recessive inheritance. (*After A. Rothmund* (1868). *Arch. Ophthal.*, **14**, 159.)



(*a*)

Precocious canities
Precocious canities and cataract
Skin affection
Left cataract
Bilateral cataract
Right cataract



(*b*)

FIG. 226.—Werner's syndrome.
(*a*) Pedigree showing dominant inheritance. (*After E. Krebs, E. Hartmann, and F. Thiebaut* (1930). *Rev. Neurol.*, **37**, 121 and 606.)
(*b*) Pedigree showing recessive inheritance. (*Personal observation. Royal Eye Hospital No.* 0/8875.)

underlying tissue. Telangiectases and pigmentation are not marked. Proptosis is not uncommon.

Available evidence points to dominant inheritance not always fully expressed (Fig. 226 *a*). Recessive inheritance is suggested by the pedigree in Fig. 226 *b*.

Congenital anhydrotic ectodermal dysplasia

In the fully developed, and generally sex-linked form, the individual is toothless, or deficient in teeth, shows fine pale scanty hair, chronic rhinitis with ozaena and, characteristically, lack of sweat glands and, in some cases, of the lacrimal glands. Stature is affected. Both inability to weep and a tendency to excessive watering of the eye have been recorded, but apparently not as constant features. Cataract has not been observed in undoubted cases.

In the less complete form, inherited in a dominant manner, microphthalmos has been observed in two families (Fig. 227).

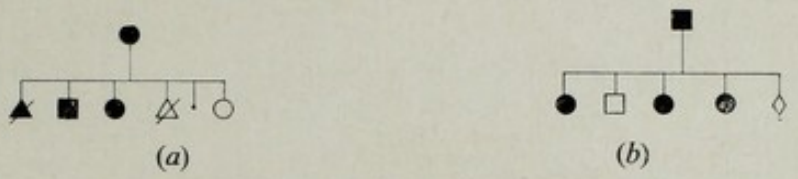


FIG. 227.—Congenital anhydrotic ectodermal dysplasia with microphthalmos.
(*a*) and (*b*) (*After H. Moon* (1876–7), *quoted by E. A. Cockayne* (1933). *Inherited abnormalities of the skin and its appendages. London; Oxford University Press.*

Congenital poikilodermia, bone anomalies and ocular lesions (*Thomson*)

It is possible that there is a type of congenital generalized poikilodermia with bone changes (aplasia, especially of the phalanges) and ocular lesions. Microcephaly, microcornea, high myopia, and partial optic atrophy have been observed.

The kerato-conjunctivitis sicca syndrome (*Sjögren's syndrome*)

Most recorded cases are sporadic, but the affection has been noted once in mother and daughter.

It is possible that the syndrome is in itself part of a more widespread disturbance involving the mucous membranes throughout the body with the Plummer-Vinson syndrome as one of the features.

PREDOMINANTLY NEURO-ECTODERMAL SYNDROMES

The phakomatoses

Pathologically the phakomatoses occupy an intermediate place between the abiotrophies and the hereditary tumours. Genetically determined minimal blemishes of the skin and possibly also in the central nervous system are present at birth or in early infancy in the whole group; some of these blemishes may grow and even become malignant. This characteristic led Van der Hoeve to suggest the generic name of phakomatoses (φακός=mother spot). Four clinically distinct types are recognized.

Neurofibromatosis

The constant features in neurofibromatosis are subcutaneous nodules, tumours along the nerve trunks, and pigmentary changes in the skin. Rather less commonly psychic troubles, anomalies of bone, and endocrine disturbances are also seen. The ocular aspects of neurofibromatosis cover a wide range: neurofibromatosis may involve almost any part of the eye so that neurofibromas may be seen in either the lids, orbit, optic nerve, and in the individual structures of the eye, such as any part of the uveal tract, the retina, the conjunctiva, episclera, sclerotic, and even the cornea. Buphthalmos may arise owing to neurofibromatosis of the ciliary nerves. Multiple small tumours or cysts may be seen in the retina.

