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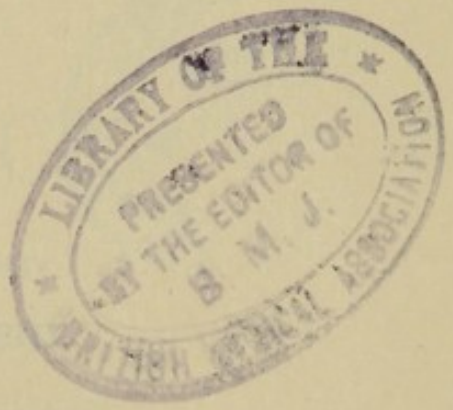
NEW PATHS IN GENETICS



by J. B. S. Haldane

HEREDITY AND POLITICS

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SCIENCE IN EVERYDAY LIFE

SCIENCE IN PEACE AND WAR

NEW PATHS IN GENETICS

by

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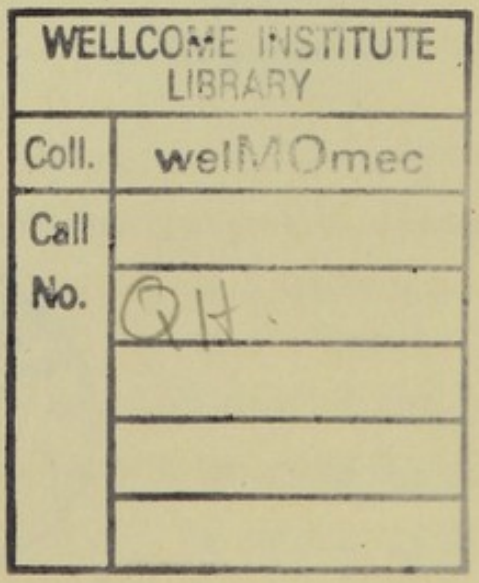

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Preface

THIS book is based on a series of lectures given in the University of Gröningen, Holland, in March 1940. At that time Holland was an island of peace and culture. It has now been swamped in the flood of war, and I do not know how many of my hosts are still alive, and how many of the survivors are in concentration camps. Alive or dead, I must thank them for their hospitality.

Professor Sirks, who was responsible for inviting me to Gröningen, asked me to deal with the connections between genetics and other branches of science, in order that my lectures should have as wide an appeal as possible. I agreed, except that I refused to lecture on racial differences, for two reasons. I have already written on this subject in my book *Heredity and Politics*. And in the event of a German invasion I did not want to increase my hosts' chances of being murdered, by criticizing the official Nazi theories on this topic.

I have, however, tried to show the relation of genetics to other sciences, and some of the lines along which it is advancing. So this book is intended quite as much for students of medicine and of embryology, biochemistry, and other branches of biology, as for geneticists.

I may be criticized for devoting too much attention to my own work. But this was inevitable if I did not propose to cover the whole field of genetical study. It would have

been somewhat impudent for a foreigner to have lectured to the countrymen of de Vries on mutation and evolution, to those of Lotsy on hybridization. I deliberately chose topics which have been studied in my own laboratory, and I thought would have some novelty for my hosts.

Under the terms of my engagement to lecture at Gröningen my lectures had to be published as a book; and indeed I have not been paid for them, nor am I likely to be. For this reason I hurried to get them into book form. But meanwhile I was called upon to undertake research for the British Government designed to save the lives of certain members of its armed forces. This research not only occupied most of my time, but left me in a state of fairly extreme physical exhaustion, as the conditions which I was investigating were of such a character as to cause loss of consciousness and other serious symptoms. Hence I have not been able to give the book all the attention that I could wish, notably in respect of references.

However, if the book is not published now it may never be published at all. I do not even know whether I shall enjoy life and liberty long enough to correct the proofs. Hence I must ask readers to forgive any minor blemishes. I conclude with the hope that genetical research may once again become possible in Europe in the near future, and that this book may do something to suggest the lines on which it is revived.

Contents

CHAPTER I

The Science of Genetics

"E se il mondo laggiù ponesse mente
al fondamento che natura pone,
seguendo lui, avria buona la gente.

Ma voi torcete alla religione
tal che fia nato a cingersi la spada,
e fate re di tal ch'è da sermone;
onde la traccia vostra è fuor di strada."[1]

DANTE, *Paradiso*, VIII, 42.

GENETICS is the branch of biology which is concerned with innate differences between similar organisms. It includes the study of heredity, but has a wider scope. For example, it includes the study of sex determination, and we do not generally speak of sex as an hereditary character, though each normal human being resembles one or other of his or her parents in this respect.

Like so many other branches of science, genetics has achieved its success by limiting its scope. Given a black and a white rabbit, the geneticist asks how and why they differ, not how and why they resemble one another. To

[1] "And if the world down there applied its mind to the foundation that nature lays, following it, it would have a good people. But you twist into a religious life one who was born to gird the sword, and make a king of one born for discourse; whence your track is off the road."

put the matter slightly differently, biologists and philosophers used to ask, "Why do two rabbits produce rabbits, and not rats, roses or bicycles?" The geneticist is able to answer the much simpler question, "Why do two pink-eyed white rabbits give only pink-eyed whites, and not blue-eyed whites, or browns, or blacks?" The answer to this easy question throws some light on the much harder first question. If, with Darwin, we hold that "varieties are incipient species," it throws a good deal.

We said that genetics deals with innate differences. What do we mean by the word "innate"? Supposing your female cat has a long tail, but one of her kittens has a short tail. This may be because the tail has been cut short, or because the father was a short-tailed or Manx cat. In the former case we say that the difference was due to environment or nurture, in the latter we say that it is an innate difference due to nature. The tailless kitten was destined to be tailless from the moment when it started life as a single cell derived by the fusion of an egg-cell from its tailed mother and a spermatozoon from its tailless father.

"Nature" has not quite the same meaning as "heredity," for animals or plants may have a genetically determined nature different from that of any of their ancestors. For example, double stocks (*Matthiola incana*) are quite sterile. All their ancestors have been single. Nevertheless we know that some singles breed true, while others throw doubles, so we can ascribe the

difference to nature, or heredity in a very broad sense of that word.

Where experiment is possible we can generally find out whether a given distinction is due to nature or nurture. We can, for example, inbreed, and produce a "pure line" of plants or animals all of which have very nearly the same nature, and subject them to different nurtures. But this is almost impossible in the most interesting of all cases, that of man. However, even in man a few experiments have been performed on monozygotic twins, who have the same nature.

I must emphasize that I do not regard the distinction between nature and nurture, or that between genotype and phenotype, which is somewhat similar, as an absolute one. This is clearly seen in the case of virus diseases. A potato may be obviously infected with a gross disease of this kind, which produces marked effects on transfer to other potatoes. Or a similar "infection" by grafting or otherwise may merely produce immunity to a known virus. We generally regard the virus as part of the environment, or nurture. But if it is transmitted to a plant from its mother, it cannot be distinguished from other extra-nuclear self-reproducing bodies, such as the chloroplasts, which are regarded as part of the plant's nature. If Lysenko[1] is correct, there is no sharp line in the *Solanaceae* between viruses causing disease and graft-

[1] Lysenko (1939). Translation in *Science and Society*, Spring 1940, p. 211.

transmissible factors responsible for morphological characters. Little's work, mentioned on page 110, suggests the same situation in mice. Nevertheless in ninety-nine cases out of a hundred the distinction between nature and nurture is relevant and useful.

Merely to observe differences, without any causal analysis, a geneticist must use many techniques. He must be a morphologist with a keen eye for slight differences. He may have to use biochemical methods, especially if he is investigating economically important characters such as the sugar content of beets or the butter content of cow's milk. And here he may have to wait on the progress of chemistry. If he is investigating human beings, he is likely sooner or later to be concerned with diseases. And he must use every resource of the diagnostician. It is notable that our exact genetical knowledge of disease is largely confined to abnormalities of the skin and eyes, on which the monographs of Cockayne[1] and Waardenburg[2] may be consulted. This is because these organs can be examined during life, whereas, for example, the internal ear and the heart cannot. If he is making a thorough study of any animal or plant, he will have to learn its pathology as well as its anatomy and physiology.

But even this will not be enough. The animal breeder will have to deal with problems of behaviour, such as

[1] Cockayne, E. A. (1933), *Inherited Abnormalities of the Skin and its Appendages* (Oxford).

[2] Waardenburg, P. I. (1932), *Bib. Gen.*, vol. 7.

the inheritance of broodiness in poultry or that of the habit of pointing in dogs. The human geneticist will be concerned with congenital mental defect, and perhaps also with congenital mental superiority. He will have to become something of a psychologist. Further, he will find a number of statements made concerning the innate abilities of different human classes and races. He will not assess these at their correct value unless he has made a study of political science.

In his study of human and animal races he will become something of an anthropologist and a taxonomist. In studying genetics in its relations to agriculture and horticulture he will need not only to know the technique of these arts, but their economics. For example, the fertility of the diploid and tetraploid forms of *Primula sinensis*, which are grown in the same cultural conditions, is inversely as the price of their seeds. As a final qualification the geneticist may have to become an historian. I had to plough my way through ancient editions of the *Almanach de Gotha* to compile Fig. 11 of this book, and Keeler[1] has produced evidence from the Chinese classics concerning the antiquity of certain mutant forms in the mouse. To sum up, the geneticist must be a jack of all trades, and it is to be feared that he may become a master of none.

The immediate results of genetical investigation are

[1] Keeler, C. E. (1931), *The Laboratory Mouse* (Harvard University Press).

the principles of what may be called formal genetics. If the environment is kept constant, most character differences are found to be due to one or more gene substitutions. That is to say organism X differs from organism Y by the substitution in its nucleus of the gene *A* for *a*, of two *A*'s for two *a*'s, of *A*, *B*, and *C* for *a*, *b*, and *c*, or in some similar manner. For example, a homozygous coloured rabbit is denoted by *CC* or $\frac{+}{+}$, an albino as *cc* or $\frac{c}{c}$. The difference is due to the substitution in the white rabbit of two inactive genes *cc* for two genes *CC* which are concerned in the production of pigment in the coloured rabbit. Similarly a short-haired coloured rabbit is denoted by *CC LL*, or $\frac{+}{+}$; $\frac{+}{+}$, a long-haired albino by *cc ll* or $\frac{c}{c}$; $\frac{l}{l}$. The parental genes pass to the offspring according to very simple laws largely due to Mendel, a knowledge of which I shall assume in my readers. They are described in every textbook of genetics.

When an organism is heterozygous for several pairs of genes, for example, the short-haired coloured hybrid $\frac{+}{c}$; $\frac{+}{l}$, then matters are somewhat more complicated. If the two gene pairs are located in the same chromosome we get the phenomenon of linkage. Thus there are two geometrically isomeric types of rabbit (to use a chemical analogy) heterozygous for recessive white *c* and recessive

yellow fat *y*. The cis-rabbit $\frac{++}{cy}$ derives both these genes from the same parent, and they usually pass into the same gamete, so that the majority of its gametes are $++$ and *cy*. The trans-rabbit $\frac{+y}{c+}$ is derived from the crossing of a white-fatted coloured rabbit and a yellow-fatted white. The majority of its gametes are $+y$ and $c+$. The rare classes of gametes (in this case $++$ and *cy*) are called cross-overs.

On the basis of such facts as these it has been possible to map the chromosomes. Any two gene-pairs which exhibit this phenomenon, called linkage, are located in the same chromosome, and if the gene-pair *Bb* lies between *Aa* and *Cc*, then *Bb* is more closely linked with *Aa* and *Cc* than are *Aa* and *Cc* with one another, that is to say, cross-over gametes are rarer. The validity of these hypotheses has been very amply demonstrated in *Drosophila melanogaster* (a small fly) and *Zea mays* (maize), where the location of the genes established by this method has been fully confirmed by a study of chromosomal rearrangements which are visible with the microscope. In these two organisms almost every gene has been located; and genes are known in almost every region of every chromosome, except for certain regions which are inert, that is to say, almost devoid of genes. Some other species of *Drosophila* are almost equally well mapped.

The studies of *Lathyrus odoratus* (the sweet-pea) and of *Pharbitis nil* (the Japanese Morning Glory) are rather less complete, but within sight of the same goal. Substantial progress has been made with *Mus musculus* (the mouse), *Gallus domesticus* (poultry), *Primula sinensis* (the Chinese primrose), and *Pisum sativum* (the pea). In many other organisms there are rudimentary maps and, as we shall see in Chapter 5, a beginning has even been made in the case of *Homo sapiens*.

The theory that genes are located in a linear order in the chromosomes was put forward by Correns[1] in 1902. Linkage was discovered by Bateson, Saunders and Punnett[2] in 1906. Genes were located in chromosomes by Morgan[3] in 1910, and the first linear order established by Sturtevant[4] in 1913.

The great success of the Morgan school led, as great scientific advances often do, to over-simplification. The genes can, for certain purposes, be represented as points on a line, and genetics are sometimes taught as if they were Euclidean points on a line without breadth. This has led to a very natural reaction, and Goldschmidt has even denied the existence of genes in normal chromosomes. As we learn to think of the genes in terms of their function, as organs in the cell, we shall reach a

[1] Correns, C. (1902), *Bot. Zeit.*, 60, Pt. II, pp. 65–82.

[2] Bateson, W., Saunders, E. R., and Punnett, R. C. (1906), Rep. Ev. Ctee. Roy. Soc., 3, p. 9.

[3] Morgan, T. H. (1910), *Am. Nat.*, 44.

[4] Sturtevant, A. H. (1913), *Journ. Exp. Zool.*, 14, pp. 43–59.

more balanced point of view. Here the history of the physiology of the nervous system should help us. When localization in the nervous system was first discovered, very mechanistic views prevailed. It was thought that each cell had a definite function determined by its connections. But later research showed, for example, that stimulation of the same small area of the cerebral cortex does not always have the same effect. It may cause movements involving different groups of muscles on different occasions. But this uncertainty is not complete. The cortical motor area can still be divided into subareas concerned with the legs, trunk, hand and arm, organs of speech, and so on. Cerebral localization is and remains a great achievement of physiology. I have no doubt that, when all the necessary corrections have been made to Morgan's theories, the localization of genes will remain as a great biological fact.

The laws which hold in the vast majority of cases in genetics are not absolute. Genes generally reproduce their like, but occasionally this process fails. The failure of a gene to reproduce its like is called mutation, at least if the new gene is capable of reproducing its like. It is characteristic of the way in which science grows that, just as the study of radioactivity has revolutionized ordinary chemistry, and thrown light on the nature of stable atoms, so that of mutation has revolutionized genetics. And yet radioactivity and mutation are both negations of the classical laws of the sciences which they

have illuminated. It would, however, be an impertinence on my part to lecture on mutation to the countrymen of de Vries. I need only say that mutation has its own laws. Dante regarded it as miraculous when he wrote:[1]

> "Natura generata il suo cammino
> simil farebbe sempre ai generanti,
> se non vincesse il provveder divino."

However, Muller has discovered how to control the rate of mutation, and it is clear that mutation is accidental rather than providential. The topics which I shall treat in later lectures are as follows.

The older geneticists such as Mendel and de Vries thought in terms of unit characters. For example, a single gene substitution was found to convert a white mouse into a coloured, or a hairless into a hairy. Similarly a single gene substitution converted a glabrous *Matthiola incana* into a hoary, and a white-flowered into one with coloured flowers. It was therefore reasonable to regard the presence of colour and hairs in these organisms as unit characters, and to speak of the gene which is responsible for hairs or colour. This was natural for workers who had been brought up on Weismann's determinant theory; but it was an unduly mechanistic theory, and like other mechanistic theories in biology it has proved unsatisfactory, for the following reasons

[1] "The generated nature would always make its road like its generators, if divine providence did not overrule it." (*Paradiso*, VIII, 133.)

among others. A single "unit character" may only develop in the presence of many genes. Thus at least two dominant genes must be present before colour develops in *Matthiola*, and these two, and two more as well, must be present before hairs are formed. Secondly, the effect of a given set of genes is in no way absolute, but depends on the environment. Thus certain human skins are almost unpigmented when not exposed to strong radiation, but in summer some develop freckles whilst others become a more uniform brown. The pigmentation of the feet, ears, and nose of the "Himalayan" rabbit depends on cold. Genes responsible for chlorophyll production in plants only achieve this end in presence of light and of iron salts, and so on. Thirdly, the modern interpretation of morphological facts is more and more in terms of processes rather than end results. For example, Vogt[1] has shown that one can homologize the processes of gastrulation throughout the Chordata, but as the temporal order of these processes may vary, one cannot homologize the forms which result from their interaction.

For these reasons Hagedoorn was already thinking of genes as determining processes nearly thirty years ago, and to-day it is beginning to be generally realized that we shall come nearer the truth if we regard the gene as responsible for a unit process than for a unit character. I do not, of course, suggest that this concept is anything

[1] Vogt, W. (1929), *Arch. Entwick*, 120.

but a step on the endless path towards truth. On the contrary, we can see the next step ahead, however dimly. We can regard the gene as an organ in the cell, just as the heart, pancreas, or femur is an organ in the body as a whole. Now in the last analysis the function of an organ depends on the other organs and the environment. The function of the heart varies quantitatively with exercise, and the blood leaving the kidney may contain more or less sodium than that entering it according to circumstances. A muscle can serve as an organ for degrading kinetic energy to heat when one runs down a hill instead of producing kinetic energy as it normally does; and so on. Nevertheless it was a great step forward for physiology when the functions of the various organs were defined. And it will be a great step forward in genetics when those of genes are defined, even though we know already from a study of position effects that they are sometimes altered reversibly when a gene is translocated to a new position relative to other genes.

In later lectures we shall examine some unit processes. We shall find one gene responsible for the production of a hormone (or a group of hormones), another for a specific oxidation, and so on. The size of a gene is roughly that of a protein molecule, and it is very possible that the genes are proteins. Thus the function of a gene, the unit process, must be defined in chemical terms. It is most unlikely that a gene is directly responsible for a

specific oxidation, in the sense of catalyzing it. There may be several links in the causal chain between the gene and the oxidation, just as there are a number of causal steps between the activity of a nerve centre and the contraction of a group of muscles. Nevertheless it is a very great step forward to establish the function of a gene or a nerve centre, if only at second or third hand.

The discovery of unit processes opens up new perspectives in biochemistry, of which I shall treat in Chapter 2. Biochemists have elucidated the steps in such a process as the transformation of glucose to alcohol and carbon dioxide by yeast. They used various methods. For example, when sulphite is added this combines with acetaldehyde, one of the intermediaries, and acetaldehyde and glycerol accumulate. When the enzyme responsible for the dismutation of those phosphates is poisoned with iodoacetate, glucose phosphates accumulate, and so on. In just the same way when a gene is transformed into one of its recessive allelomorphs it no longer performs its original function, or performs it more slowly. And a normal metabolic product is not formed, or is formed in small amounts whilst an intermediate or an alternative end-product accumulates. This enables us to trace metabolic paths which would otherwise be unknown. In the next chapter we shall see what light is thrown by this method on the metabolism of anthocyanins.

Similarly we can see what is the effect on development

of the omission of a unit process which can so far only be defined on the morphological level (for if I gained nothing else from ten years' work under so great a biochemist as Hopkins I gained the conviction that biochemical explanations are more fundamental than morphological). The morphologist might ask, "What happens to a mouse which cannot reabsorb bone once it is formed?" The geneticist can tell him. The geneticist can even answer the much more sensational question, "What happens to a mouse embryo with no notochord?" I say "embryo" because such organisms never become mice in any ordinary sense of that word. In so far as we can answer such questions it is clear that we can supplement the work of the Spemann school.

The goal of this branch of genetics is to give a complete account of the functions of every gene. As there appear to be several thousand genes in a cell, this goal would involve a fairly complete account of the biochemistry of the cell, and is some centuries ahead of us. But on the way to this distant end we shall gain a detailed knowledge of biochemistry and developmental physiology which will be of the utmost value.

In the field of individual psychology the geneticist has a similar but even harder task. No sane person doubts that environment has some effect both on character and intellectual achievement. But it is equally sure that in very similar environments different people behave differ-

ently, and that some of these differences are genetically determined. For example, some people are born destined to idiocy, at least in the present state of our medical knowledge. Some are born with the possibility of becoming executant musicians or composers, a possibility which others lack. But an attempt to describe the inheritance of "musical capacity" or "immoral tendencies" is certainly premature. A cow A will not necessarily give more milk than a cow B in all environments, nor a wheat A more grains than a wheat B. Each may have its own optimal conditions.[1] Even the most thoroughgoing materialist may expect the determination of human moral and musical achievement to be at least as complicated as that of milk-yield. So, if I express a doubt as to whether there is any such thing as congenital musical ability or moral defect, in the sense that we can say that A will inevitably excel B in one or other field when both are placed in very similar environments, I do not believe for a moment that innate differences are not concerned in this matter. I merely mean that in my opinion the amount of work which will be needed to create a human psychology as reliable as, say, our existing chemistry, will considerably exceed the entire amount which has gone to the making of existent science and technology since the first man chipped the first flint. This does not mean that the task is impossible or impracticable. It does not even mean that we should not

[1] Haldane, J. B. S. (1937), *Erkenntniss*, 14, pp. 346–57.

begin it now. Browning's grammarian may have exaggerated when he said:

> "Leave time to dogs and apes,
> Man has for ever."

But if the sun's radiation depends on the building of heavier atoms from hydrogen we probably have some thousands of millions of years. I am not, therefore, a defeatist regarding rational psychology. I believe that "Nil mortalibus ardui est," but I note that "mortalibus" is in the plural, and when one of my contemporaries claims to have built up a rational psychology I am not impressed.

A reader of the preceding paragraphs might be pardoned if he attributed to me the theory that all mutations lead to heritable defect. This is very far from being the case. On the contrary, genetically different individuals of the same species exist side by side, and in many cases a number of types seem to be about equally fit in the Darwinian sense. The study of polymorphic populations is a higher stage of genetics than the study of the individual. We have polymorphic plant populations such as those of *Primula veris* (the primrose) and *Lythrum salicaria* (the purple loose-strife) with their different style lengths, polymorphic animal populations such as those of the snails *Cepea nemoralis* and *hortensis* with their different shell colours, and finally *Homo sapiens*, a species divided into geographical races, some of which,

such as the Europeans with their great variety of eye colour, hair colour, stature, and skull shape, are highly polymorphic.

These populations may be in stable equilibrium, as with the heterostylic plants, or fairly close to equilibrium, as with European populations, where one type of eye colour does not appear to increase its frequency appreciably within a given nation during a generation. Or they may be in rapid evolution, as with *Pachys betularia* and other moths in which, in certain areas, the melanic form has ousted the original form within fifty years or less.

The study of populations demands not only laborious field work, but a formidable mathematical theory. This theory is inevitably based on the statistical theory of sampling, not only because we generally observe a sample from a larger population, but because one generation is derived from a sample of the gametes of another. In the last chapter we shall be concerned with one problem (not a very typical one) of how to estimate a particular parameter from a small sample. Besides the sampling theory proper, we are led to a number of non-linear recurrence equations referring to very large populations, such as Haldane's equation[1]

$$u_{n+1} = u_n + \frac{ku_n}{u_n + 1 - k}$$

[1] Haldane, J. B. S. (1930), *The Causes of Evolution* (Longmans' Green).

and Fisher's equation[1]

$$u_{n+1} = e^{u_n} - 1$$

Both have been solved with sufficient accuracy for practical purposes, but still require rigorous treatment. They are, however, only valid when generations do not overlap, as in annual plants. When they overlap, as in man, these equations become non-linear integral equations, whose study has barely been begun by Norton[2] and Haldane.[3] Wright[4] has attacked the same problems successfully with a different mathematical technique.

Such work is one of the preliminaries to a confirmation or disproof of Darwin's statement that "varieties are incipient species." The other preliminary is a study of the genetics of interspecific differences as revealed by crossing closely related species. Haldane[5] and later Dobzhansky[6] have sustained Darwin's thesis, and his theory that natural selection determines the course of evolution. But for a statement of opposing views I can recommend Goldschmidt[7] and Robson.[8]

[1] Fisher, R. A. (1930), *The Genetical Theory of Natural Selection* (Oxford).

[2] Norton, H. W. (1928), *Proc. Lond. Math. Soc.*, 28, p. 1.

[3] Haldane, J. B. S. (1930), *The Causes of Evolution* (Longmans, Green).

[4] Wright, S. (1931), *Genetics*, 16, p. 97, and many later papers.

[5] Haldane, J. B. S. (1930), *The Causes of Evolution* (Longmans, Green).

[6] Dobzhansky, T. (1937), *Genetics and the Origin of Species* (New York).

[7] Goldschmidt, R. (1940), *The Material Basis of Evolution* (Yale University Press).

[8] Robson, G. C. (1928), *The Species Problem* (Oliver & Boyd).

I must now pass to the applications of genetics. The most important application is to agriculture. Although a good deal remains to be done even there, probably the least hopeful field of research is the improvement of self-fertilized crop plants such as wheat and peas in European countries where the best existing types have been developed by centuries of selection. Something can certainly be done, but there is no question of doubling existing yields. The most promising fields in agricultural genetics seem to be four. First of all there is the field of tropical and sub-tropical agriculture. Here of course the Netherlands lead the way. Whatever may be our views on the rights and wrongs of imperialism there is no question that the Dutch have applied science on a vast scale to tropical agriculture, especially in Java, whilst the British, French, Belgians, and other nations with tropical and sub-tropical possessions have lagged very far behind them. The very fact that the Dutch are devoting so great an effort to their colonial agriculture shows that in their opinion it is a fruitful field.

The geneticists of the Soviet Union were confronted with a somewhat similar problem, since their agricultural plants and animals were much less developed than those of Western and Central Europe. They dealt with it partly by importing animals and plants from countries where they had been improved, and partly by selective breeding of their own. They have also tackled the special problems of Arctic agriculture, which have so far hardly

been touched in Canada and Alaska. These are interesting, but far less important than those of tropical agriculture.

A second important field is horticulture. Here the production of novelties as such is economically important. I doubt if modern tulip varieties are really any more beautiful than those of our grandparents' time. But they certainly fetch more money in the market. In the case of an agricultural plant very few mutant genes are likely to increase its yield. In an ornamental plant a substantial fraction produce attractive novelties. Each new structural gene (e.g. "Spencer" in *Lathyrus odoratus*) which finds favour with the public can be incorporated into all or almost all the existing colour varieties. The corresponding procedure in animals is the formation of "fancy" breeds such as "Fairy Swallow" pigeons with large feathers on their feet, "Sealyham" terriers, and so on. At the present time this has a minor economic importance.

A third field of great promise is that of clonally propagated food-plants, and especially fruit trees. Whereas a wheat plant is the product of many thousand generations of unconscious[1] selection, and probably ten to fifty generations of conscious selection, an apple tree has only been selected in one generation. The large majority of apple seedlings are inferior to their parents. One in a thousand may be valuable. We know hardly anything of

[1] Haldane, J. B. S. (1939), *Science and Everyday Life*, p. 25 (Lawrence & Wishart).

inheritance in apples as yet. The study of their genetics may be expected to give us trees considerably superior to any at present existing. Moreover, the modern techniques of gas storage and canning have led to new desiderata in fruits. The potato is constantly menaced by new diseases, and immunity to them can be combined with desirable characters of known types.

A new field for genetics is arising in connection with the fur-bearing animals which are rapidly being domesticated. Colour mutants of the silver fox have a novelty value like that of new flowers. But improvements of a much more substantial character are possible and probable.

The most fundamental changes of all are likely to be associated with the development of pure lines of domestic animals. Several approximately pure lines of poultry are already in existence. At least one line of dairy cattle is on the way towards purification. It is likely that fifty years hence all economic poultry production will be organized as follows. A certain number of pure lines will be in existence. But most poultry will be first crosses between them. The first cross is as uniform as the parental lines, but usually excels them in vigour. Later on the same principle may be adopted in the case of the ungulate domestic animals. The practicability of such methods has been fully demonstrated in the case of maize.

Another important field in applied genetics is medicine. The first step is a clear distinction between diseases which

are primarily determined genetically, and those which are primarily determined by the environment. This is particularly important in the case of the so-called congenital diseases, that is to say, diseases which are present at birth or soon after. Some of these, as we shall see in Chapter 4, are strictly genetically determined. At least one, the so-called hereditary syphilis, is due to pre-natal infection. Another group depends to a considerable extent on abnormal pre-natal conditions, though a genetical element is probably present too. Thus mongoloid imbecility is characteristic of the children of old mothers, congenital pyloric stenosis of the firstborn, and so on. Such diseases may turn out to be controllable by pre-natal hygiene, for example, by the administration of hormones to the mother.

Secondly, genetics enables us to distinguish between apparently similar diseases due to different causes. Thus the clinicians had described the nervous disease called Friedreich's ataxia. Bell[1] made the remarkable discovery that where this disease is due to a dominant gene the mean age of onset is 20·4 years, whilst when it is due to a recessive gene the mean age is 11·7 years, that is to say, the disease is on the average much more serious. We shall see later that this classification can be carried still further.

What use, it may be asked, is such a subdivision of the causes of disease? I think that the history of medicine

[1] Bell, J. (1939), *Treas. Hum. Inher.*, 4.

furnishes the answer. The distinction between various fevers which a hundred years ago were not clearly separable, such as typhus, typhoid, and the different paratyphoids, has shown that the different types must be countered by different prophylactic and therapeutic measures. The identification of genes may in future prove as important as the identification of bacteria to-day.

Thirdly, the geneticist must help to disentangle the parts played by nature and nurture in the genesis of such diseases as rickets and tuberculosis. We know that there is a measure of genetical determination, because monozygotic twins resemble one another much more closely than fraternal twins in their liability to these diseases. But, it may be argued, what is the use of worrying about the genetical factor when we can prevent rickets by administering enough vitamin D and tuberculosis by eliminating infection? There are several uses. In the case of rickets we assume that a certain amount of vitamin D in the diet will prevent them. It may do so in 90 per cent or even 99 per cent of children. But it is likely that a small fraction of children are so constituted genetically as to need a good deal more than the standard amount. Only recognition of the genetical factor will allow us to investigate this possibility. Similarly, if we could recognize congenital liability to tuberculosis we could take special measures to shield those who are so liable. Tuberculosis is no longer a major menace to life in Britain and some other European states. It is a growing menace

to many coloured peoples. A proper investigation of it is one of the many duties which Europeans owe to the coloured races.

It is sometimes said that an emphasis on the genetical determination of disease must lead to a defeatist view, at least as regards the individual. This is so if we regard an individual who bears a certain gene as fatally predestined to develop a particular malady. But this view should not be, and need not be, taken. A gene is no more omnipotent than a bacillus. Three hundred years ago high-grade myopia or cataract meant blindness. Each of these diseases is very often genetically determined. Now we treat the one with spectacles, and the other with operation and spectacles. Diabetes, especially juvenile diabetes, seems to be genetically determined to a large extent. It can almost always be controlled with insulin. Wibaut[1] and others claim to have cured or arrested retinitis pigmentosa with oestrone. Such facts as these should give us a hope of treating epiloia or amaurotic idiocy in the future. One of the desiderata before this can be done is a thorough genetical study of these diseases.

One part—many would say the most important part—of the field of medical genetics is the negative or preventive aspect of eugenics. Perhaps 1 per cent of all babies is born with physical defects, or at least with such a

[1] Wibaut, F. (1937), *Report of Fifteenth Concilium Opthalmologicum* (Cairo).

genetical constitution that, in the present state of medical knowledge, they are sure to develop physical or mental defects. The task of negative eugenics is to prevent their being born. As we shall see in Chapter 4, this is easy in some cases, harder in others, and in still a third group impossible at present. The prophylactic methods which have been proposed include sterilization, segregation, voluntary abstention from parenthood, limitation of inbreeding, and other methods. Here we have to reckon with two extreme views. On the one hand the authorities of the German Reich have embarked on a very extensive programme of compulsory sterilization. On the other, the late Pope, in his encyclical *Casto concubitu*, condemns even voluntary sterilization, as well as birth control, and refers in somewhat slighting terms to the conjectures of geneticists. Perhaps it will be found that the truth lies somewhere between the opinions of the Pope and the Führer, and that the best practical eugenic measures will be somewhere between the extreme programme of the Reich and the completely negative programme of the Catholic Church.

But here an important point must be made. The geneticist as such can only answer the question, "What will be the genetical consequences if a given eugenic law is enforced? If, for example, a certain group of persons is sterilized, what effect will this have on the number of persons affected with a particular abnormality in later generations?" Even this question can only be answered

in a few cases as yet. He cannot, as a geneticist, say what abnormalities are so undesirable as to warrant interference with parenthood. Nor can he say what measures of interference are best, whether a given type should be sterilized or segregated, whether persuasion or compulsion is to be preferred, and so on. These are ethical and political questions, and if he answers them he does so as a citizen, not a geneticist. It seems likely, therefore, that if some measures of negative eugenics are held to be desirable, they will be very different in a democratic and an authoritarian state, even if they are directed to similar ends.

Eugenists wish to improve races, not only by eliminating comparatively rare defects, but by increasing the frequency in the population of bearers of desirable qualities. Here the geneticist can as yet at least offer much less advice, for two reasons. In the first place, desirable qualities are much less clearly defined than many undesirable qualities. And they are much more influenced by environment. It is an established fact that the children of long-lived parents live, on the whole, longer than the average, that the children of parents regarded as intelligent are on the whole more intelligent when judged by a similar criterion. But some of these differences are due to differences of environment, and there is a serious difference of opinion as to the relative importance of heredity and environment, though both certainly have some effect.

Secondly, it is far from clear what qualities are desirable. So far eugenical propaganda has been written almost entirely from the point of view of the well-to-do class. It is assumed that the innate qualities which are believed to be most frequent among them are preferable to those of the poor. It is perhaps fortunate that Communists do not hold that the children of the bourgeoisie suffer from hereditary defects, even though they think that they are brought up with undesirable ideas and prejudices. Eugenists are distressed by the fact that in most European communities the poor breed quicker than the rich. Yet it is nearly two thousand years since Jesus[1] is reported to have said, "Blessed are the meek, for they shall inherit the earth."

I cannot here discuss the many measures which have been proposed to combat this tendency. Some of them are a naked expression of class hatred. Others, such as my colleague Fisher's[2] support for family allowances, are not. But none seem to me to have a very solid scientific foundation. Before this can be given I think that we shall need a very careful study of the interaction of nature and nurture in determining both the physique and the psychology of individuals. This study has of course begun, but it has not yet gone very far. Until it has gone a good deal further, eugenic proposals of this

[1] Gospel according to St. Matthew, v. 5.

[2] Fisher, R. A. (1930), *The Genetical Theory of Natural Selection* (Oxford).

second type will generally be expressions of their authors' political rather than biological opinions.

This leads us on to the main application to-day of genetics to politics, namely, the racial theory current in Germany, that some races are superior to others, and that inter-racial crossing has bad effects. The first of these, if not a Jewish theory, finds its first literary expression in the Jewish scriptures. In its extreme form it has little scientific basis. It is interesting to note that the same people often hold two contradictory theories. For purposes of foreign politics they claim that racial characters are unalterable, whilst in order to justify their internal policy they hold that a race can be greatly improved by eugenic measures. Both of these claims cannot be true. The former is in flat contradiction of the theory of evolution.

The extreme forms of the theory of racial superiority are demonstrably false. It may be that 70 per cent of Englishmen have innate intellectual endowments above a certain level and 70 per cent of negroes below it (if any meaning can be attached to such a statement). But it is quite certain that some negroes are intellectually superior to most Englishmen. It is of interest that one of the fifteen or so virtuosi of mental arithmetic, the "calculating boy," Thomas Fuller, was a pure-bred African who was taken as a slave to Virginia in 1724 and never learned to read or write. In one respect only is racial superiority undoubted. The Englishman is a better man

than the negro at resisting disease so long as both are compared in England. But if the comparison is made in tropical West Africa the negroes are the superior race.

The question of innate differences between the average capacities of different races for intellectual and moral performance is a very difficult one. Results of value can only be obtained where members of the supposedly inferior race have equal opportunities with the supposedly superior race, and this is very rarely the case. At present the geneticist can only say that nothing has been proved scientifically. It would, however, be surprising if small differences did not exist, and an assertion that nothing has been proved is very different from an assent to the theory of absolute racial equality. On the contrary, it seems *a priori* probable that different races will be found to have characteristic merits and defects, though only when considered statistically.

Still less cogent is the evidence that racial crossing is necessarily harmful. In animals and plants the first generation hybrids of two widely different races or sub-species are often more vigorous than either parent race in the first generation, whilst in later generations aberrant forms may occur. It is characteristic that many of the politicians who deplore race crossing do not even tell us whether they refer to the first or later generations. Meanwhile the density of our ignorance may be judged from the fact that Fleming's[1] study of the physical characters of three

[1] Fleming, R. M. (1934), *Ann. Eug.*, 9, pp. 55–81.

hundred and thirty-three products of race crossing (including one hundred and nineteen English-Chinese) in British ports has been rightly hailed as an important contribution to knowledge. I need not point out the magnificent opportunities which are available in the Dutch Indies. I believe that a few months' work there could solve such simple problems as whether there is an increase of vigour as shown by more rapid growth in the first generation of the Javanese-Dutch cross. Till such facts as these are available it is useless even to ask the opinion of the geneticist.

I have already written[1] on such questions as these, and the equally interesting question whether groups within Europe, such as the English, Germans, and Jews on the one hand, and the Nordics, Alpines, and Mediterraneans on the other, have any right to be called races. However, on this latter point I particularly recommend the very useful work of my colleague Dr. Morant.[2] He has also[3] analysed the racial doctrines of Herr Hitler, as laid down in *Mein Kampf*, and whilst he does not agree with them, he points out that they are by no means so extreme as those which are often attributed to him, and which are held by other German authors.

A geneticist, if he is honest, must say that the doctrines at present current in Germany lack scientific foundation,

[1] Haldane, J. B. S. (1938), *Heredity and Politics* (George Allen & Unwin).

[2] Morant, G. M. (1939), *The Races of Central Europe* (George Allen & Unwin).

[3] Morant, G. M. (1939), *Modern Quarterly*, 2, 3.

and that some of them are demonstrably false. But he will also add, if he is as objective as possible, that not all of them have been disproved, and that because certain questions have been answered without adequate evidence, this does not mean that they should not be fully investigated in the future.

In the following chapters I do not propose to deal with these important political and historical questions. I shall be content to draw attention to a footnote to history, namely, the royal pedigree of haemophilia. If I were asked how I believed that genetics should be applied to political theory, I should answer somewhat as follows, though I must emphasize that I am speaking as a student of society and not a mere geneticist, since a geneticist as such cannot say whether or not human freedom is desirable.

What is the best form of society? Many will describe a society in which one particular human type finds its fullest expression. Some will prefer a society where the man of learning is given the best possible opportunities. Others will regard the saint, the business man, the soldier, the artist, or the manual worker as the human type which should be encouraged. As a geneticist I believe that every human being (except perhaps for monozygotic twins) is born with different capacities. And that society enjoys the greatest liberty where there is the greatest diversity of careers, and the greatest opportunity for each citizen to choose the career for which he or she is best suited.

Freedom, said Hegel, is the recognition of necessity, and one of the hard facts which we must recognize is that men are different, and indeed unique. What is more, both politicians and writers on political science belong to exceptional types, and a society which meets with their approval may be intolerable for differently constituted people. In the remote future men may be able to control the innate capacities of their descendants. They cannot do so at present, and in view of the ideals which prevail over most of the world to-day it is fortunate that they cannot.

If we accept these premises, we can say two things about a good society. It must have as broad a culture as possible, and must not concentrate, for example, on science, art, industry, religion, or militarism. And it must not be a class society. This would only be justifiable if ability were directly inherited. But a very little observation shows that this is not in general the case. Even if the son of a mathematician, say, is more likely to have mathematical ability than the son of a farmer, yet the majority possess it in less degree than their parents. For this reason, it seems to me, the science of genetics, while fully recognizing human inequality, can be used to support a society based on "la carrière ouverte aux talents," and not one based on hereditary rank or wealth.

Lastly, genetics is of importance for philosophy. By recognizing that character is determined not only by environment but genetically, it poses the problem of the

freedom of the will in a peculiarly sharp form. I cannot discuss this problem here except to state my opinion that Spinoza's arguments for determinism are strengthened in detail, but not altered in essence, by our new knowledge; and that the existence and nature of human freedom are somewhat more clearly stated in the dialectical philosophy of Hegel and Engels than in Spinoza's subsequent argument. It is said that genetics leads to a mechanistic theory of life. It can certainly do so, and Morgan's[1] views are definitely mechanistic. But I think that here, as elsewhere, mechanism, if pushed to its logical conclusion, negates itself. Let us consider one of the central problems of genetics, namely, how a gene reproduces itself.

When a cell divides, it produces two cells in each of which, apart from mutation, every gene in the original cell is replaced by a similar gene. Doubtless structures outside the nucleus are also reproduced. But the method of their reproduction is different. For if structures outside the nucleus are artificially altered, this alteration is not copied. On the other hand, alterations in the genes produced by X-rays or otherwise are copied, at least in many cases. The biologist will be inclined to say that the gene is an elementary organism, and divides to give two "heirs" like itself. But we cannot imagine the gene swelling till it divides like an overgrown drop of water. For it does not consist of a number of like parts. If it

[1] Morgan, T. H. (1925), *Evolution and Genetics* (Princeton).

did it could not be completely changed by the hit of a single electron. Further, the gene is within the range of size of protein molecules, and may be a nucleo-protein molecule like a virus. If so, the chemists will say, we must conceive reproduction as follows. The gene is spread out in a flat layer, and acts as a model, another gene forming on top of it from pre-existing material such as amino-acids. This is a process similar to crystallization or the growth of a cellulose wall.

Now suppose that the biologist and the chemist go round to a physicist, and ask him whether he thinks the genes in the two "daughter" cells are the heirs of the original gene, or that one is the model and the other the copy. The physicist will have to say something like this: "Your alternative is a false one. I can't yet put the true answer unambiguously in words, but I can put it in symbols. Here is the difficulty. How can one distinguish between model and copy? Perhaps you could use heavy nitrogen atoms in the food supplied to your cell, hoping that the 'copy' genes would contain it while the models did not. But unfortunately all proteins in a living cell seem to exchange nitrogen with the fluid around them. So the most you could do would be to say that there was a certain probability of one gene being the model and the other the copy. No doubt if the cell divides quickly enough this probability is pretty high. But one can never say that either of your alternatives is completely correct. Remember that it is not just a ques-

tion of human ignorance. On the contrary, the impossibility of distinguishing between two things is only our human expression for a relation between them which also manifests itself in a term in their joint energy, or, if you like that word, in a force attracting them. No doubt this attraction is very small in the case of genes. But it must be there, and it may yet prove to be important in biology, as similar attractions are in physics. So you are both right and both wrong."

I think that throughout genetics an attempt to impose mechanistic interpretations such as the model and copy theory will break down in some such way as this. However, a refutation of mechanism is not a refutation of materialism. On the contrary, even if we reject Morgan's mechanism, we must be grateful to him for showing that the gene, the physical basis of heredity, is a material object.

To sum up, genetics occupies a very central position in the world of science. The geneticist must be a morphologist, a chemist, a psychologist, a physician, a sociologist, an agriculturalist, and a mathematician. Or at least he should know enough of these sciences and arts to present problems to his academic colleagues in a form which they can tackle, and to be able to utilize their services. If he confines himself to formal genetics, that is to say, a study of the laws of inheritance, he will end up as a narrow specialist, like the anatomist who confines himself to a study of the structure of the human

body. I do not wish, of course, to decry the great achievements of formal genetics in the past. Such men as Mendel, Bateson, de Vries, and Morgan have made as great contributions to science as did Vesalius or Fabricius. Nevertheless the importance of research in formal genetics is declining. In this book I shall deal with formal genetics in the last two chapters, because the formal genetics of man require special methods, and for this reason their development has lagged behind that of plants and animals.

If, however, the geneticist sees his subject in its widest bearings, he can help to bridge the gaps, not only between different natural sciences, but also between the natural sciences on the one hand and the social sciences, history, and philosophy on the other. I hope that these lectures may serve as a contribution, however slight, to this great task.

CHAPTER 2

Genetics and Biochemistry

"per mirare
la gran variazion dei freschi mai."[1]
DANTE, *Purgatorio*, 28, 36.

AMONG the first differences whose genetical determination was studied were many differences of colour. In many cases the determination turned out to be very simple, colour varieties differing in respect of a single pair of allelomorphic genes. A few of the chemical differences in crop plants, for example, the differences between varieties of maize with starch, dextrin, and sugar as their principal carbohydrate of the endosperm, were found to be equally simply determined. And the remarkable work of Garrod[2] showed that a number of human metabolic abnormalities were also inherited as simple recessives. Meanwhile it was gradually discovered that human blood group membership was genetically determined in a very simple way, and with the discovery of new antigens in the blood the same was found to hold for them.

Let us see what light is thrown on human metabolism

[1] "To admire the great variation of the fresh blossoms"

[2] Garrod, A. E. (1923), *Inborn Errors of Metabolism*, 2nd edition (Oxford).

by the genetics of metabolic diseases. In the disease called phenylketonuria or phenyl-pyruvic amentia, the urine contains considerable quantities of phenyl-pyruvic

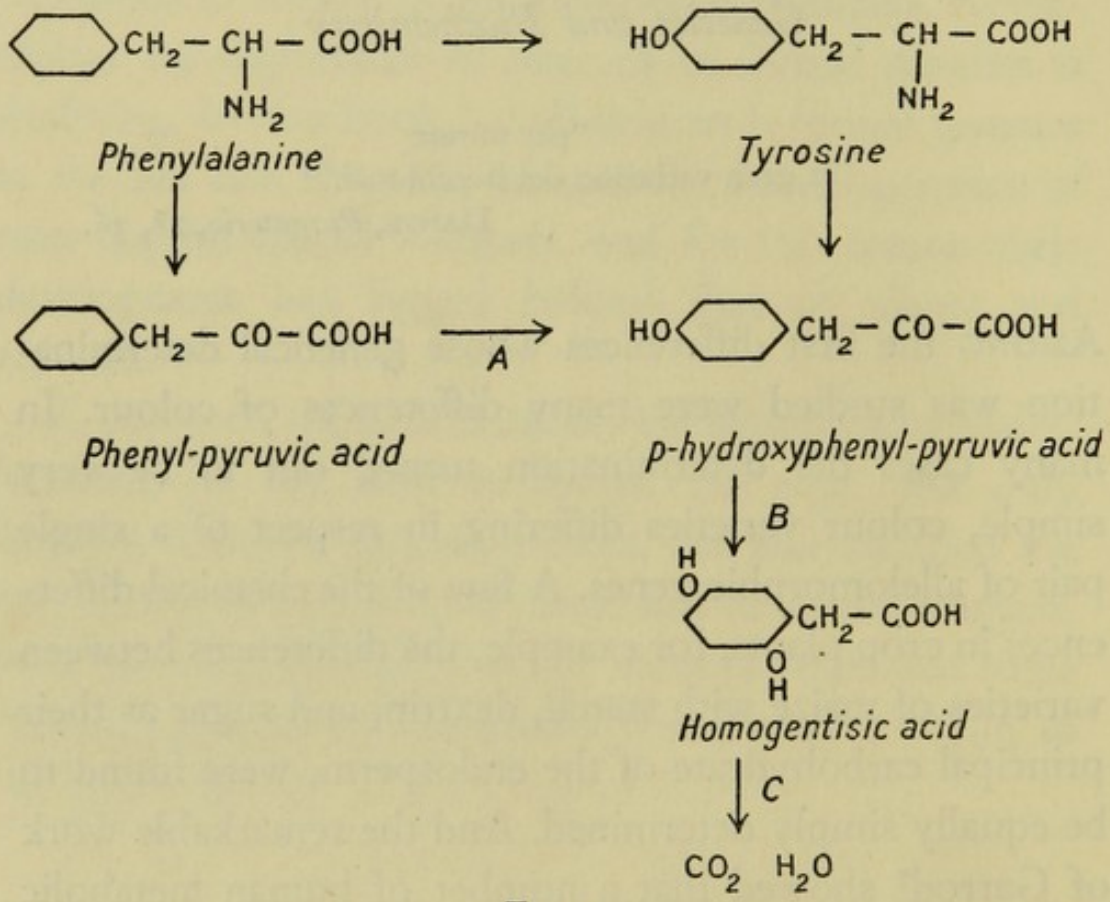


FIG. 1.

acid (Fig. 1). Since it was discovered by Föllings[1] a considerable number of cases have been described. In every case the patients were idiots or imbeciles. Penrose[2] later found that, in one case at least, there were characteristic tumours on peripheral nerve trunks. He further showed[3] with high probability that the disease is in-

[1] Föllings, A. (1934), *Z. Physiol. Chem.*, 227, p. 169.
[2] Penrose, L. S. (1939), *Lancet*, i, p. 572.
[3] Penrose, L. S. (1935), *Lancet*, ii, p. 192.

herited as a recessive. Let us see what this means. Normal people not merely do not excrete phenyl-pyruvic acid on a normal diet, but, when given it by mouth in large quantities, excrete a far smaller proportion than phenylketonurics. The majority of the human species carry two genes *PP* which enable them to metabolize phenyl-pyruvic acid. A small fraction are heterozygotes *Pp*. When two such have children, one-quarter of the children, on the average, receive a *p* gene from both parents and are *pp*, mental defectives who cannot metabolize phenyl-pyruvic acid normally. Thus the gene *p* may be regarded as an inactive or slightly active form of the gene *P*.

Bateson and Punnett regarded recessive genes as simple absences of dominant genes. But this is unlikely except in special cases, for recessive genes occasionally mutate to their dominant allelomorphs. This would be miraculous if they were mere absences, and is quite intelligible if they are dominant genes so altered that they are physiologically inactive, but can still reproduce. Muller[1] has shown that in some cases recessive genes perform the same function as normal genes, but more slowly. This can be proved by making up a *Drosophila* containing not merely two recessive genes but three or four. Such an animal may be normal or nearer to normal than a recessive with only two genes. Muller calls such partially inactive genes hypomorphs. Other recessive

[1] Muller, H. J. (1932), *Proc. Sixth Int. Gen. Cong.*, pp. 213–55.

genes show no approach to normality when a number are accumulated and seem to be inactive. These are called amorphs. The gene for phenylketonuria is probably to be regarded as hypomorphic or partly inactive, though this cannot at present be definitely proved.

The heterozygotes (*Pp*) appear to be normal, except that they have perhaps, according to Penrose,[1] an unusual tendency to develop senile dementia. Clearly one *P* gene will do the work of two almost, but perhaps not quite, completely. We have as yet no idea why this metabolic abnormality should lead to amentia. The amentia may be due to the fact that the metabolism of phenyl-pyruvic acid furnishes energy for some essential activity of the nervous system. It is possibly due to chronic poisoning by phenyl-pyruvate, though this is unlikely, as no effect of this substance on normal people has been reported.

About 1 gramme of phenyl-pyruvic acid is generally excreted per day. The work of Penrose and Quastel[2] leaves little or no doubt that it is entirely derived from the metabolism of phenylalanine (Fig. 1), from which it is derived by the usual process of oxidative deamination. Furthermore, about half the phenylalanine of the diet seems to be excreted as phenyl-pyruvic acid. It is noteworthy that in normal patients the natural antipode, *l*-phenylalanine, produces no phenylketonuria when

[1] Penrose, L. S. (1938), *Spec. Report Med. Res. Council*, No. 229.
[2] Penrose, L. S. and Quastel, J. H. (1937), *Biochem. Journ.*, 31, p. 266.

3 grammes are fed to a normal person, whilst *d*- and *dl*-phenylalanine do so.