The affection appears to consist clinically of two distinct types. In one, malignant degeneration of tumours is common, and in the other it is exceptional. As many pedigrees show irregular dominance, the gene is not fully penetrant, and, moreover,

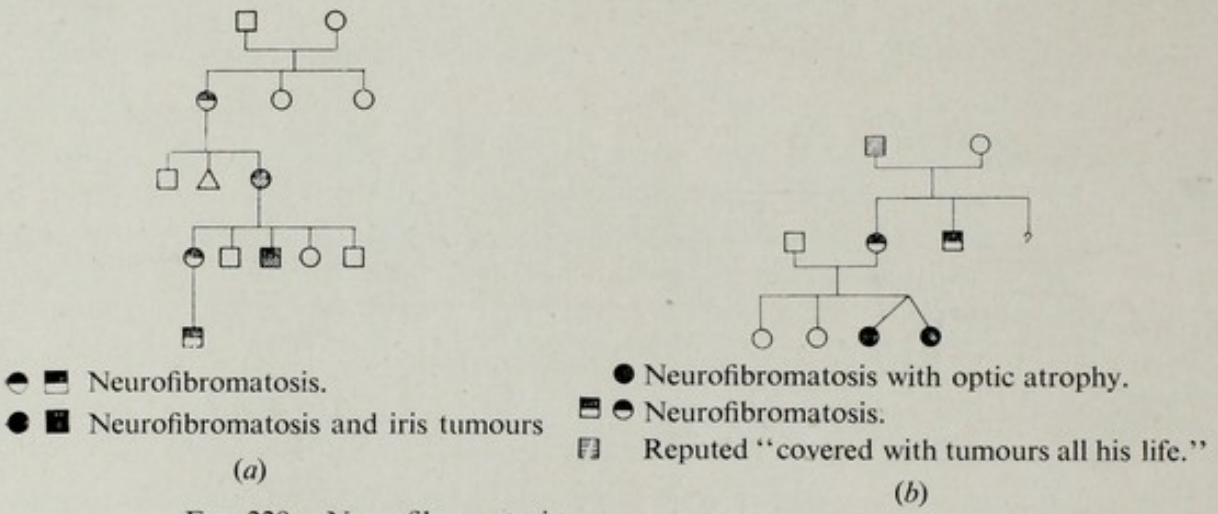
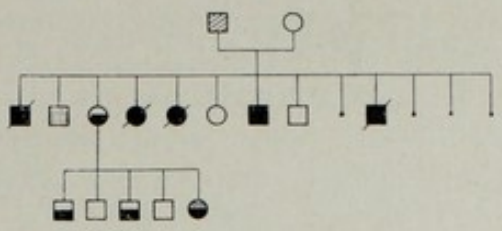


FIG. 228.—Neurofibromatosis.
(*a*) Pedigree showing dominant inheritance of neurofibromatosis over 4 generations, with iris tumours over 2 generations. (*After P. J. Waardenburg. Quoted by J. van der Hoeve* (1932). *Trans. ophthal. Soc.*, **52,** 398.)
(*b*) Pedigree showing bilateral optic atrophy in a uniovular twin in a family with neurofibromatosis. (*After E. Dresner and D. A. D. Montgomery* (1949). *Quart. J. Med. N.S.*, **18,** 93.)

the expression is variable. Some intrafamilial regularity is not uncommon. Inheritance of iris tumours is shown in Fig. 228 *a*, whilst Fig. 228 *b* shows bilateral optic atrophy in both members of a uniovular twin.

Tuberose sclerosis

The range of manifestations in individual patients extends from adenoma sebaceum alone, to adenoma sebaceum associated with epilepsy but no mental change; adenoma sebaceum associated with symptoms of cerebral tumour; and visceral tumour alone; retinal tumours may be associated with any of these types. Cerebral calcification is not uncommon. A family history of psychopathy is frequent. The affection is dominant and the range of manifestations is brought out in Fig. 229. It would, therefore, seem that whilst the penetrance of the gene is high, expression is particularly variable.