Medes[1] has described a more or less analogous metabolic error involving the metabolism of tyrosine. A patient whose disease was diagnosed as myasthenia gravis was found to excrete about 1·6 grammes of *p*-hydroxyphenyl-lactic acid when fasting or on a tyrosine-free diet. On a diet containing much protein, tyrosine and a little *l-p*-hydroxyphenyl-lactic acid appeared. Finally, on feeding up to 15 grammes *l*-tyrosine per day, *l*-3 : 4-dioxyphenylalanine appeared. Phenylalanine caused somewhat increased excretion of tyrosine and *p*-hydroxyphenyl-pyruvic acid. This very interesting condition, described as tyrosinosis, has only been described in one man, and nothing is known of its aetiology.

Another condition, which, though rarer than phenylketonuria, has been longer recognized, is alcaptonuria, in which homogentisic acid is excreted. Garrod[2] showed that it was recessive. I cannot summarize the vast and controversial literature which has been written on it, but will only mention that homogentisic acid is derived both from tyrosine and phenylalanine, and that among the numerous substances which lead to an increase in its excretion are phenyl-pyruvic acid, *p*-hydroxyphenyl-pyruvic acid, and *p*-hydroxyphenyl-lactic acid. It thus

[1] Medes, G. (1932), *Biochem. Journ.*, 26, p. 917.

[2] Garrod, A. E. (1909), *Inborn Errors of Metabolism*, 2nd edition (Oxford).

seems to represent an interference in the later stages of the metabolic paths which are interrupted in phenylketonuria and tyrosinosis (Fig. 1). It is not, of course, suggested that the paths shown are the only metabolic paths taken. The appearance of tyrosine and *p*-hydroxyphenyl-lactic acid in tyrosinosis may be explained by the reversibility of the reactions between them and *p*-hydroxyphenyl-pyruvic acid.

In alcaptonurics, ochronosis, a dark staining of cartilage, develops. They also harden, and kyphosis may supervene. Now this process, which is pathological in man, is analogous to a normal one in insects. Pryor[1] found that *Blatta orientalis* secretes its oötheca from two glands, one yielding a soluble protein, the other a dihydroxyphenol, probably 3 : 4-dihydroxyphenyl-acetic acid. This substance, in the course of oxidation, unites with the protein to form a scleroprotein. The same or a very similar reaction occurs in the hardening of the cuticle of a number of insect species. Presumably in the course of insect evolution a mutation occurred similar to that which gives rise to alcaptonuria in man.

A number of other human recessive conditions include metabolic disturbances. Garrod studied cystinuria, steatorrhoea, and haematoporphyria. Amaurotic idiocy, both juvenile and infantile, is associated with, and probably caused by, a disturbance of lipoid metabolism.

But perhaps the most interesting group is that of the

[1] Pryor, M. G. M. (1940), *Proc. Roy. Soc.*, B, 128, p. 378.

congenital photosensitivities. The best known of these is haematoporphyria (=Porphyrinuria congenita=Hydroa vacciniforme). Here the urine may be a deep red from uroporphyrin, the bones and teeth are stained, and the same substance sensitizes the skin to ultra-violet radiation. Thus blisters appear every spring, which may give rise to severe scarring. Meyer-Betz[1] produced an analogous condition in himself which lasted for some months by the intravenous injection of 10 milligrammes of haematoporphyrin, which seems to be somewhat more efficient in this respect than uroporphyrin. Precisely analogous, though rather less severe, symptoms occur on a group of cases (collected by Cockayne)[2] in which porphyrins have been vainly searched for. Whether traces of a porphyrin were present but not detected, or whether some other sensitizer is here present, is a matter for investigation.

A far more serious disease of this type is xeroderma pigmentosum. Here photophobia is the first symptom. Then, where the skin is exposed to light, we have erythema, freckling, atrophic areas, telangiectases, and finally epithelioma or sarcoma, which is generally fatal before the age of fifteen years. Usuba (vide Cockayne) claims to have rendered the skin of a normal man light-sensitive by injecting serum from a patient with this

[1] Meyer-Betz (1913), *Deutsch. Arch. Klin. Med.*, 112, p. 476.

[2] Cockayne, E. A. (1933), *Inherited Abnormalities of the Skin and its Appendages* (Oxford University Press).

disease. Siemens[1] made the very remarkable discovery that some or all heterozygotes for the disease were intensely freckled, though none of them had red hair. If this is confirmed, it is eugenically undesirable for two heavily freckled persons to marry unless one of them at least has red hair.

I have no doubt that many similar metabolic abnormalities will be discovered in other animals. Porphyrinuria appears as a recessive condition in South African cattle; Dalmatian coach dogs excrete far more uric acid than normal dogs. The error in this case is a partial failure to oxidize uric acid to allantoin. The condition is recessive. However, it is probable that the vast majority of metabolic abnormalities in animals, unless they cause abnormal pigmentation, pass undetected. The anaemias of mice described in the next chapter may be regarded as metabolic abnormalities.

Clearly the widest field is given by the study of pigmentation. Some years ago I determined to start research on it. The mammalian hair and skin pigments are far from promising, for there is no simple criterion of purity for colloidal substances such as melanin. Many of the insect pigments are crystalloids, but they can only be obtained in small amounts. I therefore determined to continue the combined chemical and genetical study of flower pigments begun by Wheldale (later Mrs. Onslow),

[3] Siemens, H. W., and Kohn, E. (1925), *Zeit. Ind. Abst. u. Vererb.*, 38, p. 1.

and was fortunate enough to interest Dr. Scott-Moncrieff in the problem. By a still more fortunate coincidence the Robinsons[1] took up the chemical study of these substances at the same time, continuing the classical studies of Willstätter. My own part in the research was small. However, apart from direction, I made a few test-tube experiments which convinced me that certain genetically determined differences in flower colour were due to differences of acidity in the sap. This was fully confirmed by Scott-Moncrieff and others.

The pigments of flowers are of two kinds. On the one hand there may be pigments in plastids. These are sometimes absent, as in the rose; they may be confined to a small area such as the central "eye" of *Primula* species; or they may be spread over the whole petal surface, as in *Cheiranthus*, *Matthiola*, and other *Cruciferae*. The plastid pigments are generally yellow ether-soluble pigments of the carotene and xanthophyll group. However, chlorophyll is also sometimes present. The plastid pigments have been little studied, but they are controlled by a separate set of genes from the water-soluble pigments. When plastid pigments and water-soluble pigments are found in the same area of a flower there may be absorption over the whole spectrum, and we get very dark flowers such as those of the wallflower

[1] Robinson, R. (1922–34 and 1926–34), "A Synthesis of Pyrylium Salts of Anthocyanidin Type," Pts. I–XXII, and "Experiments on the Synthesis of Anthocyanins," Pts. I–XXVI, *J. Chem. Soc.*

Cheiranthus cheiri, or very dark patches such as those round the eye of some types of *Primula sinensis*.

The cell-sap may also contain water-soluble pigments. They are all chemically related, but are divided into the anthocyanins, which absorb in the green and often the yellow part of the spectrum, and are therefore red, purple, or blue, and the anthoxanthins, which absorb in the blue and near ultra-violet, and are therefore yellow or colourless. But if they are colourless to human eyes they are not so to those of bees. Von Frisch has shown that bees are insensitive to red radiation, but sensitive to that in the near ultra-violet. It follows that chlorophyll, which absorbs mainly in the red, must be nearly colourless to bees. On the other hand, those anthoxanthins which are colourless to us must be coloured to them. So far as I know no wild flowers lack anthoxanthin, though a few cultivated forms do so. Hence from the bees' point of view there are no white flowers. To put the matter objectively, there are no flowers to which a bee would react as it had been trained to react to a similar object made of white paper.

When the early geneticists investigated colour they were apt to regard it as a unit character. A dominant gene *C* in *Lathyrus odoratus* was needed for the presence of colour, which was then modified by various other genes. This simple theory was shattered by Bateson, Saunders and Punnett's discovery that two different white varieties, when crossed, gave coloured hybrids.

Careful analysis showed that they were dealing with two independent gene pairs *C*,*c*, and *R*,*r*; and that *CC RR*, *Cc RR*, *CC Rr*, and *Cc Rr* plants were coloured, that is to say, that for colour to develop at least one *C* and one *R* must be present. It was still possible to postulate one gene "for" a colourless chromogen, and another for an enzyme which converted it into pigment. Such a theory became less plausible when Tammes found that three genes are needed for colour development in *Linum usitatissimum*, and Hagiwara found that four are needed in *Pharbitis nil*. The bibliographical references to these and other papers on the biochemical genetics of flower colour are given in Scott-Moncrieff's[1] and Lawrence and Price's[2] reviews, and are omitted here.

But the situation is clearest in the case of chlorophyll synthesis. Recessive "albino" seedlings containing neither chlorophyll nor yellow plastid pigments, and yellow seedlings containing no chlorophyll, are common in many plant species. The most careful study of these has been made in *Zea mays* by Eyster and others. Here at least eleven different dominant genes must be present before either chlorophyll or yellow pigments are formed, and seven others are needed for chlorophyll to be produced. Still others are needed before it is formed at anything like the normal rate. Each of these eighteen

[1] Scott-Moncrieff, R. (1939), *Ergebnisse der Enzymforschung*, 8, p. 277.

[2] Lawrence, W. J. C., and Price, J. R. (1940), *Biol. Rev.*, 15, pp. 35–58.

genes must control a different process. For if two controlled the same process one of them alone would produce some effect. This situation is sometimes found, particularly in allopolyploid plants such as wheat, where there is a gene *A* for anthocyanin production in each chromosome set, so that a plant containing none must be $a_1a_1a_2a_2a_3a_3$, and such a plant as $a_1a_1A_2a_2a_3a_3$ produces a certain amount. We can hardly suppose that each of the eighteen genes determines the production of a different substance, and that these eighteen substances are then mixed in a kind of witches' cauldron and yield chlorophyll. On the contrary, even if some are concerned with the porphyrin part of the molecule and others with the phytol part, they must act to a large extent in series. In spite of a good deal of work on recessive chlorophyll-deficient barleys by Euler and his colleagues, they obtained little result in this apparently promising field except to find that a number of different genes all produced a shortage of catalase and haemochromogen. The effect on the catalase was quantitatively different for different genes.

The fact that at least eighteen genes are needed gives us an impressive idea of the complexity of the synthetic process. If we like such a comparison, we may compare them to eighteen different students engaged on different stages of a complicated synthesis under the direction of a professor, except that attempts to locate the professor have so far failed. Or we may compare them to modern

workers on a conveyor belt, rather than skilled craftsmen each of whom produces a finished article.

However, because the theories of the older geneticists are not valid for anthocyanin or chlorophyll, it does not follow that they may not hold elsewhere. What criteria do we require before we say that some substance is the immediate product of a gene? One necessary, but of course not sufficient, condition is that whenever a certain gene is present a certain substance should also be so, that is to say, that there should be no case where a union of two parents not possessing the substance (but each contributing a gene needed for its formation) produces offspring with the substance. This criterion is in general fulfilled in the case of antigens.

Thus in the case of the human blood groups no case is known with certainty where two parents both lacking the *A* isoagglutinogen have produced a child with such a substance. In fact, the birth of such a child by a married woman would in many countries be taken as proof of adultery. The same holds of the *B* substance, the *M* and *N* substances, and so on. Further, in the case of the corpuscles of the fowl, which have a very complex antigenic structure, Todd[1] found no case where a chicken carried an antigen which was not carried by one or both of its parents. I am aware that such exceptions have been found, both in the case of species crosses by Irwin[2] and

[1] Todd, C. (1930), *Proc. Roy. Soc.*, B, 107, pp. 197–205.
[2] Irwin, M. R. (1939), *Genetics*, 24, pp. 709–21.

within species by Thomsen.[1] Nevertheless, these exceptions are rare, and it is a very general rule that a single dominant gene is responsible for the production of a given antigen.

Of course these antigens are not made from nothing. They seem, where they have been examined, to consist of a protein part, and a haptene attached to it which is responsible for the specificity, and is a polysaccharide, often if not always nitrogenous. If the haptene is the immediate product of a gene, the gene doubtless requires simple materials for it, such as hexoses and perhaps amino-sugars. If these are gene products, then the absence or inactivity of the genes responsible for their production would be incompatible with the life of the cell. We should describe such inactive genes as lethal genes. We may, then, take it as a working hypothesis that some genes produce antigens directly. Now enzymes have a similar structure to these antigens. That is to say, they are proteins, often, if not always, with prosthetic groups such as metallo-porphyrins and flavine-sugar compounds. Some of them are antigens.

It is not unreasonable to expect that enzymes will be found among the immediate products of gene action. A still further speculation is that the process by which genes produce their immediate products is the same as that by which they reproduce themselves, and that the antigen produced by a gene, presumably during its

[1] Thomsen, O. (1936), *Hereditas*, 22, pp. 129–44.

"resting" period, differs from the parent gene essentially in not being anchored to a chromosome (probably by union with nucleic acid). It is, however, unlikely that this speculation will be proved or disproved in the

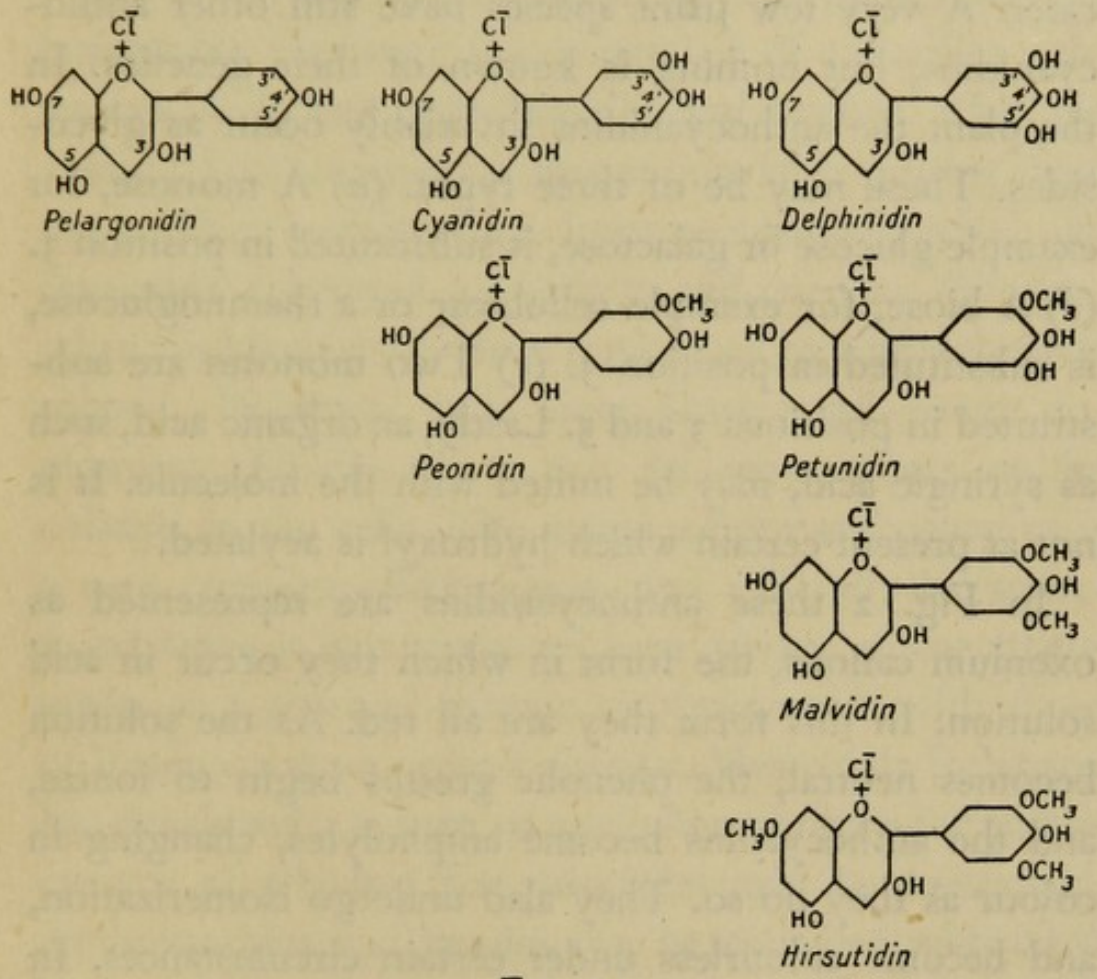


FIG. 2.

immediate future. A careful search for polysaccharides in protamines from spermatozoa would perhaps be of interest as a step towards its verification or disproof.

To return to the water-soluble flower pigments, the anthocyanins are all derivatives of pelargonidin, cyanidin, and delphinidin (Fig. 2). Cyanidin may be methylated

in the 3′ position, 3′-*O*-methyl cyanidin being called peonidin. Similarly 3′-*O*-methyl-delphinidin (petunidin) and 3′-5′-*O*-dimethyl-delphinidin (malvidin) are common. 7-3′-5′-*O*-trimethyl delphinidin, or hirsutidin, is much rarer. A very few plant species have still other anthocyanidins, but nothing is known of their genetics. In the plant the anthocyanidins invariably occur as glycosides. These may be of three types. (*a*) A monose, for example glucose or galactose, is substituted in position 3. (*b*) A biose, for example cellobiose or a rhamnoglucose, is substituted in position 3. (*c*) Two monoses are substituted in positions 3 and 5. Lastly, an organic acid, such as syringic acid, may be united with the molecule. It is not at present certain which hydroxyl is acylated.

In Fig. 2 these anthocyanidins are represented as oxonium cations, the form in which they occur in acid solution. In this form they are all red. As the solution becomes neutral, the phenolic groups begin to ionize, and the anthocyanins become ampholytes, changing in colour as they do so. They also undergo isomerization, and become colourless under certain circumstances. In a flower an anthocyanin probably exists as a mixture of several ionic species. It is a general rule that an anthocyanin is bluer the more alkaline the medium in which it is dissolved and the more hydroxyl groups it carries. Thus solutions of a delphinidin glucoside near the neutral point are bluer than those of the corresponding pelargonidin or malvidin glucosides, but malvidin derivatives

are bluer than pelargonidin derivatives, probably because the methoxyl groups at 3′ and 5′, though they cannot ionize, help the hydrogen at 4′ to do so. Again, 3-5-diglycosides are bluer than 3-glycosides.

But this is not all. Robinson and Robinson made the remarkable discovery that a number of colourless substances, including anthoxanthins and tannins, affect the colour of anthocyanin solutions, invariably making them bluer. They seem to form loose compounds, which are reversibly destroyed by boiling, and even by diffusion, when the blueing substance is taken up by a non-aqueous solvent. Robinson calls these blueing substances co-pigments. Finally, there may be other effects of the colloids in the cells. The colour of the anthocyanins is a very complex phenomenon, and will only be understood when it is investigated by a worker whose attainments as a physical chemist are comparable with those of Robinson as an organic chemist. Meanwhile Robinson has developed a system of qualitative analysis for anthocyanins of which a few principles may be mentioned. Anthoxanthins and tannins can be extracted with ethyl acetate from an acid aqueous solution. 3-monosides and 3-biosides can be extracted with amyl alcohol from an acid aqueous solution saturated with sodium chloride. The various anthocyanins give characteristic colour reactions at different pH values, and on addition of ferric chloride. It must, however, be emphasized that this technique has occasionally led to mistakes by highly

qualified workers, and that it cannot possibly distinguish between, say, glucosides and galactosides.

The anthoxanthins fall into three classes, of which representatives are shown in Fig. 3. They are generally present as glycosides. In the different classes there may be variation in the number of hydroxyls on the isolated

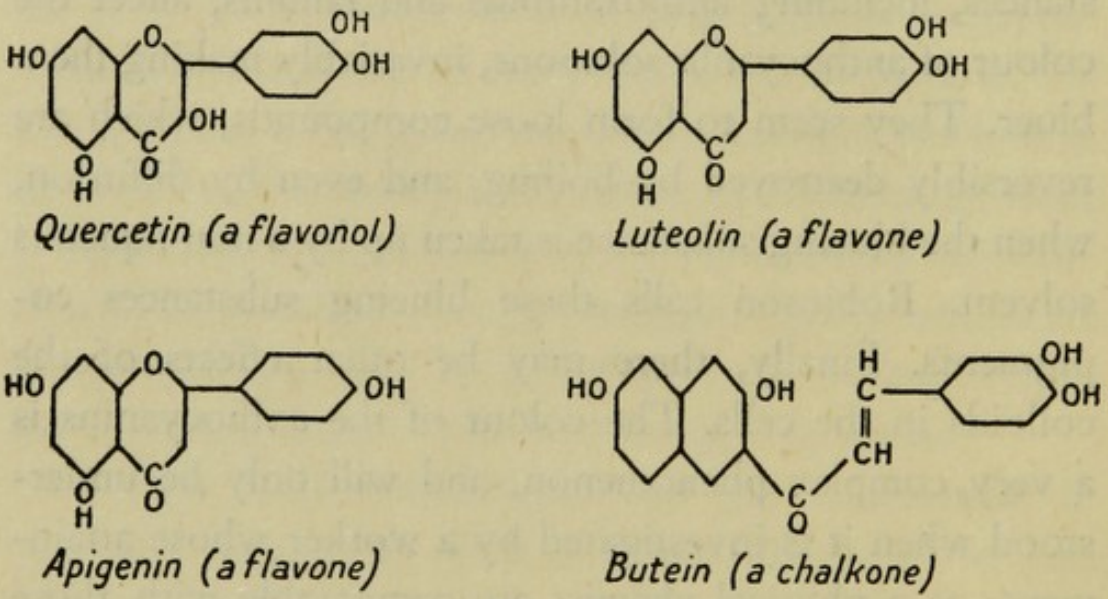


FIG. 3.

benzene ring. Their study is still in an early stage, as there is no system for their identification, and Price has shown that in the past chalkones have been incorrectly described as flavones. These substances affect flower colour in three ways. (*a*) They may be responsible for the yellow colour of petals which do not contain anthocyanin. (*b*) They may give a mixed colour with anthocyanin, for example, the chocolate colour of some dahlias. (*c*) They may alter the colour of an anthocyanin, for example, alter what would be red to magenta in

Primula sinensis. Of course (*b*) and (*c*) may, and often do, occur together, and what would be a colour change from a bee's point of view is not necessarily so from a human one, nor perhaps conversely.

With these prolegomena we may pass to the results of genetical investigation. I shall take *Lathyrus odoratus* as my type, as it has recently been investigated biochemically by Beale, Robinson, Robinson, and Scott-Moncrieff, after very extensive genetical work, mainly by Punnett. The wild type has purple flowers with the wings, as the two lateral petals are called, notably lighter and bluer than the rest of the flower. The main anthocyanin is a malvidin 3 : 5-monoside, but it is possible that this is associated with small amounts of corresponding derivatives of petunidin and even delphinidin, the partly methylated and unmethylated homologues of malvidin. The nature of the sugars is unknown. The anthoxanthin is quercetin, with a little kaempferol (the corresponding flavonol without a 3-hydroxyl). This is colourless, but a strong copigment.

The following genes are known affecting flower colour. All, except *br* and *fm*, are fully recessive. These two are nearly so.

c, white; *c'*, flaked.
r, white; *r'*, marbled.
fm, flake modifier.
m, maroon.
k, copper.

e, red.
sm, salmon.
d, dull.
co, mauve.
dw, dark wing.
br, bright.
p, picotee.
h, hooded standards.

We shall first consider the effects of these mutants one or two at a time. It is convenient to do so in terms of the activity postulated for their normal allelomorphs *C*, *R*, etc. Plants which lack either *C* or *R* have no anthocyanin, but have anthoxanthin. *r'* and *c'* (the latter with the help of *fm*) give flowers with patches of anthocyanin on a white ground. Plants without *M* or *K* have a precisely similar maroon colour, and are very susceptible to bleaching by sunlight. Neither has copigment. Hence the anthocyanin is seen in its "natural" colour. It follows that both *M* and *K* are needed for the production of anthoxanthin. Plants lacking *E* have peonidin in place of malvidin glycoside. They are therefore red. Plants lacking *Sm* are normal unless they also lack *e*. But *ee sm sm* plants have a pelargonidin glycoside, and are therefore pink or salmon. Thus when a double heterozygote *Ee Sm sm* is selfed it gives 12 purple: 3 red: 1 salmon.

Flowers lacking *D* are blue. The mean pH of the cell sap of six *DD* types was 5·34, that of the corresponding *dd* types 5·93. The difference of pH is, in some other

species, confined to the petals, and does not extend to the sap of the stem and leaves. This does not appear to have been tested in *Lathyrus*. Flowers lacking *Co* are mauve. They have less anthocyanin but more anthoxanthin, which accounts both for their pale colour and bluish tinge. Plants lacking *Dw* have the wings of the same colour as the standard. The vast majority of cultivated types are *dw dw*. *Dw* diminishes the anthocyanin and increases the anthoxanthin in the wings. *br* has no effect on the wild type, but antagonizes the effect of *co*, bringing what would otherwise be mauve plants partly back towards normal. *p* has a similar effect to *co*, but more marked. Finally, *h* has its most striking effect on the structure, but some effect on the colour, making the wings and standard more uniform. Thus *H* and *Dw* have like effects.

Besides these there are heritable differences in degree of methylation and in the sugars attached to the anthocyanidin. On the whole the more copigmented types are the more fully methylated, but even copper and maroon are not fully unmethylated. Finally, some varieties contain a considerable amount of a 3-glycoside along with the 3-5-glycoside. The genetical basis of this has not been determined.

We may classify the activities of the dominants as follows:

1. Producing anthocyanin, generally at the expense of anthoxanthin. *C*, *R*, both essential; *P*, *Co*, needed for full development.

2. Producing anthoxanthin, generally at the expense of anthocyanin. *M*, *K*, both essential; *Dw*, *H*, needed for full development; *Br* only has a marked effect on plants lacking *Co*.
3. Oxidizing. *E* is responsible for the presence of hydroxyls (which may be methylated) at 3′ and 5′, while *Sm* is responsible for the presence of one, if *E* is absent.
4. Acidifying. *D*.