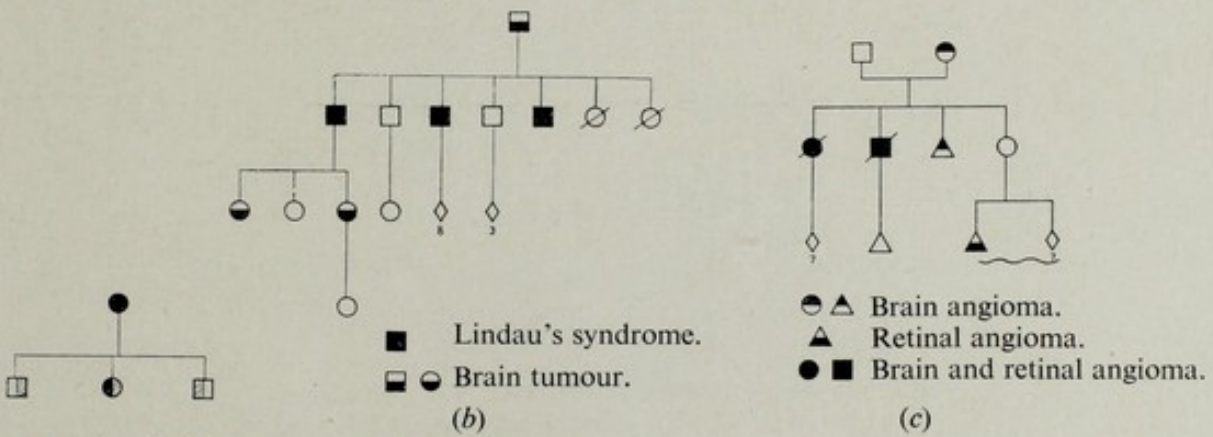
Leiosarcoma.
Epilepsy.
Retinal tumour and epileptic fits.
Retinal tumour.
Cerebral tuberose sclerosis.

FIG. 229.—Tuberose sclerosis. Pedigree suggestive of dominant inheritance and variable expression. (*After J. van der Hoeve* (1940). *In Modern Trends in Ophthalmology, Ed. by F. Ridley and A. Sorsby. Vol. I., p.* 124. *London; Butterworth.*)

Lindau's syndrome

Angiomatosis of the retina with its characteristic picture is now recognized as part of the Lindau syndrome. Calcification in the cerebellum or cerebrum is not uncommon. Cysts and tumours in the cerebellum, spinal cord, pancreas and kidney and other organs are also seen.

It would appear that the affection is dominant with variable expressions in the different members affected (Fig. 230 *a*, *b* and *c*).



Lindau's syndrome.
Brain tumour.
(*b*)

Brain angioma.
Retinal angioma.
Brain and retinal angioma.
(*c*)

Marked angiomatosis of retina, bilateral.
Marked angiomatosis of retina, right.
Ophthalmoscopically visible angiomatosis without visual defect, right.
Ophthalmoscopically visible angiomatosis without visual defect, left.
(*a*)

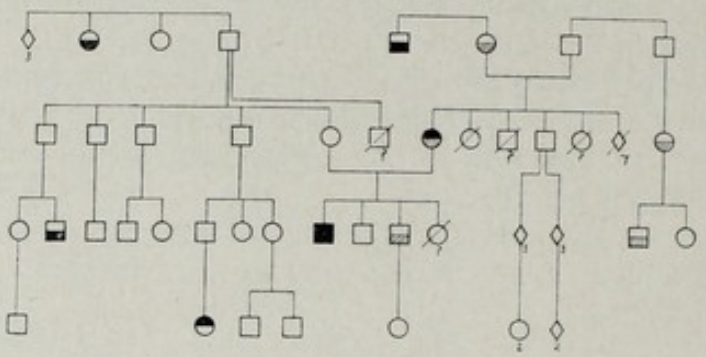
FIG. 230.—Lindau's syndrome. Pedigrees suggestive of dominant inheritance and variable expression in :
(*a*) Angiomatosis of retina. (*After L. Staz* (1941). *Brit. J. Ophthal.*, **25,** 167.)
(*b*) Brain and retinal angioma. (*After H. M. Möller* (1929). *Acta Ophthal.*, **7,** 244.)
(*c*) Brain and retinal angioma. (*After J. van der Hoeve* (1932). *Trans. Ophthal. Soc. U.K.*, **52,** 380.)

Sturge-Weber syndrome (cephalo-facial angiomatosis)

Typically there is naevus flammeus of the face, largely following the distribution of the fifth nerve on one side, together with unilateral buphthalmos and calcification in the cerebrum shown by x-ray. Localized ipsilateral skull anomalies are common, as is mental deficiency. Epilepsy and hemiplegia may occur. Buphthalmos may be replaced by chronic glaucoma, or glaucomatous optic atrophy without rise in tension.