The interaction, so far as studied, is much as would be expected. The main complications arise from the fact that *Dw*, *P*, and *H* do not act equally on all parts of the flower. The competitive effect between the first two series is noteworthy. *co co* and *pp* plants contain very large amounts of copigment, provided *M* and *K* are present, but not if one of them is absent. In this case they merely have less anthocyanin than the full-coloured types. It is not yet known whether *Dw* and *H* increase the amount of anthoxanthin in *cc* and *rr* whites, though this is likely. *H* has no effect in the absence of *K* or *M*, but curiously enough *Dw*, though it cannot produce anthoxanthin and thus make the flowers bluer, dilutes the anthocyanin of the wings in *kk* and *mm* flowers. These facts, except the last, can all be explained if the anthocyanins and anthoxanthins have a common source.

The state of affairs in *Primula sinensis* is similar, with some exceptions. No genes are known which are absolutely essential for anthocyanin production. Plants lacking *V* are white unless they also lack *B*, the gene for

copigment. But *vv bb* plants develop a little pigment. Another striking difference is that in *Primula sinensis* there are two dominant genes *G* and *D* suppressing anthocyanin, the former in the centre of the flower, including the stigma, the latter in the periphery. *G* is present in the wild type, *D* has arisen by mutation. When both are present we get a dominant white. Their action is probably similar to that of *Dw* and *H* in *Lathyrus*, but more marked.

A striking experiment is made possible by the fact that the presence of *B* can readily be detected in white flowers. *B* was first detected as a gene which turned red flowers to magenta. After Robinson's discovery of co-pigment it was found that *DGB* whites gave a strong yellow colour with ammonia, *DGb* whites a pale primrose. What is more, we can make an extract of the petals, and add it to an extract of a red *dGb* plant. The extract from *DGb* has no effect, that from *DGB* makes the red extract turn purple. Now if we cross *DD GG BB* whites with *dd GG bb* reds, we get a white F_1, but 12 *D* (white): 3 *ddB* (magenta) : 1 *dd bb* (red) in F_2, whereas the cross of *DD GG bb* and *dd GG bb* gives a white F_1 and 3 white : 1 red in F_2. Thus the result of a test-tube experiment enables us to predict the progeny to be expected two years hence. This may be called crossing *in vitro*.

As regards the oxidation of the anthocyanins, *Primula sinensis* differs in two respects from *Lathyrus odoratus*.

In the first place, there are no varieties with cyanidin derivatives. The gene *K* substitutes malvidin-3-galactoside for a pelargonidin-3-monoside, probably the galactoside. So far everything is similar to what would be the case in *Lathyrus* if all plants lacked *Sm*. But a further complication has lately arisen. *kk* plants have lately been put on the market under the name of Dazzler with a greatly increased quantity of pelargonidin. They differ from normal *kk* plants by a semi-dominant gene D_7, and perhaps by a second gene also. On crossing with *KK* plants, derivatives have been obtained with a brilliant scarlet colour, and containing both pelargonidin and malvidin derivatives. Their genetical behaviour is still obscure. Another curious complication is that the anthocyanin suppressors *D* and *G* also produce a local alkalinity in the petals, similar to that found in the absence of the gene for acidity, here called *R*.

In *Papaver rhoeas* fewer colour genes are known. The factor *P* not only causes an increased acidity of the cell sap, converting mauve to red, and lilac to salmon-pink, but it acylates the anthocyanin. There are only two types of anthocyanin, namely, cyanidin-3-diglucoside (mekocyanin) and pelargonidin-3-bioside (probably diglucoside). In the absence of the two genes *F* and *T* we have simple dominance of cyanidin over pelargonidin, and in the absence of the gene *E* no cyanidin is formed. So far, then, the genetics resemble those of *Lathyrus odoratus* lacking *E*. But both *T* and *F*

cause the production of pelargonidin bioside in plants which also carry *E. T* can be distinguished by its effect in tingeing the filaments of the anthers in certain cases, while *F* produces a characteristic flush. The most peculiar feature of *Papaver rhoeas* is perhaps that the wild type contains no anthoxanthin except at the base of the petal. Hence the presence of copigment is recessive to its absence. The copigmented plants have rather less anthocyanin.

In *Streptocarpus* (the majority of horticultural plants are interspecific hybrids) the genetics of oxidation are as in *Lathyrus*. The presence of 3-5-dimonoside is dominant over that of a mixture of 3-5-dimonoside and 3-pentose-glycoside. In *Callistemma sinensis* (syn. *Callistephus hortensis*) Wit reports a series of three allelomorphs giving delphinidin, cyanidin, and pelargonidin derivatives, and dominant in that order, whilst the presence of 3-5-diglycosides is dominant over that of 3-diglycosides. If this is confirmed it will be the first case in which the glycosidal type is determined by a single gene. It is possible, however, that Wit's work, like some of the earlier results of the Robinsons and of Scott-Moncrieff, will require revision.

As regards oxidation, all other plants so far investigated, except perhaps *Dahlia variabilis*, fit into one of the schemes outlined above. In *Tropaeolum majus*, *Antirrhinum majus*, and *Cheiranthus cheiri* the flowers of dominant types contain cyanidin glycosides, a 3-bioside,

a 3-rhamno-glycoside, and a 3-5-dimonoside respectively. In each case a recessive form contains the corresponding pelargonidin derivative, as in *Papaver rhoeas*. However, in *Tropaeolum* many types contain a mixture of pelargonidin and cyanidin derivatives. This is due to a special dominant gene, as in *Papaver*.

In *Pharbitis nil* the 3′ hydroxyl is methylated when present, and peonidin 3-5-dimonoside is dominant over the corresponding pelargonidin derivative. In *Pelargonium zonale*, malvidin 3-5-dimonoside is dominant over pelargonidin 3-5-dimonoside. Thus in every case the inability to form a more oxidized derivative is recessive.

Finally, we have some evidence from *Antirrhinum* and *Pharbitis nil*. In both these there is a recessive type of white which lacks both anthocyanin and anthoxanthin. In the latter plant the gene *Ca* is needed for any production of anthoxanthin. *C* is needed for full anthoxanthin production, and *R* and *A* are further needed before anthocyanin is formed. There is of course a great deal of scattered evidence from other plants, and a great deal which I have not mentioned concerning the genetics of pattern. What generalizations can we draw from this rather bewildering intricacy?

In the first place we can classify the genes modifying colour. We cannot in general say that blueing genes are dominant or recessive. But when we classify the dominants by their chemical effect they fall into five classes.

1. Genes controlling acidity. This is so far always dominant over alkalinity, that is to say, the blueing effect is recessive.
2. Genes favouring copigment formation, generally at the expense of anthocyanin. In this case the blueing effect is dominant, and accompanied by a dilution of the anthocyanin due to competition for the common source.
3. Genes inhibiting copigment formation, generally with extra production of anthocyanin (e.g. *Co* in *Lathyrus*). Here the blueing effect is recessive, and generally accompanied, as above, by dilution.
4. Genes substituting a more oxidized, and therefore bluer, anthocyanin for a less oxidized and therefore redder one. Here blueing is always dominant, and is often accompanied by intensification, for pelargonidin is paler than the more oxidized anthocyanidins, as well as redder.
5. Genes responsible for pelargonidin production, even in the presence of oxidizing genes of the last class. In the absence of such genes they merely intensify the colour due to pelargonidin. In their presence they produce a mixture which is redder than the cyanidin or delphinidin derivatives. They generally seem to be dominant, but not always completely so.

There may also be genes for methylation or demethylation and for adding or removing sugars, but, except in Wit's case, these processes do not seem to be simply determined. I need hardly point out the great simplification which would arise if the nomenclature of genes were standardized so that in every species, say, *A* denoted a gene for dominant acidity, *K* a gene for copigment production, and so on. Doubtless the time

for such a simplification is not yet ripe, but if genetical research on biochemical lines continues it should be ripe within ten or twenty years.

Let us now see what biochemical deductions can be drawn from this material. In the first place, the frequent competition between anthocyanin and anthoxanthin demonstrates almost beyond doubt that they have a common metabolic origin. The most complete account of this competition has been given by Lawrence and Scott-Moncrieff in *Dahlia variabilis*. However, as this

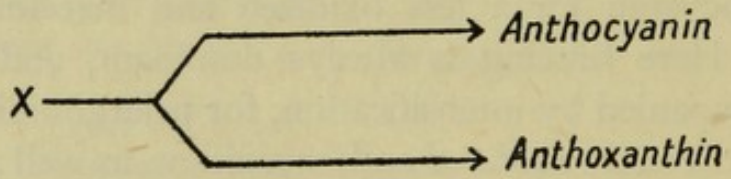


FIG. 4.

plant is a polyploid, a description of their work would take me outside the compass of these lectures. On the other hand, the evidence from such a plant as *Lathyrus* shows that anthocyanin can be formed when anthoxanthin is not, or conversely. We can therefore symbolize the metabolic paths as in Fig. 4, and rule out the theories that anthocyanins are derived from anthoxanthins, or conversely.

Thus the gene *Ca* of *Pharbitis* controls a process on the common path, *C* in the same plant being an adjunct, whilst *R* and *A* control processes on the upper path. On the other hand, in *Lathyrus*, *C* and *R* control processes on the upper, *K* and *M* on the lower path, whilst

no gene is known controlling the common path. How far, we may ask, does synthesis proceed in common? Certainly the oxidation or reduction of the "right-hand" benzene ring is not completed before the paths diverge. Some plants may have corresponding anthocyanins and flavonols (for example, cyanidin and quercetin in *Zea mays*), but this is not necessarily so. Thus in *Dahlia variabilis* the anthocyanin may be a derivative of cyanidin, of pelargonidin, or a mixture, whilst the flavone apigenin (one phenolic group) and the chalkone butein (two phenolic groups) may also be present. But we do not find any constant correlation of pelargonidin and apigenin, or cyanidin and butein. Similarly, so far as is known at present, the anthoxanthin of *Lathyrus odoratus* is kaempferol (one phenolic group) whatever the anthocyanin. It is possible that the sugar residues of anthocyanins and anthoxanthins vary together, but if so the sugar may be attached after or before the rest of the molecule is determined.

So far, then, there seems to be little doubt, and the genetical facts support Robinson's theory of synthesis. But there is more dispute as to the relations of the different anthocyanins. Scott-Moncrieff took the view that two distinct processes were involved, namely, general and specific anthocyanin production. The mechanism of general production is illustrated by *Lathyrus odoratus*. Here the anthocyanin is the same throughout the plant (except that the degree of methylation may vary), and

mixtures of differently oxidized types are not found. She considered that oxidation was an active process, that is to say, not that pelargonidin galactoside was first formed and then oxidized to delphinidin galactoside in *Primula sinensis*, but that at some stage in the process a monophenol was oxidized to a triphenol. On the other hand, she attributed the production of mixtures and the boosting of the pure pelargonidin in others to a specific anthocyanin production entirely independent of the "general" genes for oxidation.

Robinson, Lawrence, and Price take a different view. They argue that all anthocyanins and anthoxanthins arise from a hypothetical intermediate with two phenolic groups in the 3′ and 4′ positions. Such an intermediate $C_{15}H_{16}O_8$ could be produced from two hexose groups which form the rings, and an intermediate triose, by aldol concentrations, with no net oxidation or reduction, but only the loss of seven water molecules. The anthocyanins and anthoxanthins would then be formed by oxidations and reductions of the middle part of the molecule. In this case cyanidin derivatives are more primitive than pelargonidin or delphinidin. The former must arise by reduction, the latter by oxidation.

They support this view by a very interesting argument. Where the colour of anthocyanin performs an important function in attracting insects or birds, they may be expected to be modified from the primitive form, mutant colour types being favoured by natural selection.

Where, however, such colour is not important, we should expect to find the primitive type, namely, cyanidin (and peonidin) glycosides. This hypothesis is fully borne out by facts. Lawrence and Price found that the anthocyanin in the young leaves was a cyanidin derivative in 93 per cent of the genera examined. For the autumn leaves the corresponding figure was 95 per cent, for permanently pigmented leaves 76 per cent, for fruits 69 per cent, and for flowers only 50 per cent. They ascribe the well-known frequency of blue forms in temperate climates to the importance of bees in pollination. Tropical flowers, which are more often pollinated by red-sensitive birds and *Lepidoptera*, are more often red, either because they contain pelargonidin or deep yellow carotinoids.

Neither theory explains very adequately the pallor of many recessive mutants containing pelargonidin. On the first theory it should accumulate if it or its precursor is not oxidized, though possibly a reversible reaction prevents this accumulation. On the second theory, if all the diphenolic precursor is not reduced, some of it should remain to form cyanidin. I am personally not wholly convinced by the biochemical argument for the primitive nature of cyanidin. Metabolic processes involving carbohydrates, for example, fermentations, generally include oxidation and reduction except where we are only concerned with the formation and destruction of glycosidic linkages. I am quite prepared, however, to believe that cyanidin, as a final metabolic product, is primitive. But

this does not prevent its being formed, even in the most primitive plants, by the oxidation of pelargonidin or a precursor with no phenolic groups in the 3′ and 5′ positions. If this is so, then the absence of a dominant gene for oxidation results in the production of pelargonidin derivatives. They are due to what may be called biochemical neoteny, just as the neotenic persistence of embryonic gills in the *Urodela* is due in some cases to a lack of thyroxin. It may be that the conception of neoteny will find application in the field of biochemistry, as it has in the field of morphology. For example, Needham[1] pointed out that animals whose eggs are closed so that the products of nitrogenous metabolism cannot diffuse out have a uricotelic metabolism, that is to say, produce uric acid instead of a soluble substance such as urea or trimethylamine oxide. It is at least conceivable that the change first occurred in embryonic life, and only later on in the adult. Needham was also, I think, the first to apply Teissier and Huxley's morphological conception of allometry to biochemical development. It is likely that comparative and developmental biochemistry will take over a number of morphological conceptions.

This controversy will, I think, only be resolved by biochemical research. I had hoped that the next step would be the detection of enzymatic differences between different varieties, for example, some phenol-oxidase might have been found in flowers containing cyanidin,

[1] Needham, J. (1938), *Biol. Rev.*, 13, pp. 225–51.

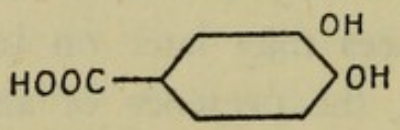
but not in those containing pelargonidin. However, owing to circumstances which have nothing to do with genetics, I have now no opportunities for personal research or the direction of research in this interesting field.

Let us now try to look at the genetics of flower pigments from a different standpoint. Supposing that the anthocyanins, like the sugars, amino-acids, and alkaloids, did not absorb in the visible part of the spectrum, what should we have found? Probably very little. We know that there are hereditary differences of acidity in fruits, and such differences may later on be found in other organs. However, the presence of an indicator in the petals has led to their discovery there, even though it was necessary to use a glass electrode before they could be measured. In *Primula sinensis* the coral-flowered plants containing pelargonidin derivatives are peculiarly susceptible to "damping off," a mould infection, and appear also to be less resistant to cold than the normal varieties. A comparison of different lines might have led to the discovery of biochemical differences. But this is rather unlikely. Probably the pelargonidin-containing plants would have been eliminated by selection. I have very little doubt that among the various weakly plants which are destroyed or at least not used for breeding there are many interesting biochemical mutants.

A particularly interesting case has been studied by Rieman[1] and others in the onion, *Allium cepa*. The bulbs

[1] Rieman, G. H. (1931), *J. Agricult. Res.*, 42, 5.

of this plant may be unpigmented, or pigmented either with an anthocyanin or an anthoxanthin. The nature of the former is unknown, but from its colour it cannot be a pelargonidin derivative. The anthoxanthin seems to be quercetin. Plants which are fully coloured with anthocyanin or anthoxanthin are resistant to infection by the organism of smudge disease, the fungus *Colletotrichum circinans*. Those which are only tinged with colour show a partial resistance. The resistance was



Protocatechuic Acid

FIG. 5.

shown by Link, Angell, and Walker[1] to be due to the presence in the outer scales of the onion of a water-soluble substance identified as protocatechuic acid (Fig. 5), which has also been detected in other plant structures. It is clearly related to cyanidin and quercetin, from which it can be derived by treatment with strong alkalis. It may be a stage in their synthesis, though this is not in accord with Robinson's theory. It may be derived from the breakdown of one or both of them, or of a common precursor. A search for phenolic acids in plants whose pigmentary genetics have been fully analysed might

[1] Link, K. P., Angell, H. R., and Walker, J. C. (1929), *J. Biol. Chem.*, 81, pp. 369–75.

throw much light on the metabolism of pigments. The presence of pigment in onions depends on the presence of a dominant gene, but its formation is also inhibited by another gene, completely when this gene is present in the homozygous form, not always so in heterozygotes. The genetical situation is not fully cleared up, but susceptibility to smut disease is associated with absence of pigment however this is determined genetically.

If anthocyanins and flavones were invisible we should have the information that resistance depended on a dominant and a recessive gene. If we further knew that resistance was due to protocatechuic acid, we should speak of genes determining the presence of this substance. Very possibly resistance to disease is determined in an equally simple manner in other cases where there are no colouring matters to give a clue. Incidentally the data on the onion throw a good deal of light on the biological function of colour. They do not stand alone. Detlefsen and Roberts[1] showed that the early post-natal death-rate of black mice was higher than that of their agouti (wild colour) litter mates, but did not investigate the causes of death. These deaths occurred before the colours could be scored, so they cannot be a consequence of the colour, but must depend on the metabolic processes leading up to it. Similarly, the chocolate (or brown) gene in mice seems to cause an increase in size. There are numerous similar cases in *Drosophila*. In fact, the

[1] Detlefsen, J. A., and Roberts, E. (1918), *Genetics*, 3, pp. 573–98.

colours of animals and plants are indices of their metabolic processes, and though colours may have a protective or warning function, this is not necessarily the basis of their selective value.

In this chapter I have only touched a part of a very wide subject. In particular I have omitted any discussion of the work on insect eye colours and mammalian pigments, though the former has demonstrated the existence and genetic control of colourless precursors which reach the eyes from other organs. Two important new fields have been opened by the work of Raistrick and his colleagues on mould pigments, and that of Winge on yeast crossing. Genetical work with moulds should throw light on the metabolic origin of their pigments; and since yeasts have been very extensively studied from a biochemical standpoint, their genetics will be of great interest for a variety of metabolic problems. A number of the problems connected with hormone production and action which will be mentioned in the next chapter will undoubtedly be susceptible of biochemical investigation later on. But at present we know so little about the mode of action of most hormones that they are better considered under the heading of developmental physiology.

We see that a geneticist cannot possibly neglect biochemistry. I hope that I have also shown that the study of genetics is not without value to the biochemist.

CHAPTER 3

Genetics and Development

"Poi siete entomata in difetto,
Sì come verme, in cui formazion falla."[1]
DANTE, *Purgatorio*, X, 128.

IN this chapter I shall take my examples almost wholly from the genetics of the mouse and rat, and this for two reasons. The developmental physiology of insects has been illuminated by the pioneer work of Goldschmidt, and his book[2] deals with the work of his successors in this field, whilst Waddington[3] is dealing with it in England. And I have had the honour and pleasure of watching the work of Dr. Grüneberg (one of two colleagues whom I owe to the generosity of the present German Government), and the advantage of perusing the manuscript of his monograph on the genetics of the mouse, which is now ready for the press. Some of his work will be described in this chapter.

Consider two pairs of mice, one pair black and white, the other full-sized and dwarf. Genetical analysis shows that each pair differs by a single gene substitution. Had

[1] "Since you are as it were defective insects, like the grub in which development is lacking."

[2] Goldschmidt, R. (1938), *Physiological Genetics* (New York).

[3] Waddington, C. H. (1940), *Organizers and Genes* (Cambridge).

the white mouse carried one dominant gene it would have been black; had the dwarf carried one normal it would have been full-sized. The genes are present in every cell nucleus of the body. The differences between the members of each pair extend over various parts of the body, each composed of millions of cells. We can ask a very fundamental question. Is the difference between two homologous organs, say the feet or the dorsal skins, due to the genes in the cells of these particular organs, or to those in the cells of other organs? In the first case we say that the gene is autonomous in its action; in the second case that it is non-autonomous or heteronomous. We shall see that this distinction, like so many in biology, breaks down when it is pushed too far. But it is a useful distinction. Because we cannot say whether *Euglena* is a plant or an animal, we do not conclude that the distinction between plants and animals is meaningless. In the example given we shall see that the action of the colour gene is autonomous, that of the size gene heteronomous.

The large majority of colour genes, both in plants and animals, seem to be autonomous. In particular Reed[1] has transplanted skin between embryonic and new-born mice. In every case the skin, and the hairs growing from it, developed the colour which they would have shown in the mouse from which they came. Reed also obtained very interesting results on the genesis of pattern in cases

[1] Reed, S. C. (1938), *Journ. Exp. Zool.*, 79, pp. 330–54.

where a gene is responsible for a pattern. Similar results have been obtained in birds. This does not, of course, imply that colour development is autonomous in the sense that a given set of cells will produce a certain type of hair and feathers, no matter in what environment. On the contrary, birds' feathers are very strongly influenced by the hormones of the gonads and thyroid. But the genes which differentiate the various breeds of poultry as regards colour do not act by influencing these glands, though they may influence the response of the skin to their secretions.

Colour development in insects is generally autonomous, as shown not only by the frequency of mosaics, but by the effects of transplantation. Beadle, Ephrussi, and many others, have transplanted eye rudiments from one larva into another. Under favourable circumstances the resulting imago has a third eye under the dorsal cuticle of its abdomen. An eye from a larva of a white-eyed race remains white in any host, and similarly for most colours. But two scarlet mutants, "vermilion" and "cinnabar," which lack a brown pigment present in the normal eye, develop the wild type colour in wild type larvae. And eyes from a wild type larva transplanted into vermilion or cinnabar develop the mutant colour. Extensive work has shown that certain of the normal organs produce colourless precursors or hormones which pass from them to the developing eyes. These substances are not specific for the species, or even the order. Thus one

of the recessive mutants of *Ephestia Kühniella*, a moth, lacks the precursor which is lacking in vermilion *Drosophila*. Probably further research will show heteronomous colour genes in vertebrates.

All colour genes in plants seem to be autonomous, as is shown by the practice of grafting. A white or yellow rose continues to give white or yellow flowers when it is grafted on a red-flowered briar as stock. The autonomy is not quite absolute, as small mutant patches of coloured cells in white petals generally have a border of pale-coloured cells, as if the anthocyanin could diffuse to a slight extent. We should expect a greater degree of autonomy in plants than in animals, for in plants there is no intercellular vascular system, and the substances passed from one cell to another are probably all crystalloids. On the other hand, some of the vertebrate hormones, such as insulin, are proteins, while at least one other, thyroxin, is normally attached to a protein molecule as thyreoglobulin. The plant hormones so far known are all small molecules. But their very existence suggests that gene action in plants is not fully autonomous.

For developmental physiology only heteronomous genes are of much interest. We can only follow intracellular processes by biochemical methods, and the last chapter has shown how little we know of the precise nature of genic interaction within the cell. On the other hand, we can study the interaction of different organs in the case of genes whose action is not autonomous.

The simplest cases of heteronomy seem to depend on diffusion between neighbouring cells. Reed transplanted embryonic skin between normal and waved mice. The latter have hair with a slight wave. When a piece of skin from a white waved mouse was transplanted on to a black straight-haired mouse (more accurately a mouse destined to develop black straight hair, for the embryonic skin has no pigment and no hair) the white waved patch is surrounded by some black waved hairs. Similarly, if a patch destined to develop white straight hairs is grafted onto a black waved mouse, some of the white hairs on the patch develop waves. Presumably a hormone diffuses through the skin for the distance of a few cells.

Of the better understood examples of heteronomous action the simplest depend on the control by the gene of one or more hormones. Snell[1] discovered a recessive dwarf form of mouse, which was further studied by Smith and Macdowell,[2] Kemp,[3] de Beer and Grüneberg,[4] and others. These mice weigh from 5 to 8 grammes, as compared with 20 to 30 grammes in a normal mouse, and 75 grammes in a very fat one. Growth begins to slow

[1] Snell, G. D. (1929), "Dwarf, a New Mendelian Recessive Character in the House Mouse," *Proc. Nat. Ac. Sci.*, 15, p. 733.

[2] Smith, P. E., and Macdowell, E. C. (1930, 1931), *An. Rec.*, 46, p. 249; 50, p. 85.

[3] Kemp, T. (1933, 1935, 1938), *Act. Path. Scand.*, Supplement 16, pp. 189–93; 26, pp. 10–11; 37, pp. 290–305.

[4] de Beer, G. R., and Grüneberg, H. (1940), *J. Gen.*, 39, pp. 297–300.

down at twelve days, and stops at about seventeen days, when there is generally some loss of weight and a considerable mortality. Later there is generally a slow increase in weight and length. The main difference between their growth curves and those of normal mice is between the seventeenth and thirty-fifth day. Not only are they small, but their proportions are different from those of normal mice; for example, the tail and ears are shorter. They are sluggish, and their basal metabolism is about 60 per cent of that expected from their size. Hence they survive longer than normal mice if starved. Both sexes are sterile.

The thyroid, thymus, gonads, and adrenals are infantile. The anterior pituitary is small, and contains no eosinophil cells. When rats' anterior pituitaries are transplanted below their skin at frequent intervals they resume growth, and may reach normal size. Males may be fully fertile, but females have no regular oestrous cycle. Possibly they could be rendered fertile by transplanting anterior pituitaries from donors at appropriate stages of oestrus and pregnancy. The thyroid and adrenals become normal, so it is clear that the primary defect is in the anterior pituitary. An assay of the anterior pituitaries of the dwarf mice shows the absence of the thyreotrophic hormone, prolactin, and growth hormone (if this latter is to be regarded as a single substance). On the other hand, gonadotrophic hormone seems to be present in normal amounts. Naturally enough

there is not complete agreement as to which hormones are present, nor will there be until the hormones of this gland have been definitively separated. There is a possibility that the eosinophil cells, which are completely absent in the dwarf pituitaries, are diminished in number in the heterozygotes.

The normal allelomorph of the gene for dwarfism is presumably responsible for the development of the eosinophil cells, and the production of a group of hormones. In every other cell of the body this gene would seem to be inactive, or at any rate to be of no great importance. There is nothing surprising in this. Genes are known in *Drosophila* which affect a single pair of bristles. But as this gene for non-dwarfism happens to be essential for a key group of cells, the effects of mutation spread to every organ of the body.

In *Drosophila melanogaster* a lethal recessive gene produces giant larvae which do not metamorphose, but carry out an extra moult, and then die. There is also a giant race, differing from the normal in respect of two genes, in which an extra larval moult occurs before metamorphosis. These forms seem to be due to hormonic abnormalities, but in view of the rather complex relation between moulting and metamorphosis in *Hemiptera* it is too early to say just what hormonic abnormality occurs in them.

It is possible, and indeed probable, that genes exist which produce smaller changes in the activity of various

endocrine glands. However, this is not as yet certain. On the other hand, genes are known without doubt which control the response of other tissues to the internal secretions. Few organs are more conspicuously sensitive to hormones than the feathers of certain breeds of poultry. They react in particular to variations in the amount of thyroxin or of the steroid hormones produced by the gonads. A complication arises because very large doses of the sex hormones produce hypothyroidism, presumably by inhibiting the thyreotrophic activity of the anterior pituitary.

In the wild type of poultry, and in many domestic breeds, there are conspicuous differences in the plumage of the sexes, both as regards structure and colour, the male having a much greater variety of feather types than the female. In self-coloured breeds, such as whites, blacks, and buffs, and in some others, there is little difference in colour between the sexes, and in the barred breeds the colour difference is due to the fact that the male has two genes for barring and the female only one. The male is therefore lighter in colour. However, there are some breeds in which the feathers of the two sexes are similar both in colour and structure, both sexes having a female type of plumage. These include the Campine, the Sebright bantam, and the "henny" varieties of the Old English gamecock.

The henny character is due to an autosomal dominant gene whose manifestation is limited to the male sex.

This was first conclusively shown by Punnett and Bailey,[1] who cleared up a number of difficulties due to incomplete dominance in certain cases. In a normal dimorphic breed castration has little effect on the male plumage, though it has some, and greatly reduces the comb, while abolishing the spur. The female castrate, on the other hand, develops plumage of the male type. Castrates of either sex develop plumage of the female type when treated with oestrone. In the "henny" breeds castration of either sex causes the growth of a male type of plumage. It was natural enough that early workers, for example, Boring and Morgan,[2] suggested that the testis of the henny feathered male, but not of the normal male, secreted a hormone of the female type. Roxas[3] transplanted testes between males of normal and henny-feathered breeds, and obtained no change of plumage, so this hypothesis is disproved. The gene must act on the feather-producing tissues, and not on the gonads.

Its mode of action has been made fairly clear by the work of Parkes and his colleagues. Deanesly and Parkes[4] found that the castrated Sebright bantam male required about one-twentieth of the dose of oestrone to produce female plumage which was needed in the castrated Brown Leghorn male. Only a part of this difference was due to

[1] Punnett, R. C., and Bailey, P. G. (1921), *Journ. Gen.*, 11, pp. 37–57.
[2] Boring, A. M., and Morgan, T. H. (1918), *J. Gen. Physiol.*, 1, p. 127. [3] Roxas, H. A. (1926), *J. Exp. Zool.*, 46, p. 43.
[4] Deanesly, R., and Parkes, A. S. (1936), *Brit. Med. Journ.*, 1, p. 257; (1937), *Quart. Journ. Exp. Physiol.*, 26, pp. 393–401.

the lighter weight of the bantam. They also found that testosterone and three other androgenic hormones, namely, dehydro-androsterone, androstenedione, and *trans*-androstenediol, in doses of 1 milligramme per day, feminized the plumage of castrated Sebright males, while androsterone did not. On the other hand, the corresponding dose of oestrone is 0·05 milligramme. These quantities do not transform castrated Leghorn males. It may be that huge doses of testosterone would act on a Leghorn, but they would be unphysiological, and would inhibit the activity of the anterior pituitary, and through it of other glands.

The dominant gene for henny feathering then reduces the concentration of oestrone needed for feminization, and also renders the feather-producing cells sensitive to most of the male hormones in their physiological concentrations. In all probability the henny feathers are due to the testosterone secreted by the testis of the male birds, and not to any traces of oestrogens which they may produce.

The mutant in the mouse in which the interference with normal development is most completely understood is "myelencephalic blebs." Little and Bagg[1] obtained a race characterized by eye and foot defects. Little and McPheters[2] studied its genetics, and Bonnevie[3] and

[1] Little, C. C., and Bagg, H. J. (1924), *J. Exp. Zool.*, 41, pp. 45–92.
[2] Little, C. C., and McPheters, B. W. (1932), *Genetics*, 17, pp. 674–88. [3] Bonnevie, K. (1934), *J. Exp. Zool.*, 67, pp. 443–520.

Plagens[1] worked out its development. Genetically it is at first sight rather unsatisfactory. In a general way the defects are recessive. But the progeny of recessives may contain a few normals. By selection within lines homozygous for the main recessive gene it is possible to obtain races in which the two defects are very rare, races in which both eye and foot defects are found in the majority, and finally races in which they were common in the eyes but not the feet. As it stood, the case was one of the scandals of mouse genetics. One could postulate a recessive gene, and indeed it was clear that all the members of a line derived from two abnormals carried such a gene. For even the normal members of such a line generally had some abnormal progeny. But the mode of action of the gene appeared to be utterly capricious. It was cleared up by the simultaneous work of Bonnevie and Plagens.

In a stock homozygous for the recessive gene all embryos show an abnormality when about 7 millimetres in length, or about twelve days from fertilization. In the myelencephalon of many, if not all, mammals and birds at this stage there is a foramen called the *foramen anterius* which is later obliterated by the growth of the cerebellum. It lies in front of the future choroid plexus, and *a fortiori* of the future foramen of Magendie. In the abnormal line large amounts of fluid pour out of the foramen and form blebs under the skin. As a result the blood is greatly concentrated. It is not known whether the primary defect

[1] Plagens, G. M. (1933), *J. Morph.*, 55, pp. 151–83.

is an over-secretion of cerebro-spinal fluid or an inadequate reabsorption. The blebs travel under the epidermis. Some remain on the back, and are gradually reabsorbed. Their only post-natal effect is a slight retardation of hair growth on their sites. Others move along the tail with no definite effect. But those which reach the feet or eyes have serious results. There is generally some haemorrhage, and the clot is organized as scar tissue. Thus syndactylism is common, hypodactylism rare, and polydactylism still rarer. The foot may be flexed dorsally or ventrally. Seventeen types of foot defect were distinguished. Serious haemorrhages in the eye region cause pre-natal death, less serious ones marked atrophy of the eyes, which are never opened, and minor ones atrophy of the lids.

We note that only those organs are injured which are actively differentiating at the time. And indeed the time at which the blebs are formed is essential. A similar event before the closure of the neural tube would merely lead to dehydration, one at a later stage to hydrocephalus. The eyes and feet are affected because, at the time in question, they are actively differentiating and therefore vulnerable, and by the time the clots have been organized the capacity for self-regulation has disappeared. Presumably the genes responsible for the eye and foot defects lie in cell nuclei somewhere in the central nervous system. Certainly the genes in the eye and foot cells are not responsible. This analysis should make us very

suspicious of such vague phrases as "stigmata of degeneration" applied to human beings. Where various defects occur irregularly in a pedigree they may yet be due to a single gene substitution. Finally, they show the unprofitable nature of speculations as to causation in abnormal development. No amount of theorizing on eye and foot defects would have led to the correct result. I believe that the same moral holds concerning speculations regarding normal development.

Brachyury is a dominant character in mice, and brachyuric mice are always heterozygous. The homozygous form is lethal, the embryo dying and being reabsorbed before birth. Thus if *T* is the gene for brachyury and *t* its normal allelomorph, *Tt* × *tt* (brachyuric × normal) and the reciprocal cross give 1 *tt* : 1 *Tt*, whilst *Tt* × *Tt* gives 1 *tt* : 2 *Tt* among the mice which survive to birth. These facts were determined by Zavadskaia.[1] Complications occur in some lines due to other genes (or perhaps chromosomal abnormalities). Chesley[2] examined the development both of *Tt* and *TT* mice. The lethal homozygotes can be distinguished at eight and a half days, when there are four to eight somites. At this time the somites are rather irregular, as is the neural tube, and blebs are present dorsally. At nine days the blebs disappear, but the neural

[1] Dobrovolskaya-Zavadskaia, N., Kobozieff, N., and Veretennikoff, S. (1934), *Arch. de Zoöl.*, 76, pp. 249–388. (Résumé of many earlier papers in *C.R. Soc. de Biol.* and elsewhere.)

[2] Chesley, P. (1935), *J. Exp. Zool.*, 70, pp. 429–59.

tube and somites become irregular, especially in the posterior region. At ten days there is a reduction in size of the posterior region, a complete absence of segmentation, and no limb buds, which are present in normal embryos. At ten and three-quarter days the *TT* embryos die, and are soon reabsorbed.

The most striking features in sections are irregularity of the neural tube and, above all, entire absence of the notochord except for a few groups of cells which may represent fragments of it. It is tempting to suppose that the primary effect of the gene substitution is on the mesoderm, leading to the absence of the notochord and failure to form somites, while the other results are secondary. This is the view taken by Lehmann,[1] who points out that the notochord is formed from the "organizer" region, which is responsible for the evocation of the neural tube in the ectoderm above it. But Lehmann made it highly probable that this organizing activity does not stop at this stage. On treating young *Triton* gastrulae with LiCl he found that the notochord is not formed in the region between the mid-brain and pronephros, and that the parts of the central nervous system lying above the gap, notably the hind-brain, are under-developed. If gastrulae are treated at a later stage, the fore and hind ends of the notochord are affected, and the fore-brain is small or absent. There is often cyclopia. The disturbances at the caudal end are less striking, but

[1] Lehmann, F. E. (1936), *Naturwissenschaften*, 24, pp. 401–7.

where somites are abnormal the vertebral column is also abnormal. Lehmann points out that the reported disturbances described by Chesley occur later in development than those which he produced, as the notochord is at least partly formed.

Ephrussi[1] showed that the skin cells of *TT* embryos on the point of death would proliferate in serum, and that isolated tissues would live for a month or more. Not only would they live, but mesenchyme cells from the posterior part of the body would differentiate and produce cartilage, which is absent from normal embryos when the lethals die. This observation is of some philosophical interest. The *TT* mice appear to die, not through the weakness of any particular cells, but because the cells of the whole body do not constitute a properly co-ordinated system, just as the genes and cytoplasm of an inviable embryo do not constitute such a system. In general a whole organism is more viable than its parts. We are apt to think that this is an example of some great philosophical principle by which wholes are superior to their parts. Actually it may only be a result of natural selection. Perhaps we are led into a philosophical error by the state-worship which is inculcated by the ruling class, and for which, of course, all kinds of metaphysical justifications have been found. I personally hold the opinion that the modern type of state is a self-destructive system like the *TT* mouse embryo, and that those of us

[1] Ephrussi, B. (1935), *J. Exp. Zool.*, 70, pp. 197–204.

who escape the approaching histolysis (to use Bateson's[1] words concerning the fate of the society of which he was a member) may find ourselves members of a state of a radically different type resembling the Soviet Union in many respects, and destined to perish, though not catastrophically, within a few generations. This is not anarchism; it is the view which was held by Lenin.[2]

The *Tt* embryo can be distinguished from the normal *tt* before the end of the ninth day. The notochord is present but abnormal, developing diverticula and defects. These are frequently accompanied by irregularities in the neural tube in the tail but not in the body. These in turn seem to give rise to irregularities in the intervertebral spaces. At birth the tail is variable. It may lack a few vertebrae only, or even all. A fleshy filament often projects beyond the bony parts. The vertebrae may be irregular, causing kinks in the tail, or the distal vertebrae may be separated from the proximal by a gap. Or the tail may be absent or represented by a fleshy filament or pear-shaped appendage. More rarely there are irregularities in the sacral and lumbar vertebrae, which may give rise to paraplegia of the hind legs. The type of abnormality differs to some extent in different families, probably due to modifying genes. To sum up, it may be suggested that the normal mouse (and presumably

[1] Bateson, W. (1912), *Biological Fact and the Structure of Society* (reprinted in *William Bateson, Naturalist*, Cambridge, 1928).

[2] Lenin, V. I. (1917), *State and Revolution*.

every normal chordate) carries a pair of *t* genes which are required for the development of the notochord and the formation of somites. *T* (which may be a chromosomal deficiency) is the absence or inactivity of one of these genes. Mice with only one *t* develop a somewhat inadequate notochord. The other abnormalities are secondary to those of the notochord. Only later work will show whether this hypothesis is correct.

Another lethal ("gray lethal") in the mouse was discovered by Grüneberg.[1] The mice were originally detected by the complete absence of yellow pigment in their coats. Much to Dr. Grüneberg's annoyance, all the young mice showing this new colour character died soon after weaning. A further examination showed that their teeth had not erupted. The incisors are small teeth quite unlike the permanently growing incisors of rodents. The molars are imprisoned in the jaw bones. It was clear that the animals died after weaning because they could not eat hard food. But when given soft food which was quite adequate for their normal litter-mates, they only lived for a month or so at most. The cause of death is unknown, though both the blood phosphate and liver glycogen are very low in the terminal stage, and the thymus degenerates earlier than usual.

Further examination showed a number of skeletal abnormalities, of which the most striking is that the

[1] Grüneberg, H. (1935), *Proc. Roy. Soc.*, B, 118, pp. 321–42; (1937), *Journ. Anat.*, 71, pp. 237–44.

marrow of long bones, such as the tibia, is filled with spicules. This gave Grüneberg the clue to an abnormality which accounts for a good deal else. There is no secondary reabsorption of bone, once it is formed, although cells are present which cannot be distinguished histologically from normal osteoclasts. But they do no work. Hence the long bones not only contain spicules, but have a clumsy shape, since the broad heads are not reabsorbed as the bone grows in length. For the same reason the teeth cannot escape from their alveoli. The exception to this proves the rule. The lower incisor grows, and, taking the line of least resistance, some of it actually erupts backwards through the mental foramen in the mandible. Other abnormalities are probably remoter consequences. Thus the zygomatic arch is unusually shallow.

In this case it appears that secondary bone reabsorption all over the body is to be regarded as a unit process controlled by a single gene. However, the same gene is also concerned in the formation of yellow hair pigment, the persistence of the thymus, and some process (perhaps glycogen formation in the liver) which is essential for life. The nature of the causal connection is completely obscure. The only suggestion comes from the fact that glycogen formation involves esterification with phosphoric acid, and osteoclasis may do the same. Thus if the cell phosphate were removed as a carbohydrate ester the resulting local shortage of inorganic phosphate would cause local dissolution of bone, such as occurs all over

the body in osteomalacia. Perhaps a quantitative study of phosphoric esterases might yield a result, and, if so, further light might be thrown on the biochemistry of yellow pigment formation. This is, of course, pure speculation, which I should not publish did I see any chance of personally testing the hypothesis in the near future.

We do not know whether the gene in question is autonomous or acts through a ductless gland or some other organ of internal secretion. If the latter were the case, the gene would be an exception to the general rule that skin and hair pigment formation is autonomous. Moreover, the condition develops at a time when no abnormality can be detected in any of the viscera.

A much clearer case is afforded by Grüneberg's[1] disease of the rat. This is due to a recessive lethal which kills the rats at any age from a few days to four weeks. Death may occur from any of a variety of causes, the most common being pulmonary haemorrhage and circulatory failure characterized by purple engorgement of the claws. There are a number of anatomical peculiarities. The most striking is a hypertrophy of the cartilaginous ribs, as a result of which the thorax becomes rigid and fixed in the inspiratory position. It is, however, smaller than usual, even for the reduced size of the rat. There is generally kyphosis of the cervical vertebrae, and respira-

[1] Grüneberg, H. (1938), *Proc. Roy. Soc.*, B, 125, pp. 123–44; Fell, H. B., and Grüneberg, H. (1939), *Proc. Roy. Soc.*, B, 127, pp. 257–77; Engel, S., and Grüneberg, H. (1940), *Journ. Gen.*, 39, pp. 343–49.

tion is entirely diaphragmatic. Other cartilages, for example, the trachea, are also hypertrophied. The lungs are small and lie behind the heart. They were at first thought to be emphysematous, but later it appeared that the presence of large air spaces rather than fine alveoli was a foetal character. There is an arrest of pulmonary development, presumably due to the inability of the lungs to grow. Chronic asphyxia results, and if the rat lives long enough, the right ventricle hypertrophies, presumably in response to an abnormally high resistance in the pulmonary circulation. A further compensatory effect is an increase in the haemoglobin and the erythrocyte counts. In five litters from six to twelve days old the median value of the haemoglobin of the lethals was 22 per cent above that of the normals, that of the erythrocytes 15 per cent above that of the normals. One lethal which survived to fifteen days had a haemoglobin no less than 49 per cent above the mean of its sibs. The haemorrhages are probably due to intense respiratory efforts of the diaphragm.

All the symptoms can plausibly be attributed to the hypertrophy of the cartilage, resulting from intense cell proliferation. Fig. 6 (slightly modified from Grüneberg) shows the causal nexus. For details reference must be made to his papers. The deltoid ridge of the humerus is the insertion of the pectoralis major muscle, which is presumably affected by the abnormal form of the thorax. The nostrils of rats which die as sucklings are often

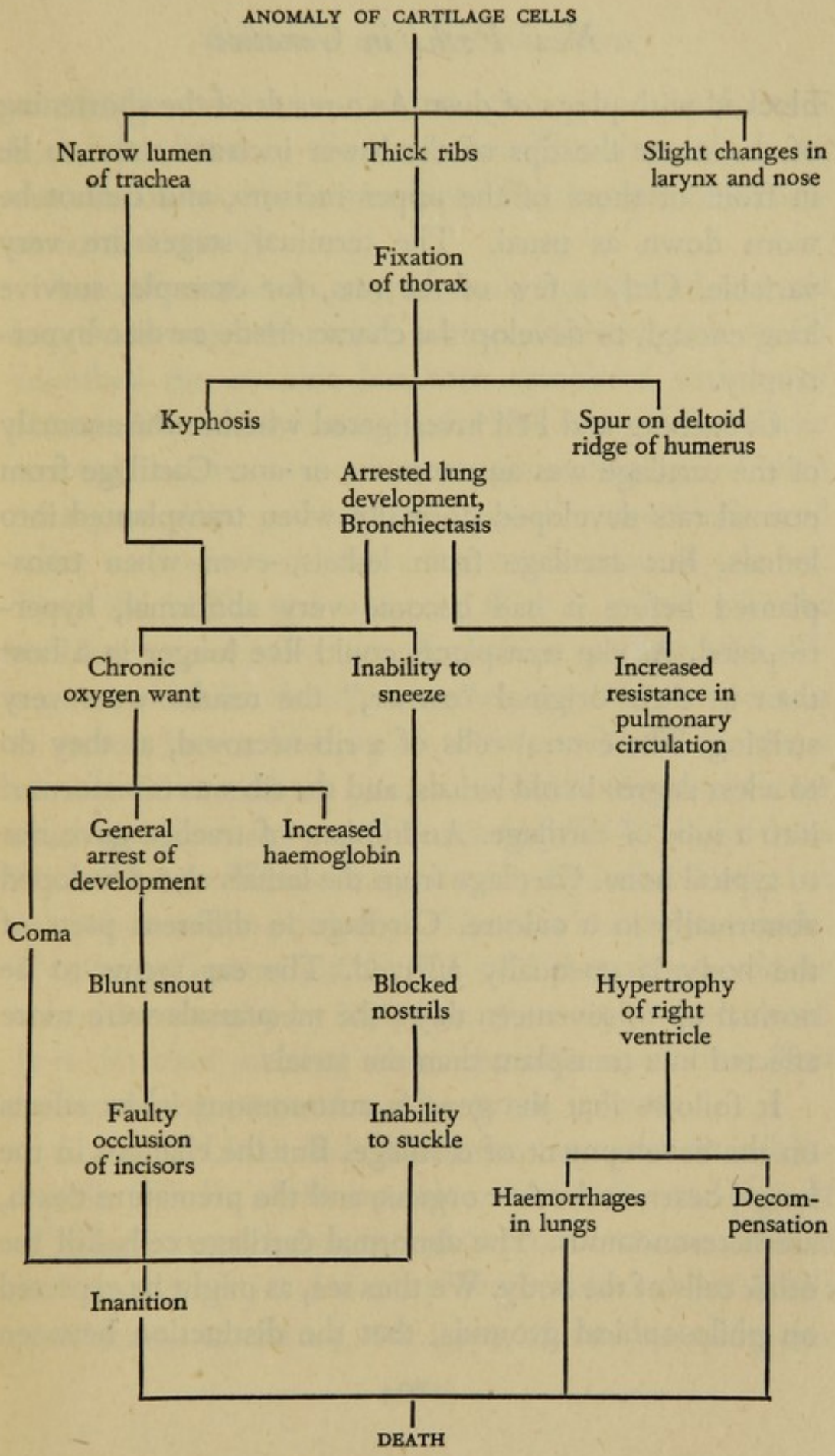

ANOMALY OF CARTILAGE CELLS
Narrow lumen of trachea
Thick ribs
Slight changes in larynx and nose
Fixation of thorax
Kyphosis
Spur on deltoid ridge of humerus
Arrested lung development, Bronchiectasis
Chronic oxygen want
Inability to sneeze
Increased resistance in pulmonary circulation
General arrest of development
Increased haemoglobin
Coma
Blunt snout
Blocked nostrils
Hypertrophy of right ventricle
Faulty occlusion of incisors
Inability to suckle
Haemorrhages in lungs
Decom-pensation
Inanition
DEATH

FIG. 6

blocked with plugs of dust. As a result of the shortening of the snout the tips of the lower incisors come to lie in front of those of the upper incisors, and cannot be worn down as usual. The terminal stages are very variable. Only a few of the rats, for example, survive long enough to develop the characteristic cardiac hypertrophy.

Grüneberg and Fell investigated whether the anomaly of the cartilage was autonomous or not. Cartilage from normal rats developed normally when transplanted into lethals. But cartilage from lethals, even when transplanted before it had become very abnormal, hypertrophied. As the transplants could live longer in a host than in their original "owner," the results were very striking. The central cells of a rib necrosed, as they do to a less degree in old lethals, and the rib was transformed into a tube of cartilage. An implant of trachea gave rise to typical bone. Cartilage from the lethals also developed abnormally in a culture. Cartilage in different parts of the body is unequally affected. The ear seems to be normal up to seventeen days, the metatarsals were more affected in a transplant than the tarsals.

It follows that the gene is autonomous in its effects on the development of cartilage. But the changes in the lungs, heart, and other organs, and the premature death, are heteronomous. The abnormal cartilage cells kill the other cells of the body. We thus see, as might be expected on philosophical grounds, that the distinction between

autonomous and heteronomous gene action, useful as it is, breaks down in the long run. This does not mean that the distinction is worthless. But it must be understood dialectically.

A number of cases of genetically determined anaemia have been reported in the mouse. In every case so far described the anaemia has been associated with other abnormalities. The black-eyed white mice of the fancier are well known to be heterozygous. Matings of such mice give about one ordinary piebald : two black-eyed white or black-eyed with a few small coloured patches. Thus the black-eyed white is $W^1w\,ss$, where s is the well-known recessive gene for white spotting, and W^1 a gene which in the heterozygous condition converts a ss mouse into a black-eyed white, a SS or Ss into a mouse with a piebald pattern in which the patches are much smaller than in ss. The missing W^1W^1 individuals from $W^1w \times W^1w$ matings do not die before birth, but at birth or within a few days. They are intensely anaemic. However, Gowen and Gay[1] found that they could be reared to maturity by injections of normal mouse blood. It is not clear whether these injections saved their lives by furnishing corpuscles, a hormone, or both.

Recently Little and Cloudman reported an allelomorph W^2. Its effects on colour are similar to those of W^1, but it is not lethal, though it produces some anaemia in homozygotes, and they are less viable and less fertile

[1] Gowen, J. W., and Gay, E. H. (1932), *Am. Nat.*, 66, pp. 289–300.

than normal mice. De Aberle[1] has investigated the haematology of W^1W^1 mice, and Grüneberg[2] that of W^2W^2 and W^1W^2. Their results are summarized in

TABLE 1

BLOOD OF MICE AT TIME OF BIRTH

(After Grüneberg)

Genotype	Erythrocytes	Haemoglobin	Colour index
ww	1	1	1
W^2W^2	0·51	0·66	1·3
W^1W^2	0·31	0·53	1·7
W^1W^1	0·14	0·25	1·8

Table 1. It will be seen that the anaemia is of macrocytic type, like human pernicious anaemia; however it is not curable by liver extracts. The large cells are of a foetal type, and the anaemia may be regarded as an arrest of development. This comes out very clearly from a study of the colour indices, which in the normal mouse drop from 1·1 at birth to 0·51 at maturity, while the volume of a corpuscle is also halved. The colour indices of the W^2W^2 mice at all ages are about 1·3 times those of normals. So the latter lag behind the normals. Thus the colour index of W^2W^2 mice eleven to twenty-three

[1] De Aberle, S. B. (1927), *Am. J. Anat.*, 40, pp. 219–49.
[2] Grüneberg, H. (1939), *Genetics*, 24, pp. 777–810.

days old is about the same as that of normals three to ten days old. The difference in the colour indices is entirely due to the size of the corpuscles, the amount

TABLE 2

RATIO OF ERYTHROCYTE NUMBERS IN *ff* AND NORMAL MICE

(After Grüneberg (unpublished), based on data of Kamenoff, Mixter, and Hunt)

Age in days	Erythrocytes, *ff*/FF
14	0·52
15	0·54
16	0·75
17	0·75
18	0·64
Birth	0·74
0	0·88
7	1·01
14	1·03
21	1·20
28	1·09

of haemoglobin per unit corpuscular volume being unaffected by age or genotype. W^2W^2 mice can regenerate blood after haemorrhage, and produce up to 40 per cent extra haemoglobin in response to oxygen want, as do normals.