It would appear that mono-symptomatic forms are not uncommon, so that angioma of the choroid or buphthalmos may be the only aspect of the affection. On the other hand there are also observations of angiomas in the cerebellum and spinal cord, raising the question whether the fundamental lesion is not one of capillary angiomatosis and, as such, the relationship with haemangiomatosis of the Lindau syndrome becomes close.

The affection is probably dominant, with different members of the families showing somewhat different lesions corresponding to the site of the capillary angiomas (Fig. 231).



■ Sturge-Weber syndrome.
Epilepsy.
Naevus of skin.
Migraine.
Died in infancy of convulsion.
Died in infancy, ? affected.

FIG. 231.—Sturge-Weber syndrome. Pedigree suggestive of dominant inheritance and variable expression. (*After G. Koch* (1940). *Z. ges. Neurol.*, **168,** 614.)

Other neuro-ectodermal syndromes

Mongolian idiocy

The dwarfed stature, mongolian facies, seborrhoeic skin, large tongue, and mental defect, constitute a characteristic syndrome. Minor anomalies are present in the skull.

A characteristic subcapsular cataract is frequently present, and in about one-third of patients there is high myopia.

The affection has been recorded in sibships. Most mongolian idiots are born to aging mothers. It is likely that the affection is genetically determined but becomes manifest only under particular maternal environmental conditions.

Congenital hereditary ataxia, dwarfing, mental deficiency and congenital cataract

Marinesco and his associates, as also Sjögren have described this combination as a definite clinical entity. The affection appears to be recessive.

Sjögren has also recorded an allied syndrome in which spastic diplegia replaced the ataxia. This, too, appears to be recessive.

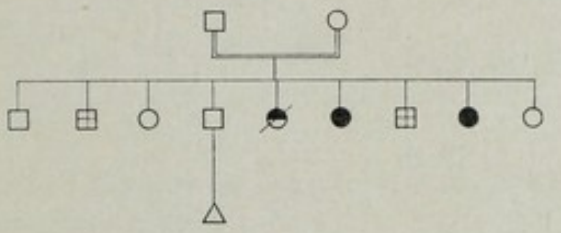
The syndrome of Rud

Typically there is association of congenital ichthyosis, infantilism and epilepsy. In one case there was arachnodactyly and retinitis pigmentosa.

The exact significance of ocular aspects of this syndrome, and the genetic status of the syndrome, are uncertain.

The Laurence-Moon-Biedl syndrome

In the pentad of obesity, hypogenitalism, mental deficiency, polydactyly, and retinal dystrophy of the retinitis pigmentosa type, the ocular changes are almost constant, whilst some of the other components may be lacking. The retinal



⊞ Deaf-mute.
Polydactyly, died young.
● Laurence-Moon-Biedl syndrome.

FIG. 232.—Laurence-Moon-Biedl syndrome. Pedigree showing deaf-mutism in an affected sibship. (*After R. A. Burn* (1950). *Brit. J. Ophthal.*, **34**, 65.)

dystrophy itself may take the form of typical retinitis pigmentosa, atypical variants, a macular lesion with pigmentary disturbance such as seen in juvenile amaurotic idiocy, or a combination of retinitis pigmentosa and macular dystrophy. Of the many subsidiary features—such as atresia ani, syndactyly and various skeletal anomalies—congenital deaf-mutism is significant, and may perhaps appear as a variant to the retinal dystrophy (Fig. 232).

The rate of consanguinity in the Laurence-Biedl syndrome is high; as no case of direct transmission of the syndrome is known, and as the affection has been recorded in sibships, the recessive character of the affection is beyond doubt (Fig. 233). Earlier attempts to explain the apparently disconnected components of the syndrome on the basis of two or more genes must be regarded as untenable, and the fact that partial—and frequently only minimal—manifestations are observed in the ascendants, cannot be taken as proving the transmission of a dominant gene responsible for some features in addition to a recessive gene responsible for others. The most likely reading is that which sees the affection as the result of a recessive gene in the duplex state, and the partial manifestations in ascendants as the expression of the gene in the simplex state. There is a definite excess of males, presumably due to sex limitation in the manifestation of the gene.