There is another gene which causes anaemia in mice. This is a recessive described by Mixter and Hunt[1] and Kamenoff.[2] This gene produces a flexed tail in a majority of the recessives, and a majority have a white spot on the belly. But all of them are anaemic at birth. However, they recover rapidly after birth, and further examination shows that the anaemia is mainly pre-natal. In Table 2 the bloods of flexed-tailed and normal mice are compared. The first part gives ages after conception, the second after birth. Recovery seems to be complete within a week of birth. The two stocks had different ratios at birth, as a result of other genes or of environmental conditions. The anaemia is hypochromic, that is to say, the amount of haemoglobin per corpuscle is less than normal. Thus the anaemia, as judged by haemoglobin content of the blood, is more severe than appears from the table.

It would seem, then, that the normal allelomorphs of *W* and *f* control different unit processes. The former is concerned with the normoblastic production of the adult type of corpuscle in the bone marrow, the latter with the megaloblastic production of the foetal type, largely in the liver. Much further work is needed, particularly on foetal W^2W^2 mice. But it is clear that if the nature of the unit processes can be discovered a good deal of light will be thrown on blood formation.

[1] Mixter, R., and Hunt, H. R. (1933), *Genetics*, 18, pp. 367–87.
[2] Kamenoff, R. J. (1935), *Journ. Morph.*, 58, pp. 117–55.

Nothing is known as to the relation between the effects of these genes on pigmentation and tail structure on the one hand and on blood formation on the other. The other effects may possibly (though I think improbably) be secondary to those on the blood. Or both may be resultants of some unknown primary process. Possibly the dilution of melanin in rats with iron deficiency may turn out to be relevant to this question.

All the genes so far discussed are concerned in the early part of the life cycle. But the life cycle of metazoa includes death. Death may be due to environmental causes such as accident (an inorganic agency), aggression by an organism of larger or comparable size (for example, a predator or a homicide), or by a smaller organism or virus (infectious disease). But besides this category of "nurtural deaths" there are natural deaths, that is to say, deaths due to an internal breakdown of the organism. Paradoxically enough, natural death is probably rare in nature except in animals or plants with a sharply defined life cycle. Conspicuous examples of natural death are those of the mayflies (*Ephemeridae*), and the Pacific salmon *Onchorhynchus*, which die after mating, like operatic heroes. A fair fraction of human deaths in old age may be regarded as natural, even if they are complicated by a terminal infection. Natural death in higher forms can best be studied in small animals such as mice, which can be protected from infection, kept under standard conditions, and reared in large numbers.

A large fraction of the deaths of senile mice is due to cancer. The epoch-making work of the Bar Harbor group has shown that "spontaneous" cancer not only has a genetical basis, but at least in one case depends on an agent, perhaps a virus, which can be transmitted by the milk. However, the incidence of cancer is to a large extent genetically determined. I cannot deal here with this enormously complicated question, except to point out that in view of the close chemical analogy between genes and viruses it is not inconceivable that some viruses may be genes detached from the chromosomes and reproducing in the cytoplasm, a view adumbrated by Muller before the chemical nature of viruses was known.

Research on spontaneous cancer in mice showed the necessity for a study of pure lines, for the simple reason that only a fraction of all mice live to advanced ages such as two years, by which time tumours have developed in most members of a susceptible line. Hence little can be learned from a study of individual mice. Even in a carefully controlled environment the age of onset is fairly variable. The same applies, of course, to other senile processes. Everyone who has undertaken numerous post-mortem examinations of a pure line of mice has been struck with the frequency of particular lesions within one line which are absent in others.

The most extensive study of this phenomenon known to me was made by my colleague Dr. Gorer.[1] He studied

[1] Gorer, P. A. (1940), *Journ. Path. and Bact.*, 50, pp. 25–30.

the kidneys of three pure lines of mice, namely, Strong's *A* albinos, Little's *C*57 blacks, and Strong's *CBA* agoutis. All three lines occasionally develop metaplasia of the parietal layer of the glomerular capsule to cubical or even columnar epithelium. This condition is found in mice of all ages, but is commonest in old *CBA* mice.

The glomeruli may also undergo hyaline degeneration, beginning in the tufts, and later spreading as an exudate between the tubules. The lesion resembles that of human amyloid disease, but does not stain strongly with iodine. Similar changes have been found in the adrenals, but not in the liver or spleen. It is confined to the *C*57 line, and was found in twelve out of twenty-two members of it aged over sixteen months. It was present in all four mice of this line aged over twenty-five months which were examined. It has not been found in the other two lines. Nothing is known of its incidence in hybrids.

Cystic disease is very common in the *A* line. This begins with focal necrosis in the renal papillae, which may later slough off. Then the tubules and glomeruli dilate. If the disease is more advanced in one kidney than the other, this may degenerate to a fibrous rudiment before the less affected kidney has killed its owner. Macroscopically visible cystic disease was found in forty-eight out of sixty-seven mice of this line over ten months old, including twelve out of thirteen over fourteen months, and all of eleven over eighteen months. It has not been found in any of forty-three *CBA* mice over

sixteen months old, but it has been found in ten out of one hundred and thirty-five $C57$ mice over ten months old, and its beginnings were found on histological examination of two more. The youngest was nineteen months, and eight of the twelve were over two years. In America, Andervont found it in *A* but not in $C57$, nor in the hybrids between them. Probably it would have been found in hybrids which lived for over two years.

Clearly at least two gene differences (possibly allelomorphic) must be concerned in the genetics of cystic kidneys. If so, the gene in *A* is recessive. Unfortunately the war has interrupted Gorer's research on this question, but it is clearly soluble, given sufficient time. The gene, if it is a gene, for cystic kidneys kills its bearers if other causes spare them. It can in fact be regarded as a lethal gene in a broad sense of this phrase, though, of course, when geneticists write of lethal genes they mean genes which kill their bearers before they can breed.

It is, I think, probable that all mice and all men carry genes which, in any existing environment, would cause their death after a sufficient number of years. It is highly probable that many plants do not, since they can be propagated clonally for an indefinite period. The oldest zygote known to us, by the way, is not one of the Californian big trees, but the saffron crocus, which is quite sterile and, since it is represented in Minoan paintings, must be over three thousand years old. Perhaps some animal clones such as coral polyps are still older.

In man there is good evidence that arteriosclerosis and some other senile diseases are largely genetically determined. It is natural that such genes should accumulate as the result of mutation, for there is no selection against genes which act after the reproductive period. If this is so, the indefinite prolongation of human life demands not merely the abolition of war and infection, and a vast reduction of accidents, but the abolition of these genes. Such a task is not impossible, though it would probably take some hundreds of centuries. It will presumably be one of the main tasks of the world community once our planet has been made a happy enough place for our descendants to consider such a goal worthy of their efforts.

In this chapter I have attempted, not indeed to give a survey of developmental genetics, but to show how some genetical factors are concerned in development. I do not think that any reader can question the importance of the facts disclosed, both for genetics and developmental physiology. I am perfectly aware that the facts are peculiarly "scrappy." We are much farther from a classification of the genes concerned, say, in the development of a mouse's tail than from a classification of those concerned in the development of anthocyanin in the sweet-pea. And no wonder, for the process is much more complicated.

It is instructive to compare the procedures of the geneticist and the experimental embryologist. The em-

bryologist does what he thinks is the same experiment, say the injection of a steroid which acts as an evocator into a number of embryos. The results are rarely uniform, because of the great difficulty of standardizing the experiment. The geneticist can obtain his end product, abnormal animals, in much greater numbers than the embryologist, and in favourable cases the results are much more uniform. But he does not know the nature of the initial "experiment." He has to work back to this as best he can. It is quite clear that these two lines of work are complementary. Only rarely, as in the cases of the dwarf mice and of the mouse embryos with no notochord, have the embryologists and geneticists made contact, so to say. But we can look forward to further contacts. In particular the restoration, by biochemical means, of normal development in dwarf mice seems to point the way. If we can successfully make good the inactivity of a gene, we can often learn what is that gene's normal function. And at the same time we are presented with material which enables us to study the activity of a hormone or some such substance under standard conditions.

Finally, the study of abnormalities of mammalian development gives us a background against which to study human congenital diseases, just as the study of infectious disease in animals has made it possible to tackle human infectious diseases. In the next chapter I shall discuss some human abnormalities in the light of the knowledge which animal experiments have given us.

CHAPTER 4

The Genetics of Some Human Abnormalities

"Bestemmiavano Iddio e lor parenti,
l'umana specie, il luogo, il tempo, e il seme
di lor semenza e di lor nascimenti."[1]

DANTE, *Inferno*, 3, 103.

MUCH of this chapter will not be novel. However, in England at least, there is so much muddled thought and statement on this topic that, before we come to the growing point of our subject, it is desirable to recapitulate some facts which should be well known. An abnormality is sometimes described as congenital if it is noticeable at birth, but not otherwise. This is most unsatisfactory. There is very little doubt that a child's future eye colour is determined when it is born, and indeed long before. However, the colour changes greatly in the first few years, and the future colour cannot be ascertained at birth. The same is true of a number of diseases which, like eye colour, are not present but are determined at birth, and a few of which we shall discuss in this chapter.

Among those abnormalities which can be detected at birth or soon after we can distinguish between those

[1] "They blasphemed God and their parents, the human kind, the place, time, and seed of their begetting and of their birth."

which are genetically determined wholly or in large degree, and those in whose determination pre-natal environment plays an important part. The latter group include pre-natal infections such as congenital syphilis, and such pre-natal injuries as amputation or partial amputation of a limb by a loop of the umbilical cord.

But in a large group of cases the causal analysis is quite incomplete, and yet statistical methods enable us to say a great deal about the mode of determination. Genetical segregation is a process little influenced by birth order or parental age. The only known exception occurs in the case of linkage. The frequency of crossing over between two genes may vary with maternal age in *Drosophila* and probably does so in other organisms. This is, however, certainly irrelevant to the data of human genetics which have so far accumulated.

Consider the case of mongoloid imbecility. This condition occurs sporadically among the children of normal parents, with a frequency which, according to Penrose,[1] exceeds 1 per 10,000 births. The low viability of the abnormals had led most writers on the subject to give a much lower figure, and certainly reduces the social importance of the condition as compared with that of other types of mental defect. The low consanguinity rate among parents excludes determination by a single recessive gene. Several other possibilities are open. However, the most striking feature of the statistics is the high age

[1] Penrose, L. S. (1932), *Journ. Gen.*, 25, pp. 407–22.

of the mothers. Of course, high maternal age is correlated both with number of previous births and with paternal age. Penrose was, however, able to show that, for a constant maternal age, neither the number of previous

TABLE 3

ANALYSIS OF 217 FAMILIES INCLUDING ONE OR MORE MONGOLOID IMBECILE

(After Penrose, *Proc. Roy. Soc.*, B, 115, 1934)

Mother's age	Total births	Per cent mongols
17–19	13	23
20–24	128	10
25–29	213	7
30–34	255	11
35–39	234	27
40–44	151	54
45–48	37	59
Total ..	1,031	22

births nor the father's age was relevant. Table 3 shows how maternal age influences the frequency of this condition. The small rise in frequency among young mothers is thought to be an effect of primogeniture rather than youth.

Clearly, then, unfavourable pre-natal conditions associated with maternal age are one of the determining

conditions of mongolism. But what are the others? Beyond doubt genetical factors are concerned. Not only is a couple more likely than the average to produce a second mongol if they have produced one, but the sib

TABLE 4

PERCENTAGES OF POLYDACTYLOUS GUINEA-PIGS IN FOUR LINES

(After Wright)

Mother's age, months	A	B	C	D
3–5	29·3	34·6	68·1	81·0
6–8	7·4	28·2	54·4	69·5
9–14	9·6	21·9	28·8	50·0
15–	6·1	12·1	22·0	30·2
Average ..	11·9	21·4	38·4	55·8
Total offspring	386	676	498	416

of such a parent is more likely to do so. Adequate data are not yet available, but it appears probable that the father as well as the mother is responsible. Wright[1] has examined similar cases in *Cavia porcellus*. Table 4 shows the results for polydactylism in four inbred and nearly pure lines of guinea-pig. It will be seen that polydac-

[1] Wright, S. (1926), *Am. Nat.*, 60, pp. 552–59.

tylism is determined both by nature and nurture, the predominant but not the sole factor in nurture being the mother's age. This table is very instructive as a warning against a one-sided interpretation of human data. The extreme eugenist will read it horizontally, the extreme environmentalist vertically. The biologist will read it both horizontally and vertically.

There is some indication that other human defects show a similar correlation with maternal age. In the case of mongolism, exhaustion by previous pregnancies is not an important factor. It may prove to be so in other cases. A second group of defects is particularly frequent among the first-born. Since the first birth is generally more prolonged than subsequent ones, it is more likely to result in injury, especially head injury, to the child, as well as to the mother. This may account for the higher frequency of epilepsy among the first-born. But it cannot possibly account for the higher frequency of other defects. The most striking of these are gross defects of the nervous system, such as anencephaly and pseudencephaly, and congenital pyloric stenosis. Clearly the first pregnancy is particularly liable to be abnormal not only in its termination at birth, but in its earlier stages. One can, of course, speculate regarding possible endocrine upsets, but there is absolutely no suggestion as to why one of these should produce a hypertrophy of the pyloric sphincter. Nor is there yet any strong evidence as to the part played by genetic factors in determining these con-

ditions. It is not known whether any abnormalities are characteristic of the children of young mothers as such.

We now pass to abnormalities whose genetical determination is well understood. The simplest cases are those due to autosomal dominant genes, for example, the pedigree of Fig. 7. The abnormal individuals are liable

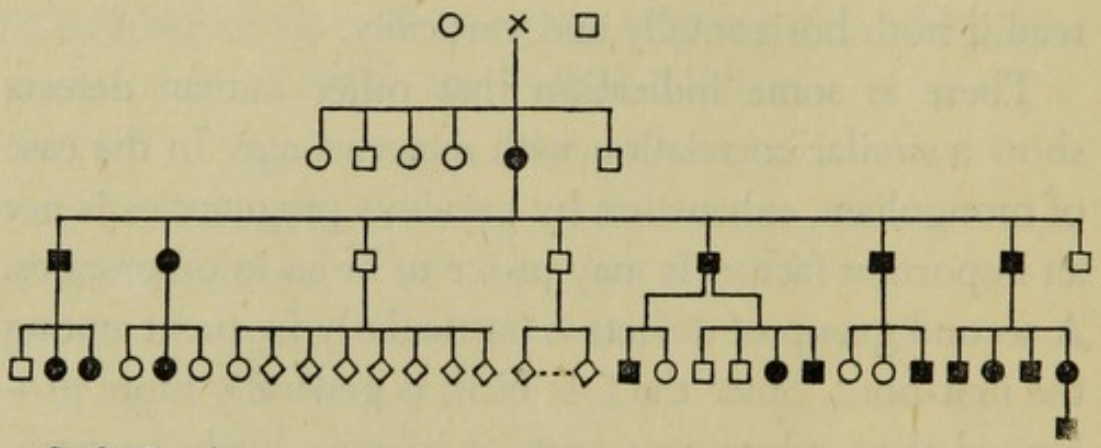
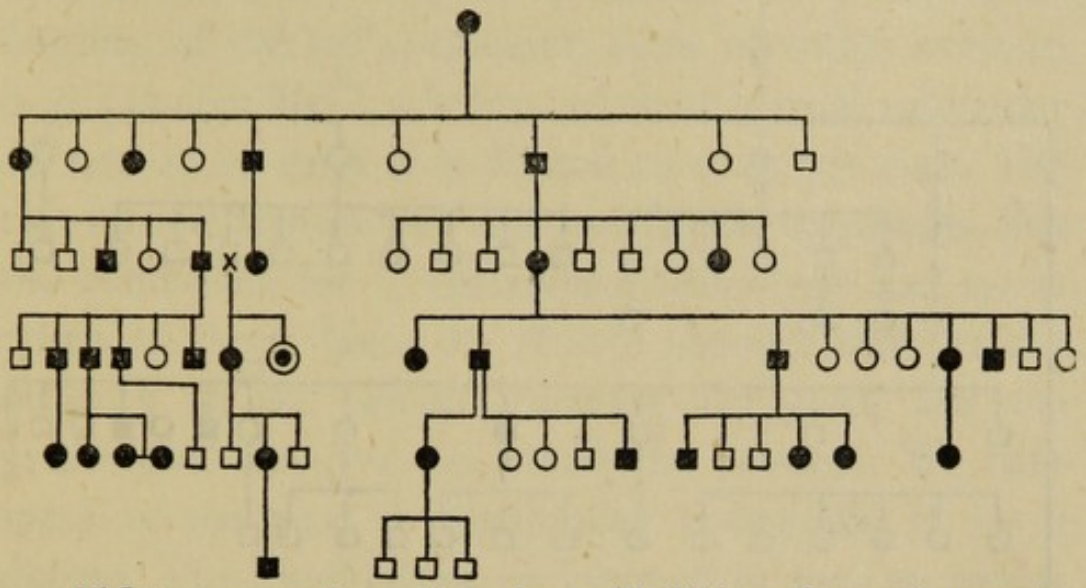


FIG. 7—PEDIGREE OF SEVERE BLISTERING OF FEET
(After Haldane and Poole, in the press)

to severe blistering of the feet in hot weather. About half the children of abnormals are abnormal, and there is no transmission through normals. If we represent normals as *bb*, abnormals as *Bb*, everything is explained, except the origin of the first *Bb* who appeared in a very respectable Wiltshire family in the middle of the nineteenth century, and was almost certainly not an adulterine bastard but a mutant. Clearly, except for mutants, nega-

tive eugenic measures such as sterilization would soon abolish abnormalities inherited in this way.

What, we may ask, are homozygous abnormals *BB*? No one knows. But in a few cases we can answer with some probability. Fig. 8 is a pedigree of brachyphalangy.



All Spouses normal, except as shown. All children of normals normal
◉ *Grossly abnormal, probably homozygous*

FIG. 8—PEDIGREE OF BRACHYPHALANGY
(After Mohr and Wriedt, *Publ. Carneg. Instn.*, 295, 1919)

The abnormality was a slight shortening of the middle finger.

It will be seen that two abnormals married and had one short-fingered daughter, and a second with gross skeletal abnormalities, including the absence of all digits. Fortunately she died in early childhood. She was probably a homozygote. Now, if a gene with similar effects occurred in mice, I am sure that even my colleague Dr. Grüneberg would not at once detect it in the heterozygous condition, whilst even I should do so in homo-

zygotes. The gene would in fact be described as a recessive. Possibly at a later stage Dr. Grüneberg might detect a slight digital shortening in heterozygotes. We can now see one reason why dominant genes for abnormalities

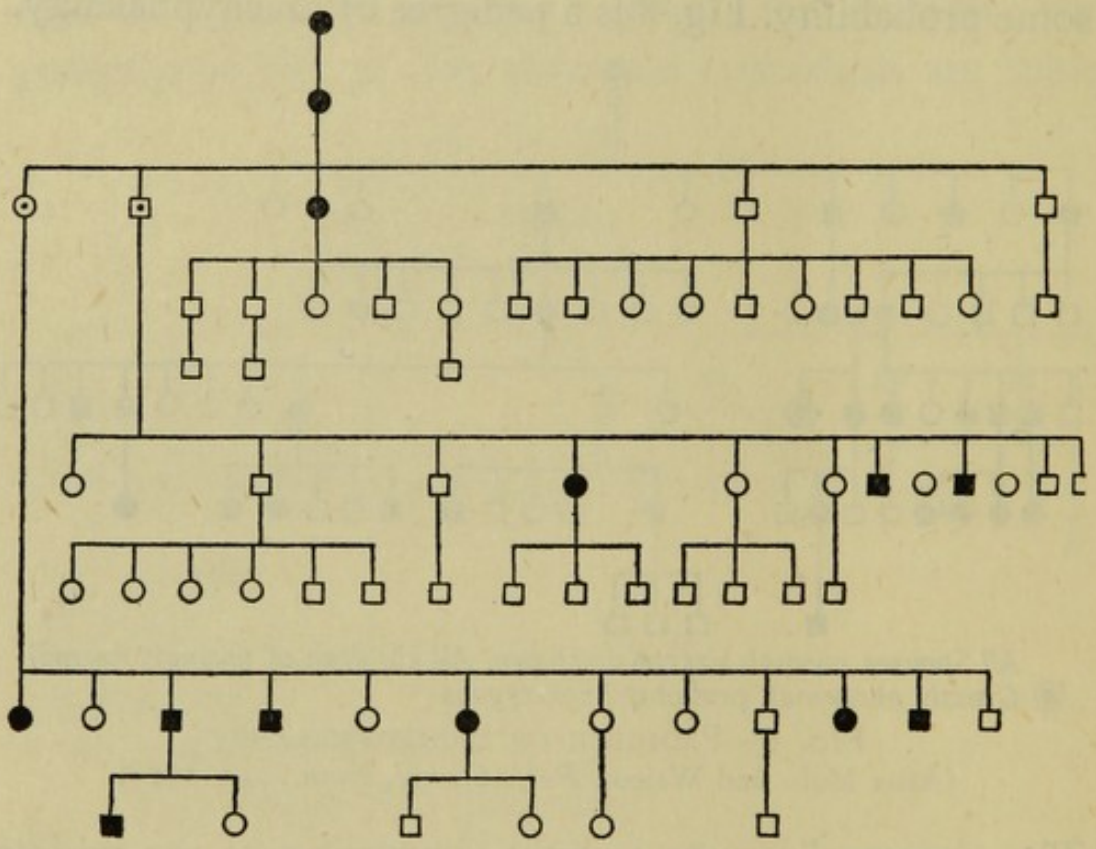


FIG. 9—PEDIGREE OF ACHOLURIC JAUNDICE
(After Campbell and Warner, *Q. J. Med.*, 19, 1926)

appear to be so much commoner than recessives in man, whereas the opposite is true in most animals and plants. There is another reason which we shall discuss later.

A good many dominant genes are irregular in their manifestation. Fig. 9 is a pedigree of acholuric jaundice, a disease in which haemolysis occasionally occurs, but

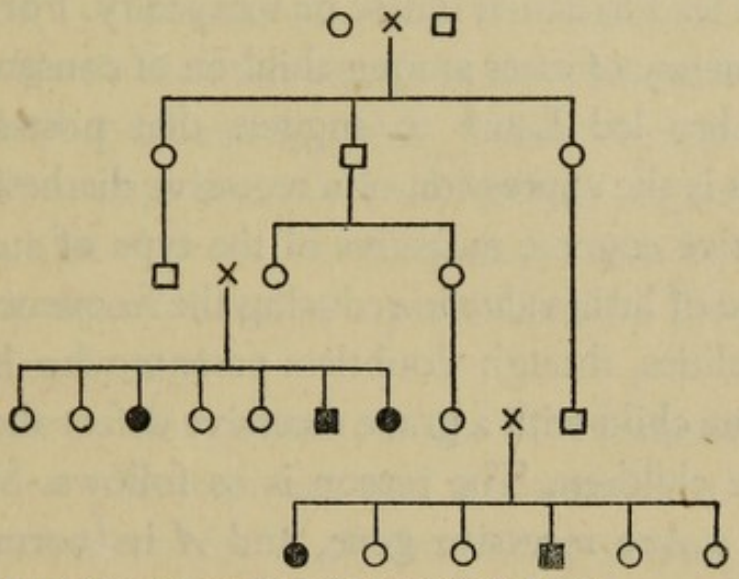
the bile pigments produced from the haemoglobin do not occur in the urine. It is sometimes fatal. It will be seen that the disease was transmitted by two individuals who did not manifest it. The abnormality of the patients showed itself even between attacks of jaundice, in fragility of the red corpuscles, some of which burst in 0·75 per cent NaCl solution, whereas normal corpuscles do not do so until it is diluted to 0·45 per cent. The two normal transmitters also had fragile corpuscles. But the conditions for a widespread haemolysis had never arisen in them. Here the disease showed itself in the majority of the persons carrying the gene, and the presence of the gene can readily be detected. We may speak of the gene as determining a diathesis, if not a disease. The fragility can be lessened to such an extent by splenectomy that no more attacks occur, whereas very little can be done for most hereditary abnormalities. For this reason the patients are often very grateful and co-operative, and it is much easier to compile pedigrees than in most such cases. It may be added that if it were desired to wipe out this condition by sterilization, it would be necessary to sterilize not only the unfit, but also healthy carriers of the gene.

A number of other abnormalities "run in families," that is to say, are transmitted over a number of generations, but often by healthy persons. These are thought to be due to dominant genes which only manifest themselves in a fraction of the individuals carrying them.

Where this fraction is large, negative eugenic measures are at least a practical possibility, whatever may be their ethical or political desirability. Sometimes, however, the diathesis is common but the disease rare. Sickle-cell anaemia is a fairly rare disease of American negroes. It is associated with jaundice and ulcers of the legs, and is generally fatal. The red blood corpuscles assume a peculiar sickle-shaped (or if a less politically tinged word be preferred, crescent-shaped) form. Some of the relatives of patients have a few sickle-shaped cells. This condition, which is called sickleaemia (a word which might well be replaced by drepanaemia or drepanocytosis), was found in 7 per cent of a large sample of coloured people in Baltimore, and is inherited as a dominant. Less than 1 per cent of those who carry this gene develop serious anaemia. Here eugenic measures are out of the question. The problem is to discover what causes the onset of severe anaemia, and if possible to use prophylactic measures to prevent this. A number of other anomalies of the blood, for example, the presence of oval red corpuscles similar to those of the *Camelidae*, which is also determined by a dominant gene, appear to be quite harmless.