Mental deficiency, hypogenitalism, Friedreich's ataxia, and choroidal sclerosis have been observed by Kapuscinski in 1934 in a sibship with three affected members. The parents were not consanguineous, and the family antecedents were clear. In the original cases recorded by Laurence and Moon in 1866, as in the cases recorded by Kapuscinski, polydactyly was absent. Paraplegia was subsequently recorded by Hutchinson, who spoke of the fundus changes as due to "disease of

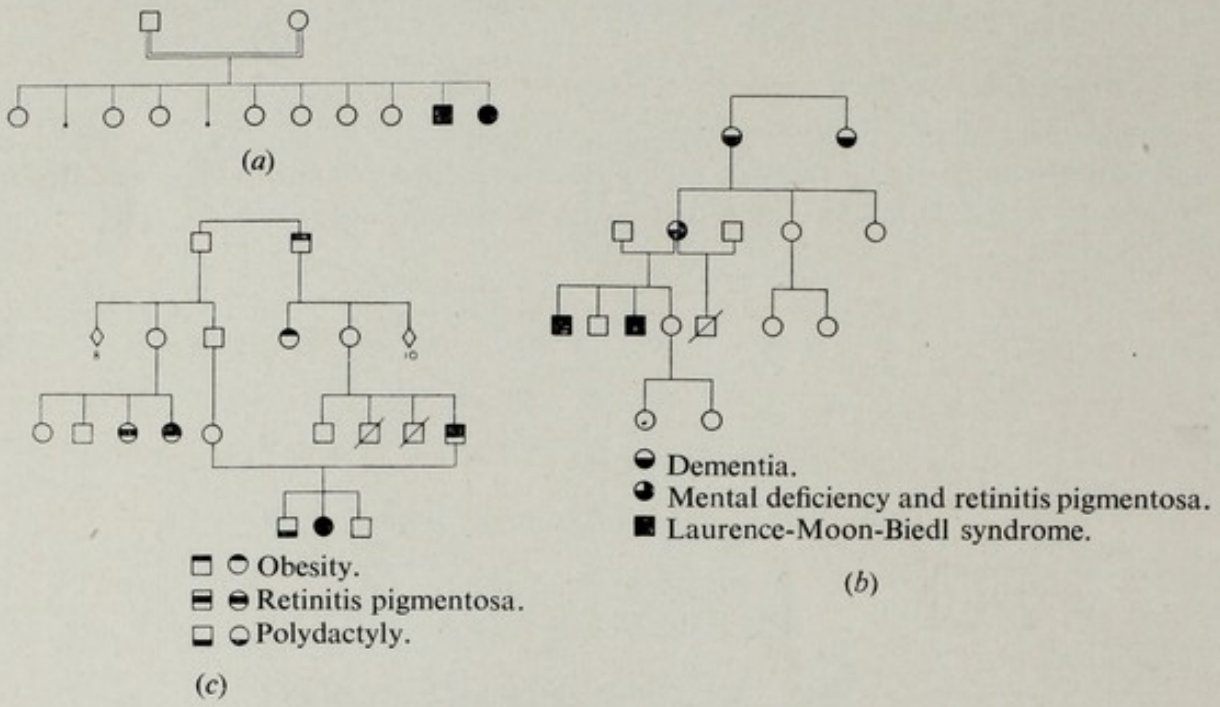


FIG. 233.—Laurence-Moon-Biedl syndrome. Pedigrees.
(*a*) Recessive inheritance. (*After A. Sorsby, H. Avery and E. A. Cockayne* (1939). *Quart. J. Med., N.S.*, **8**, 51.)
(*b*) and (*c*) Partial manifestation of the syndrome in ascendants (*b*). (*After L. van Bogaert and P. Borremans* (1936). *Ann. Méd.* (*Paris*), **39**, 54.)
(*c*) (*After T. C. Laborne* (1944). *Ophthalmos.*, **3**, 250.)

the choroids". Franceschetti holds that it would be more correct to speak of the Laurence-Hutchinson syndrome as referring to a neurological disturbance, and of the Bardet-Biedl syndrome for the affection generally called the Laurence-Moon-Biedl syndrome. As the Laurence-Biedl syndrome frequently carries a wide range of subsidiary disturbances, and the significance of these features is not yet fully assessed, this distinction into two entities must await pathological or genetic support.

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