A number of inborn abnormalities are generally described as familial rather than hereditary. They are rarely if ever transmitted from parent to child, but are often found in several sibs (brothers and/or sisters). In some cases familial diseases have been shown without much

doubt to be due to an autosomal recessive gene. Among the criteria are the frequency of consanguineous unions among the parents of the abnormals, and the frequency of abnormals in families which contain at least one. This is not, of course, 25 per cent, but somewhat more, since, for example, only seven-sixteenths of all families of two



All matings non-consanguineous except as shown

FIG. 10—PEDIGREE OF PERONEAL ATROPHY
(After Steinthal, *Arch. Rass. v. Gessell. Biol.*, 21, p. 425, 1929)

produced by the union of two heterozygotes include one or more recessives, and the total of such families including at least one recessive contains 57 per cent of recessives. The statistical technique for dealing with the problem has been discussed by Lenz, Weinberg and others, and recently by Haldane.[1]

Fig. 10 is part of a pedigree of recessive progressive muscular atrophy, beginning in the peroneal muscles of

[1] Haldane, J. B. S. (1938), *Ann. Eug.*, 8, pp. 255-62.

the legs. Besides frankly metabolic diseases, a good many nervous diseases are inherited as autosomal recessives. Many of these, for example, phenylketonuria and the amaurotic idiocies, have a metabolic basis, and others may turn out to have one. Just as with dominants, there are doubtless cases where the recessive diathesis may or may not lead to actual illness or incapacity. For example, the frequency of cases among children of consanguineous parents has led Lenz[1] to suggest that post-scarlatinal nephritis is the expression of a recessive diathesis.

Negative eugenic measures of the type of sterilization would be of little value in reducing the frequency of such abnormalities, though doubtless parents who have produced one child with a grave recessive defect should have no more children. The reason is as follows. Supposing a to be a rare recessive gene, and A its normal allelomorph, then most people are AA. Suppose a small fraction $2x$ to be Aa, then in a strictly out-bred population the frequency of recessive (aa) zygotes is x^2. Thus, if x^2 is $\frac{1}{40{,}000}$, $2x$ is 0·01, or 1 per cent of normal people carry the recessive gene. Actually the frequency of recessives is $ax + x^2$, where a is a number, about 0·001 in Britain, according to Haldane and Moshinsky,[2] which expresses the intensity of inbreeding. Thus, if $2x = 0{\cdot}01$, the

[1] Lenz, in Baur, Fischer, and Lenz (1931), *Human Heredity* (George Allen & Unwin).

[2] Haldane, J. B. S., and Moshinsky, P. (1939), *Ann. Eug.*, 9, pp. 321–40.

frequency is raised from 25 per million to about 30 per million. The frequency among the children of parents who are first cousins is $\frac{1}{16}x(1 + 15x)$, or in this case 336 per million. It follows that the total prevention of inbreeding would lead to a drop of only 17 per cent in the number of abnormals, and it would be wholly impracticable to root out the gene by sterilization, even if we could detect heterozygotes, which we cannot do at present. With rarer recessives inbreeding plays a greater part; thus, if $x = 0{\cdot}001$, the frequency could be reduced from about 2 per million to 1 per million by the prevention of inbreeding.

Some genes are carried on the *X* chromosome, of which a man possesses one and a woman two. A very few are carried on the *Y* chromosome, present in men only. At the lecture slides were shown of pedigrees illustrating the effect of a gene on the *Y* and of a dominant gene on the *X*. These are so rare as to be unimportant. However, a well-defined group of abnormalities is caused by recessive genes on the *X* chromosome, or more accurately on that part of the *X* chromosome which has no homologue in the *Y*. These are called sex-linked recessives, perhaps better completely sex-linked recessives. Such a gene is transmitted by an affected man to none of his sons, but all his daughters. The daughters are normal but heterozygotes, that is to say, transmitters. Half their sons are abnormal, and half their daughters

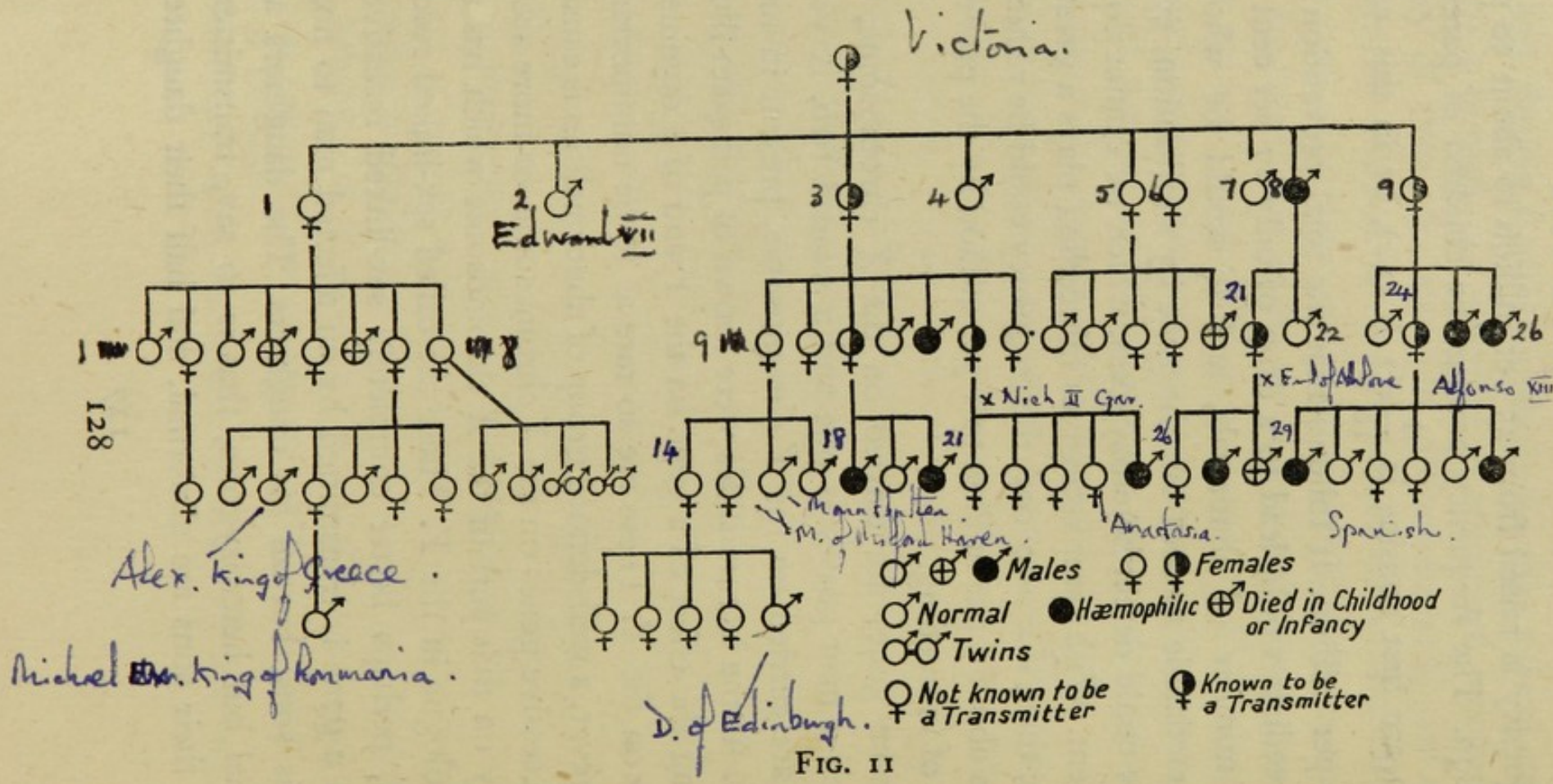

Victoria.
Edward VII
x Nich II Czar.
x Empress of Abyssinia
Alfonso XIII of Spain.
Alex. King of Greece.
Michael King of Roumania.
D. of Edinburgh.
Anastasia.
Spanish.
Males
Females
Normal
Hæmophilic
Died in Childhood or Infancy
Twins
Not known to be a Transmitter
Known to be a Transmitter

FIG. 11

I (1) Victoria 1819–1901, Queen of England.

II (1) Victoria 1840–1901, × Frederick, later Emperor of Germany. (2) Edward VII 1841–1910, King of England. (3) Alice 1843–1878, × Prince Louis of Hesse. (4) Alfred 1844–1900, Duke of Edinburgh. (5) Helena 1846–1923, × Prince Christian of Schleswig-Holstein. (6) Louise 1848–1940. × Duke of Argyll. (7) Arthur 1850– , Duke of Connaught. (8) Leopold 1853–1884, × Princess Helena of Waldeck. (9) Beatrice 1857– , × Prince Henry of Battenberg.

III (1) William II 1859–1941. Emperor of Germany. (2) Charlotte 1860–1919, × Duke of Saxe-Meiningen. (3) Henry 1862–1921, Prince of Prussia. (4) Sigismund 1864–1866. (5) Frederica 1866–1929. (6) Waldemar 1868–1879. (7) Sophia 1870–1932, × Constantine, King of Greece. (8) Margaret 1872–1937, × Frederick, Duke of Hesse-Cassel. (9) Victoria 1863–1924, × Prince Louis of Battenburg (Marquess of Milford Haven). (10) Elizabeth 1864–1918, × Grand Duke Sergius of Russia. (11) Irene 1866– , × Prince Henry of Prussia (III (3)). (12) Ernest 1868–1937, Grand Duke of Hesse. (13) Frederick William 1870–1873. (14) Alexandra 1872–1918, × Nicholas II, Tsar of Russia. (15) Mary Victoria 1874–1878. (16) Christian Victor 1867–1900. (17) Albert 1869–1931. (18) Victoria 1870– . (19) Louise 1872– . (20) Harold 1876–1876. (21) Alice 1883– , × Earl of Athlone. (22) Charles Edward 1884– , Duke of Albany. (23) Alexander 1886– , Marquess of Carisbrooke. (24) Victoria Eugenie 1887– , × Alfonso XIII of Spain. (25) Leopold, 1884–1922, Lord Mountbatten. (26) Maurice 1891–1914, Prince of Battenberg.

IV (1) Feodora Maria 1879–1898, × Henry XXX of Reuss. (2) George 1890– , King of Hellenes. (3) Alexander 1893– , King of Hellenes. (4) Helena 1896– , × Carol of Roumania. (5) Paulos, 1901– . (6) Irene 1904– . (7) Catharine 1913– . (8) Frederick Wilhelm 1893–1916, Prince of Hesse. (9) Maximilian 1894–1914. (10) Philipp 1896– . (11) Wolfgang 1896– . (12) Richard 1901– . (13) Christoph 1901– . (14) Victoria 1885– , × Prince Andrew of Greece. (15) Louise 1889– , × Crown Prince of Sweden. (16) George 1892– , present Marquess of Milford Haven. (17) Louis 1900– . (18) Waldemar 1889– , Prince of Prussia. (19) Sigismund 1896–1927. (20) Heinrich 1900–1904. (21) Olga 1895–1918, Grand Duchess. (22) Tatiana 1897–1918, Grand Duchess. (23) Marie 1899–1918, Grand Duchess. (24) Anastasia 1901–1918, Grand Duchess. (25) Alexis 1904–1918, Tsarevitch. (26) May 1906– , × Captain Henry Abel-Smith. (27) Rupert 1907–1928. (28) Maurice 1910–1910. (29) Alfonso 1907–1939, Prince of Asturias, Count of Covadonga. (30) Jaime 1908– (31) Beatrice 1909– . (32) Maria 1911– (33) Juan 1913– . (34) Gonzalo 1914– .

V (1) Michael 1921– King of Rumania. (2) Margaret 1905– × Godfrey of Hohenlohe-Langenburg. (3) Theodora 1906– , × Margrave of Baden. (4) Cecilia 1911-1937, × Grand Duke of Hesse. (5) Sophia 1914– , × Christopher of Hesse. (6) Phillipos 1921– , Prince of Greece.

FIG. 11.—PEDIGREE OF ROYAL HAEMOPHILIA

heterozygous. The disease only appears in females when an abnormal man has children by a heterozygous woman.

The commonest disease transmitted in this way is colour-blindness, which is present in about 2½ per cent of Western European males, while the most serious is haemophilia. Fig. 11 represents the pedigree of haemophilia in some of the royal families of Europe. Full details are given by Haldane.[1] I wish to add that Dr. Waardenburg informed me at Groningen that the brothers (III 4 and III 6) of Kaiser Wilhelm II of Germany, who died young, were almost certainly not haemophilics. In this pedigree it was, for obvious political reasons, difficult to obtain sure evidence that a given individual was haemophilic. The opposite holds for other pedigrees, as some members of haemophilic families, who were actually normal, appear to have been reported as haemophilics in order to avoid military service. Such are some of the impacts of politics on genetical research!

Certain sex-linked genes are incompletely recessive, giving rise to a much milder abnormality in heterozygous females than in affected males. One such is anidrotic ec.odermal dysplasia, in some pedigrees at any rate. The males have no sweat glands and very poor teeth and hair. The females can sweat to some extent, and their teeth and hair are less affected.

It is possible that a few well-defined abnormalities are cytoplasmically transmitted, that is to say, are trans-

[1] Haldane, J. B. S. (1939), *Keeping Cool* (London).

mitted by an affected female to all her children, whilst a male does not transmit them. Imai and Moriwaki[1] believe that the diathesis of Leber's disease (hereditary optic atrophy) is transmitted in this manner. If so, it is not obvious why it should be far commoner in men than women. Other workers consider that it is due to a sex-linked gene which is incompletely recessive, and occasionally shows up in heterozygous women.

A point which should be stressed is the remarkable simplicity of the type of inheritance shown by a large number of abnormalities, including all those so far discussed. In every instance the difference between an abnormal and a normal depends on a single gene, or in the case of recessives on two genes in the same locus. The main gene may of course be associated with modifiers, a point to which we shall come back later. These may even sometimes suppress its action. But no clear case has yet been adduced where two genes in different loci are needed for the production of an abnormality, although Hogben[2] has suggested with some plausibility that this may be so for ateleiosis, one type of dwarfism. I think that the pioneers of Mendelism would have been surprised at the simplicity of the genetics of much human disease. They were accustomed to find a large number of gene differences between animal breeds. For example, the silkie fowl differs from the normal in respect of its

[1] Imai, Y., and Moriwaki, D. (1936), *Journ. Gen.*, 33, pp. 163–68.
[2] Hogben, L. (1932), *Journ. Gen.*, 25, pp. 211–40.

crest, its small double comb, its feather structure, its absence of feather pigment, and its black dermal pigment, all of which are due to distinct genes. Doubtless a god who went in for "fancy" human breeding could have produced a race combining albinism, monilithrix, acrocephaly, brachydactyly, and webbed toes, each due to a different gene. But even in animals cases are rare in which the compresence of several genes in different loci, each without effect by itself, is needed to produce an abnormality. Such cases are frequent in polyploid plants, but this is because they possess two or more sets of chromosomes, each with very similar genes.

Doubtless where an abnormality is a graded character, like stature, it will be found that a number of genes are concerned, reinforcing one another in a complicated manner. This will probably turn out to be the case for susceptibility to the commoner types of cancer, a disease whose onset also depends on environmental factors, such as exposure to irritants, sexual activity or inactivity, and so on. Only a few of the rarer types of cancer, for example, those which result from polyposis coli, xeroderma pigmentosum, and neurofibromatosis, seem to be controlled mainly by a single gene. The results obtained on inheritance of tumours in *Drosophila melanogaster* prove that more complex cases can be analysed. But a prerequisite to the analysis was the establishment of data on linkage which made it possible to locate a gene in a particular chromosome. We shall see in the

next chapter how the human chromosomes are being mapped.

Let us now turn to the question of mental defect, which is to a very large extent congenital. This is most simply shown from the data of Diehl and v. Verschuer,[1] who found that if one of a pair of twins was a mental defective, the monozygotic co-twin was also a defective in 88 per cent of the cases studied, the dizygotic co-twin in 7 per cent of cases only. Earlier workers on the subject played with the truly fantastic idea that all or most cases of mental defect were due to a single gene. Now, where an organ can be carefully examined, we find that it is subject to very many different congenital diseases. Cockayne[2] lists one hundred and twelve different genes responsible for skin diseases, and Waardenburg's[3] monograph discloses the existence of nearly as many genes for eye diseases. This is so for the very simple reason that the skin and the interior of the eye can be examined during life, and differential diagnosis has gone very far. On the other hand, we know very little concerning the types of congenital deafness, because the internal ear cannot be examined during life, and, as it lies in the body's hardest bone, it is not even very accessible after death. The

[1] Diehl, K., and v. Verschuer, O. (1933), *Zwillingstuberkulose*, pp. 122–25.

[2] Cockayne, E. A., *Inherited Abnormalities of the Skin and its Appendages*, Oxford University Press, 1933.

[3] Waardenburg, P. J. (1930), *Das menschliche Auge und seine Erbanlagen. Bibliographia Genetica.* Nijhoff. 's Gravenhage.

cerebral cortex is much more complicated than the eye, and it would be most surprising if it did not go wrong for a greater variety of causes. If we had tried to investigate the inheritance of blindness, instead of that of cataract, retinitis pigmentosa, optic atrophy, and so on, one at a time, we should never have got far. And yet there are people who still claim to investigate the inheritance of mental defect as a well-defined character, and even to base eugenic programmes on their results.

"Non ragioniam di lor, ma guarda e passa."[1]

We pass on to the work of Penrose,[2] who studied 1,280 mental defectives in an institution at Colchester, and 28,921 of their relatives. This work has lifted the whole study to a new and higher level. Penrose's first task was a diagnosis of specific disease in as many cases as possible. Table 5 summarizes certain of his results. The diagnosis was, of course, much more detailed. For example, the group in which head injuries were diagnosed was about equally divided between injuries at birth and afterwards. The victims of inflammatory disease included cases of encephalitis and meningitis. The endocrine group included thyroid and multiple cases. The neurological group included victims of seven different diseases with neurological symptoms, for example, several different

[1] "Let us not speak of them, but look and pass on," as Dante said about certain particularly futile persons on the borders of hell.

[2] Penrose, L. S. (1938), Medical Research Council, Special Report Series, No. 229.

types of paralysis, some of which are diseases of known or suspected genetical determination. For example, Penrose brings forward strong evidence that congenital

TABLE 5

1,280 MENTAL DEFECTIVES

(After Penrose)

Diagnosis	Per cent	Per cent M.D. Parents	Per cent Related Parents
Syphilis	3·9	6·0	0·0
Trauma	1·9	0·0	0·0
Inflammation ..	1·6	7·1	0·0
Endocrine	6·9	5·1	3·4
Mongolism	4·9	1·6	1·6
Neurological ..	7·5	2·5	9·5
Skeletal	11·1	4·2	4·2
Epileptic	16·4	6·9	3·8
Miscellaneous ..	6·8	5·2	3·4
Psychopathic ..	15·9	6·4	3·4
?	24·1	14·6	2·9
Total	100·0	7·7	3·5

diplegia is due to a recessive gene. The group with skeletal defects included microcephalics, others with cranial and spinal defect, and a smaller number showing defects such as syndactyly which have no obvious causal association with mental defect. The miscellaneous group

included such well-defined clinical entities as phenylketonuria and epiloia. The psychopathics showed emotional disturbances. Finally, about one-quarter of the total had no associated defect. In this group the mental defect was generally of a fairly mild character.

Syphilis can, of course, be made into a rare disease by a combination of medical and social measures. Medical students in Denmark must travel abroad to see serious cases. A congenital syphilitic child was shown to me as a great rarity in an Amsterdam children's hospital. Unfortunately I had seen a number of them in England. The abolition of syphilis is a very important eugenic measure, but its discussion lies outside the scope of this book. Some of the traumatic cases would have been saved by a better obstetrical service. Perhaps a third of the endocrine cases were cretins, who could have been made nearly normal by sufficiently early thyroid medication, and many of the others suffer from syndromes which will be treatable at a future date. Finally, it is likely that a large fraction of the psychopathic group are described as mental defectives because they cannot or could not be educated. Their mental defect was generally fairly mild. In a substantial fraction of these cases it is likely that psychiatric methods would have rendered them sufficiently normal to pass out of the class of mental defectives. Thus anything from 5 per cent to 20 per cent of the mental defect could have been prevented or cured by hygienic measures. Probably the most important of

these is psychiatry, which has a great field among children.

The percentage of mentally defective parents is somewhat misleading. Mental defect is not a sharply marked character. The figures given refer to parents whose "mental ratio" corresponding roughly to I.Q. was considered to be below 70 per cent, or whose "mental age" was under ten years. Of course some persons with a mental age over ten are certified as defectives, and some with a less mental age escape certification. However, the third column of Table 5 allows us to give a rough answer to the question, "What proportion of mental defect would have been avoided had all persons with a 'mental age' under ten years been prevented from breeding?" In 1·6 per cent of cases both parents were defectives by this standard, in the remainder one or both parents were normal. Thus, if all defective parents had been sterilized or segregated, 15 per cent of these mental defectives would not have been born. However, intelligent eugenical measures might have had a slightly greater effect. For among the defectives we find cases where the parents suffered from well-defined dominant diseases such as epiloia, neurofibromatosis, and Huntington's chorea, which may cause mental defect, but did not always do so in the case of these parents. And among the epileptics there were 17 per cent of cases where one or both parents were epileptic, though not generally mental defectives. Thus negative eugenic measures of

one kind or another might have eliminated 20 per cent or less of all cases. Heredity is strongest in the undefined or residual group, which are mostly mild, and seem to represent the "tail" of the normal distribution of intelligence. If so, their condition is due to the compresence of a number of genes, none of which by itself would produce mental defect if substituted in a normal individual.

The last column gives parental consanguinity. In the hospital population the corresponding rate is about 0·6 per cent according to unpublished work which Dr. Julia Bell kindly allows me to quote. The most striking amount of consanguinity is found among the neurological cases, where congenital diplegia appears to be due to a recessive gene or genes which, however, do not have a constant effect. Thus, among the sibs of diplegic defectives occurred defectives who were not paralysed and diplegics who were not defective, whilst one case of microcephaly with hemiplegia had a mentally normal but diplegic sib. Another consanguineous union was responsible for the only case of cerebromacular degeneration in the series. Other recessive defects with high consanguinity among the parents were phenylketonuria and deaf-mutism. We may conclude that recessive genes are less important than partially dominant ones, but that a total prevention of inbreeding would have prevented 3·5 per cent of the mental defect observed. No less than 13 per cent of the consanguineous unions were illegal (uncle-niece) or incestuous (brother-sister); 56 per cent

were first-cousin marriages. Thus, if unions of first cousins and closer relatives could be prevented, about 2·5 per cent of mental defect would be abolished.

Thus we see that three methods are available in the prophylaxis of mental defect. Ordinary hygienic measures and segregation or sterilization would eliminate about 15 per cent each, whilst the prevention of inbreeding would have a slight but not negligible effect. If we are to eliminate mental defects of genetical origin or to reduce them to the lowest possible level, we shall have to find means of detecting irregularly dominant genes in individuals who are not defective, and recessive genes in heterozygotes. Two methods are available. In the first place such genes may be detectable by actual examination of individuals. Penrose has shown how this may be attempted. On the one hand, epiloia (tuberous sclerosis) and neurofibromatosis (von Recklingshausen's disease) are dominants which only give rise to mental defect if the tumours characteristic of them occur in certain parts of the brain. But sufferers from these diseases, whether defective or not, should not breed. On the other hand, heterozygotes for certain recessives are not completely normal. Thus heterozygotes for phenylketonuria seem fairly often to develop senile dementia. If this condition could be recognized early in life, it might be possible to eliminate it gradually, and to forbid or discourage unions of two heterozygotes. The second method involves the mapping of the human chromosomes, which will be

discussed in the next chapter. But either of these methods involves, as a preliminary, the classification of mental defects, and an analysis of their genetical basis. Here Penrose has made a substantial contribution by demonstrating the recessive nature of phenylketonuria and diplegia, which between them accounted for 5·3 per cent of his cases. But a century may elapse before even a majority of cases of mental defect can be assigned to their proper genetic basis. This will be important for the following reason. Just as to-day we can say that, in order to think, a man must be able to metabolize phenylpyruvic acid, we shall be able to state a number of other similar conditions. This will inevitably give us a good deal of information concerning the physico-chemical basis of mind which could hardly have been obtained by any other means.

We must now try to answer some very fundamental questions. Some dominant genes affect every individual carrying them. It would therefore appear at first sight that they must have been transmitted through an unbroken series of abnormals from the remote past. In particular, if we believe that the whole human race was descended from Adam and Eve, or Noah and his wife, these individuals must have combined a fantastic series of dominant physical and mental defects, besides being heterozygous for hundreds of recessives. If we do not believe in the existence of these persons, we probably believe that in palaeolithic times man was a comparatively

rare animal. If so, it would seem at first sight that abnormal genes must have been very common in palaeolithic man. Looking at the question from a Darwinian standpoint, the matter becomes even more contradictory. Some dominant genes considerably lower the fitness of their carriers. By this I mean fitness in a strictly Darwinian sense. I do not mean fitness for football, music, war, love, or mathematics. I mean a quantity which can be given a definite numerical value. Its exact specification is a complicated matter involving a number of integrals, as may be seen from the discussion on pages 25–35 of Fisher's *The Genetical Theory of Natural Selection*; and even Fisher's treatment is not final. I shall content myself with defining fitness in the case when generations do not overlap, as in annual plants or insects, and where the sexes are present in equal numbers at birth or hatching. In this case the fitness of a genotype is the mean number of offspring produced by an individual of that genotype, if the species is hermaphrodite, or half that number if the species is bisexual. The individuals must be counted at corresponding times in each generation. If the fitness exceeds unity the number of members of the genotype will increase, if it is less than unity it will diminish, provided that Mendelian segregation occurs. A loss of fitness may be due to subnormal survival or subnormal reproduction. In a series of papers[1] I have

[1] Bibliography in Haldane, J. B. S. (1932), *The Causes of Evolution* (Longmans, Green).

worked out the theoretical effects of various situations as regards fitness (for example, the way in which a population will change when mating is at random and a dominant genotype is eliminated in one sex only, as in animal breeding where fathers but not mothers are rigidly selected).

For our purpose it is sufficient to note that if the fitness of a rare dominant, divided by that of the general population, is f, the frequency after n generations will be the original frequency multiplied by f^n. Thus, if $f = \frac{1}{2}$, the frequency will be reduced to one-millionth in twenty generations, and in practice the gene will become extinct. Sex-linked recessives are extinguished rather more slowly. Approximately one-third of such genes are exposed to selection at any moment. The frequency of recessive males diminishes approximately in a geometric series whose common ratio is $\frac{1}{4}(\sqrt{8f+1}+1)$. Thus, if $f = \frac{1}{2}$, the frequency of recessives in each generation is 80·9 per cent of that in the preceding one, and it is reduced to one sixty-ninth in twenty generations. On the other hand, in an outbred population autosomal recessives are very slowly eliminated, because the vast majority of the genes are in heterozygotes, and not exposed to selection. Thus, if the fitness is zero, as in the case of infantile and juvenile amaurotic idiocy, then in a random mating population the frequency is reduced from $\frac{1}{c^2}$ to $\frac{1}{(c+n)^2}$ in n generations. Thus in twenty

generations it would only be reduced from one in 10,000 to one in 14,400. The slight degree of inbreeding which exists in most human populations would increase this rate, but would not double it.

All these calculations have their value, like calculations about perfectly smooth surfaces and perfectly elastic balls. But they neglect the fact of mutation. By mutation I mean the process by which new genes arise. In the pedigree of Fig. 7 the woman who first showed the abnormality was the daughter of highly respectable parents, both free from it, as were her five sibs. The abnormality is very rare; in fact it was unknown until 1938. It is, of course, possible that her mother committed adultery with one of the very few men in England suffering from the complaint in question. But seeing that rare dominants must arise at some time or other by mutation, I think it is far more likely that mutation occurred. Certainly mutation has been observed in animals or plants on many thousands of occasions where any such explanation is absolutely excluded. Mutation is a wide term, used to cover on the one hand changes in a single gene and on the other structural changes in one or more chromosomes, sometimes producing an effect visible under the microscope. Mutations involving a single gene may be conceived of as happening in two ways. The gene may change, and the changed gene may then reproduce. Or the process of reproduction may go wrong, one of the "daughter" genes being a bad copy of the other, a copy

which is subsequently reproduced. We may compare these possibilities with glosses on the one hand and copyists' errors on the other in the reproduction of ancient manuscripts. There is good evidence that X-rays produce mutations of the first kind. The work of Anderson-Kotto[1] on variegated ferns suggests that the second sometimes occurs.

Here I must mention a controversy on human mutation between Professor Sirks[2] and myself.[3] He agrees with me that the gene for haemophilia suddenly appears in families where it has not been known before. But he thinks that this event is due to a chromosomal rearrangement by which the gene, which was previously present in a *Y* chromosome, crosses over into the *X*. I have given reasons for doubting this interpretation. It may be that as a Marxist I am prejudiced in favour of the view that mutation involves real novelty, and not a mere rearrangement. But at least I have given a variety of other arguments in favour of my opinion. Only posterity will decide whether Professor Sirks or I was right. But, fortunately, the nature of the mutational process has no bearing on the argument which follows.

However a gene for haemophilia appears in the *X* chromosome, it does so abruptly. Queen Victoria had such a gene in one of her *X* chromosomes. Her father

[1] Anderson-Kotto, I. (1930), *Zeit. Ind. Abst. u. Vererb.*, 56, pp. 115–201.

[2] Sirks, M. J. (1937), *Genetica*, 19, pp. 417–22.

[3] Haldane, J. B. S. (1938), *Genetica*, 20, pp. 423–30.

did not carry it, for he was not haemophilic. Her mother may have been heterozygous. If so, she did not give the gene to her other son, nor was it present in a number of her male ancestors and other relatives. We can be sure of this, since, owing to the craze for bleeding in the medical profession in the late eighteenth and early nineteenth century, haemophilia would certainly have been fatal to any member of a royal house, even if a poor man, less exposed to the doctor's lancet, might have survived.

Now mutation, as in this case, increases the number of harmful genes in the population, whilst selection lowers it. If mutation and selection go on at steady rates, and the breeding system of the population does not alter, they will come into equilibrium, as I pointed out in 1927.[1] The equilibrium values can easily be calculated in a stationary population. Just as many genes are eliminated by natural selection as arise by mutation. If N be the number of births per year, x the frequency of the abnormality, f its fitness, and μ the frequency of mutation per chromosome per generation, then in the case of a rare autosomal dominant the number of new cases per year is $2\mu N$, while the number eliminated is $(1-f)xN$. So $x = \frac{2\mu}{1-f}$, or $\mu = \frac{1}{2}(1-f)x$. Thus the mutation rate can be roughly calculated from the frequency. For severe diseases f is less than $\frac{1}{2}$, so the mutation rate is from a

[1] Haldane, J. B. S. (1927), *Proc. Camb. Phil. Soc.*, 23, pp. 838–44.

half to a quarter of the frequency. Similarly, in the case of an autosomal recessive, $\mu = (1 - f)x$, and in that of a sex-linked recessive $\mu = \frac{1}{3}(1 - f)x$. It can further be shown that in the case both of dominants and sex-linked recessives equilibrium is reached very quickly.

On the basis of this extremely simple argument Gunther and Penrose[1] and Haldane[2] simultaneously calculated the rates at which two abnormal human genes arose by mutation from their normal allelomorphs. Penrose dealt with epiloia, an autosomal dominant which causes tumours in the brain, heart, kidneys, and other organs, and characteristically a peculiar butterfly-shaped rash on the face. It lowers fitness so severely that a pedigree rarely lasts for three generations, and a large fraction of all cases is sporadic, that is to say, due to mutation. Pedigrees of haemophilia are often somewhat longer, because two-thirds of the genes are in women, and therefore shielded from selection. However, it lowers the fitness even more drastically, the fitness of haemophilics being less than one-quarter, since the majority die before they are old enough to beget children.

In each case the mutation rate is about 10^{-5}, that is to say, about one normal gene per 100,000 mutates to its abnormal allelomorph in each generation. These figures may well be out by a factor of 2 or 3, but the rate can hardly be as high as 10^{-4} or as low as 10^{-6}.

[1] Gunther, M., and Penrose, L. S. (1935), *Journ. Gen.*, 31, pp. 413–423. [2] Haldane, J. B. S. (1935), *Journ. Gen.*, 31, pp. 317–26.

If mutation is equally likely to occur at each nuclear division, the rate per division is about 10^{-7}, since there are about 2^{47} cells in a human body, and though the number of divisions in the germ track is unknown, it is probably of the order of fifty per life cycle. The genes in question are among the most mutable in man, so any human craftsman cannot but admire a process which at its worst goes wrong about once in ten million times. The corresponding rates in *Drosophila* per generation are rather less, being between 10^{-5} and 10^{-6} for the most mutable genes, such as the normal allelomorph of white eye. However, the *Drosophila* rates per year are much greater.

In a few pedigrees haemophilia is a comparatively mild disease, causing an occasional death only, but some of the haemophilics can live a fairly normal life, and many marry, and hand the disease on to their daughter's sons. In these pedigrees the fitness is probably well over one-half. We are dealing with a different gene, since all the haemophilics in one pedigree are mildly affected, so that modifying genes cannot be responsible. But as both the genes for haemophilia are sex-linked recessives they are almost certainly allelomorphs. It follows that the mutational process gives rise to the mild allelomorph much more rarely than the severe one, perhaps only about 1 per cent as frequently. For, of course, when the mild gene once occurs it is much more slowly eliminated than the severe one. Here again there is a full analogy with

animal data. In *Drosophila melanogaster* the eye colour mutates to white more frequently than to all its allelomorphs, such as apricot, eosin, and cream, put together. In the domesticated rodents albinism appeared before the allelomorphic genes intermediate between albinism and full colour, such as chinchilla, "Himalayan," and extreme dilution. It is remarkable that, though we know rather little about some aspects of human genetics, such as linkage and the determination of hair and eye colour, which are well understood in rabbits and mice, we know more about others. Thus more different genes are known in man than in any other animal except some *Drosophila* species. And man is the only vertebrate in which mutation rates are even roughly known. These facts are so because in man a very rough genetical survey has been made of some hundreds of millions of individuals, and occasionally we have fairly accurate knowledge of the frequency of an abnormality in a population of some millions, for example, that of Sweden or of Greater London.

In the case of dominants and sex-linked recessives a large fraction of the mutant genes in the population are exposed to selection, and therefore most human populations are near to equilibrium, though, of course, the progress of medicine has raised the fitness of some unfit types, and mutation rates may have altered in either direction as the result of recent environmental changes. If so, however, our estimates are of average mutation

rates during the last few generations, and are quite valid so far as they go. But autosomal recessives are nowhere near equilibrium, and will not be for many thousand years, so far as can be seen at present.

Common sense shows that the approach to equilibrium is very slow. Suppose that we had a population mating at random in which there are a million births per year. By a population "mating at random" I do not mean one practising sexual promiscuity, but one in which an individual is no more and no less likely to mate with a relative than an unrelated person, and no more and no less likely to mate with a person heterozygous for the same recessive gene as himself than with a homozygous normal. Suppose such a population to be originally free of a recessive gene, but that mutation suddenly begins at a rate of one per hundred thousand. For simplicity suppose the recessive to have a fitness of zero. Then at equilibrium ten babies per year on an average will be born with the disease. Under these circumstances 0·63 per cent of the population will be heterozygous for the gene. Even if there were no selective elimination it would take 316 generations, or about eight thousand years, for this state to be reached. Allowing for elimination, it will take 175 generations to reach half-way to equilibrium, about 300 to reach three-quarters of the distance to equilibrium, and more than 1,000 before the equilibrium is closely approached. In a moderately inbred population, where, as we saw, the number of heterozygotes is slightly

less for a given proportion of homozygotes, the rate of approach is slightly quicker, but still of the same order. The time needed to reach even half-way to equilibrium is measured in thousands of years.

Now the equilibrium has been upset, and very sharply upset, within historic time. In mediaeval Europe most of the population were peasants. The burghers were a small fraction of the population, and hygienic conditions in the towns were probably so bad that the death-rate was higher than the birth-rate. The rural population was highly inbred, most marriages taking place within a village or a small group of neighbouring villages. Even where the canon law was strictly observed, spouses were generally related to some extent. Under such conditions recessive genes generally come together in a homozygote within relatively few generations of mutation. Equilibrium is reached within a few centuries. This condition prevails to-day in many primitive peoples. Of course the genes are not evenly spread. In any particular community most recessives will be absent, but one or two may be far above the equilibrium value for the population as a whole. In a few tribes albinism is very common. The important and careful researches of Sjögren[1] have disclosed groups of villages in northern Sweden where particular types of recessive mental defect are extremely common among the peasants.

Such must have been the situation in mediaeval Europe.

[1] Sjögren, T. (1935), *Ann. Eug.*, 6, pp. 253–318.

Perhaps the majority of villages were unaffected, but here would be a group in which albinism was very prevalent, there microcephalic idiocy, foetal ichthyosis, or some then unrecognizable metabolic disease such as cystinuria, condemning its victims to a lingering and very painful death from "the stone." Doubtless in such cases a local saint was credited with the prevention or cure of the local malady. Then came the gradual growth of towns, and finally the industrial revolution. The villagers flocked into the towns. A man from Toller Porcorum heterozygous for albinism no longer married his third cousin from Toller Monachorum carrying the same defect, but a woman from Yspitty Yfan or Helions Bumstead heterozygous for xeroderma pigmentosum. Neither of these recessives appeared in their children. This process is probably not yet complete. The frequency of first-cousin marriages in Prussia fell from 0·71 per cent in 1875–80 to 0·20 per cent in 1921–26, and may still be falling. On the other hand, the corresponding French figure is steady at about 1 per cent over the same period. The frequency of recessive zygotes fell drastically. But as selection was suspended the frequency of the genes began to rise as a result of mutation. This process, as we saw, is exceedingly slow. I have calculated[1, 2] that in some cases the frequency of recessives is now about 5 per cent of its

[1] Haldane, J. B. S. (1939), *Ann. Eug.*, 9, pp. 232–37.

[2] Haldane, J. B. S. (1940), *Ann. Eug.*, 10, pp. 417–21 (corrects an error in above paper).

equilibrium value, and that it will only rise to half its equilibrium value in three thousand to thirty thousand years, depending on the mutation rate.

There is a most interesting exception to this general rule. It is furnished by the Jews, among whom inbreeding, in some countries at least, is very high, probably as high as among the peasants of mediaeval Europe. In fact, in the calculations referred to I assumed for mediaeval Europe the coefficient of inbreeding actually found among the Jews of Hohenzollern, and also among another religious minority, an isolated Protestant community surrounded by Catholics in South Germany. The Jews are no more afflicted by dominant abnormalities such as Huntington's chorea or sex-linked recessives such as anidrosis than the rest of humanity. Perhaps they are rather less so, since eugenic ideas of a rather primitive kind are prevalent among them, and circumcision eliminates many haemophilics in infancy. But they are very prone to autosomal recessive diseases such as the amaurotic idiocies and haematoporphyria. This is not due to any "racial taint." In fact, calculation shows that the genes for these diseases must be unusually rare among Jews, because inbreeding leads to a greater selection against them. It is a matter for investigation whether some of the other respects in which Jews differ from their neighbours are due to their inbreeding rather than to their genetic make-up on the one hand or their peculiar traditions on the other.

In the above discussion I have assumed complete recessivity. Penrose believes that this is not true for a number of genes, which when homozygous cause grave mental defect and, when heterozygous, mild psychoneurosis or senile dementia. If so, selection on heterozygotes will have an important effect, and it is possible that in some existing societies selection may favour genes reducing intelligence or self-control.

We can now see a second reason for the rarity of human recessives. They are not rare because recessive mutations are any rarer than dominants. On the contrary, recessive mutations are probably much commoner. For example, juvenile amaurotic idiocy, which is recessive, has a frequency of $3 \cdot 8 \times 10^{-5}$ among all births in Sweden. If it is well below its equilibrium frequency, as seems certain, that frequency, and therefore the mutation rate, may be as high as 10^{-4} or even higher. Human recessives are rare because geneticists have confined their studies almost completely to the peoples of Western Europe, North America, and Japan, among whose ancestors inbreeding has rather recently been relaxed. Of these, Japan is the most inbred, and it is noteworthy that one recessive condition, Oguchi's disease of the retina, was described in Japan before any cases were studied in Europe. Nevertheless, in the next few thousand years the frequency of recessive diseases will gradually increase in urbanized communities, unless we can find means of detecting recessive genes and either eliminating them or

at least preventing them from coming together. There is still another possibility, namely, that a way will be found of preventing mutation. If so, I hope that this road will not be taken. For mutations are the raw materials of evolution, and if our descendants forgo the possibility of further evolution in order to abolish a few congenital defects they will show themselves to be as short-sighted as we are to-day.

One obvious method for the discovery of human recessive genes has recently been taken by the Medical Research Council. This body supported an enquiry at a number of hospitals concerning consanguinity among the parents of patients. Over seventy thousand cards were filled in by hospital authorities and analysed by that indefatigable investigator Dr. Julia Bell, who kindly permits me to quote from her work now in the press. It was hoped that a number of conditions would be more frequent among the children of consanguineous parents than among the general population, and that thus new recessive conditions would be discovered. Actually Bell lists twenty-nine conditions in which the consanguinity rate appears to be high. Some of these, such as steatorrhoea, muscular dystrophies, and juvenile diabetes, have already been attributed, in some cases at least, to recessive genes. Others, such as congenital luxation of the hip, talipes, and osteo-arthritis, are novel suggestions, and further investigation is called for. The most striking item on the list is cancer of the uterine cervix. Bell's

negative evidence is equally striking. There is, for example, no suggestion of recessivity for goitre, hernia, pyloric stenosis, harelip, cervical ribs, or spina bifida. The publication of Bell's work will be of great importance for human genetics.

We see the human races, then, as battlegrounds for a struggle between mutation and selection, just as the continents are battlegrounds between orogenesis and erosion. I do not flatter myself by suggesting that a first attempt to describe this struggle is not incorrect in many details. Such a struggle never leads to a mere equilibrium. The geological struggle has given us the whole series of sedimentary and many of the igneous rocks. The struggle between mutation and selection has given us, not only human congenital defects, but probably most of the wide range of innate human diversity. Evolution, on the other hand, if we accept a modified Darwinism, has been largely brought about by the rare cases where mutations, either singly or several at a time, increased fitness. But the actual struggle has, I believe, had evolutionary effects. Fisher[1] was the first to suggest this, in connection with his theory of the evolution of dominance, a theory which I can only accept to a limited extent. Whatever view we may take on this question, there is no doubt that genes which reduce the unfitness of mutants will for that reason tend to spread through the population. They will almost invariably have some other effects, and thus a species

[1] Fisher, R. A. (1931), *Biol. Rev.*, 6, p. 345, and other papers.

will change, however slightly and slowly. We have here a possible purely internal cause for evolution, which may account for some slow evolutionary trends. In the next chapter we shall consider the evidence for the existence of such modifying genes.

As a result of the struggle between mutation and evolution, a human population includes not only grossly unfit genotypes, but large numbers of slightly unfit ones. In fact, for a given mutation rate, a genotype which reduces the fitness by 1 per cent will be a hundred times as common at equilibrium as one which reduces it to zero. These slightly disadvantageous genotypes may be of value in two ways. They may be of supernormal fitness in a different environment, and thus render a race elastic against environmental changes, and they may be of value to society. The most intelligent men and women are not necessarily the most healthy and fertile. Further, it is probable that too great genetical homogeneity would be unfavourable to social development. Differentiation of function is a prerequisite of civilization, though the Soviet Union has shown that class divisions are not; and this differentiation can probably develop most easily where there is a fair amount of innate diversity. Such a discussion inevitably leads us outside the field of genetics. I have only included it because I have desired to show that the struggle between mutation and selection is of very great importance from a number of standpoints. I believe that when its implications are fully worked

out it will be seen to be one of the major facts of biology.

Naturally enough, given the philosophy prevailing in that country, this problem is being attacked in the Soviet Union. For example, Olenov, Kharmac, Galkovskaya, and Muretov[1] summarize their own work and that of Dubinin and his colleagues on the annual cycle in populations of *Drosophila melanogaster*. These go through a "mediaeval" phase in winter when they consist of small isolated groups, and lethal and sub-lethal recessive genes are eliminated. In the summer the populations are larger and more mobile, and such genes accumulate. Thus in the life of *Drosophila melanogaster* a year corresponds to the two thousand years or so between the peaks of the Greco-Roman civilization and of our own.

[1] Olenov, J. M., Kharmac, I. S., Galkovskaya, K. F., and Muretov, G. D. (1939), "Factors Responsible for the Genic Composition of Wild *Drosophila melanogaster* Populations," *C.R. Ac. Sci.*, U.R.S.S., 24, p. 466.

CHAPTER 5

The Formal Genetics of Man

"Considerate la vostra semenza."[1]

DANTE, *Inferno*, 26, 118.

AFTER the Morgan school had shown the possibility, in *Drosophila*, of locating genes at different points in the chromosomes, it was clear that the genetics of any organism would include, not only an account of its genes, and of their interaction during development, but also a map of the chromosomes based on their linkage relations. Such mapping is fairly fully accomplished in some species with small chromosome numbers, such as maize with ten pairs, and a good deal is known about linkage in the mouse, with twenty pairs, and the rabbit, with twenty-two. But this was carried out by careful and very systematic experiment. When a new gene appears in the mouse it is tested with a number of other genes simultaneously, and linkage detected if possible. Experimental methods are out of the question in man, and we must search for individuals who are segregating for two or more gene pairs at a time. The statistical technique suitable for such investigations was first worked out by Bernstein.[2] I showed that some of his methods could be

[1] "Consider your origin."

[2] Bernstein, F. (1931), *Z. Ind. Abst. u. Vererb.*, 5, p. 113.

improved, but my own were unduly cumbrous, and were greatly simplified by Fisher.[1] When, however, I actually discovered (or claimed to have discovered) linkage in man, and attempted to estimate it, it became clear that Fisher's methods were not ideal, and he[2] improved them still further. Penrose[3] has made further suggestions. In another case of linkage I had to use methods of a wholly different character, which will be described here.

Bernstein envisaged a systematic search, using the blood group genes as "markers." I am a fundamentally lazy man, and like to see definite results when I do make an effort. Moreover, Bernstein, up till 1933, was head of a statistical institute, and I am not. So I embarked on or encouraged investigations which were likely to yield positive results, even if of limited value. I have, therefore, confined my studies to one chromosome. If two genes are both sex-linked they should exhibit mutual linkage in doubly heterozygous females, though if the chromosome is long enough (or, more accurately, if it forms sufficiently numerous chiasmata) the linkage may be very slight. Now the human *X* chromosomes carries two quite common recessive genes allelomorphic with one another, namely, those for protanopia and deuteranopia, or red-blindness and green-blindness, one or other of which is found in about 2·4 per cent of western European *X*

[1] Fisher, R. A. (1935), *Ann. Eug.*, 6, pp. 187–201 and 339–51.
[2] Fisher, R. A. (1936), *Ann. Eug.*, 7, pp. 87–104.
[3] Penrose, L. S. (1935), *Ann. Eug.*, 6, pp. 133–36.

chromosomes. Haemophilia is much rarer, but it has the great advantage that it cannot escape notice, and that the haemophilics in a given area are mostly patients of quite a few physicians.

With the aid of a grant from the Medical Research Council, Dr. Wright tested a number of haemophilics and their brothers in London, and less systematic searches were made elsewhere. Drs. Bell and Riddle then followed up the positive results, and compiled three pedigrees. The credit for priority in this matter belongs to Madlener, who published the first pedigree illustrating the linkage of haemophilia and colour-blindness. It must, however, be added that Madlener's pedigree, by itself, containing as it did one member less than to-day, was not sufficient to establish the existence of linkage with certainty, still less to estimate its intensity. This can only be done by a very large pedigree, or a combination of several small ones. Let us now see how the pedigrees are treated. Fig. 12 shows the members of Madlener's much larger pedigree who are relevant to the calculation of linkage. If x is the frequency of crossing over between the genes c and h for colour-blindness and haemophilia, and $y = 1 - x$, we ask what is the probability of getting just the amount of crossing over occurring in the pedigree, in this case none. We take the pedigree of haemophilia as given, and starting from the colour vision of any colour-blind male, we ask what is the probability that the others had the colour vision found. A was *ch*.

So α must have been $\frac{+\ +}{c\ h}$. B is *ch*. Now given that he is *h* (haemophilic), the probability that he is also *ch* is y. Similarly for C and D. β bore a haemophilic son, so she is $\frac{+}{h}$. She bore a colour-blind son, so she is also $\frac{+}{c}$. Both genes must have come from her mother α. The

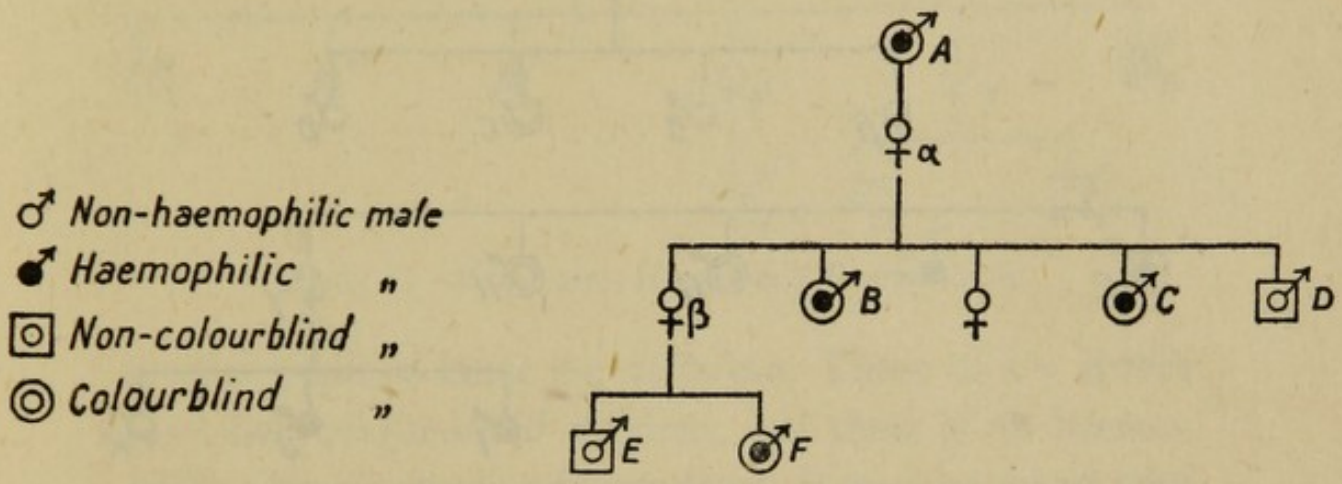


FIG. 12—MADLENER'S PEDIGREE

probability of their keeping together is y. Similarly the probabilities of E and F being as found are y. Hence the overall probability for the whole pedigree is y^6. We have so far assumed that all the genes for colour-blindness in the pedigree came from one source, namely, A. But they might also have come from A's wife or α's husband. Making allowance for these possibilities and putting $p = 0{\cdot}014$ for the frequency of genes for deuteranopia in X chromosomes, we find

$$P = (1 - p)y^3[(1 - p)y^3 + px^3]$$

The detailed argument leading to this formula is given by Bell and Haldane.[1]

Now let us consider a pedigree where the two genes are in repulsion (Fig. 13). A was haemophilic, and married α, who was heterozygous for colour-blindness,

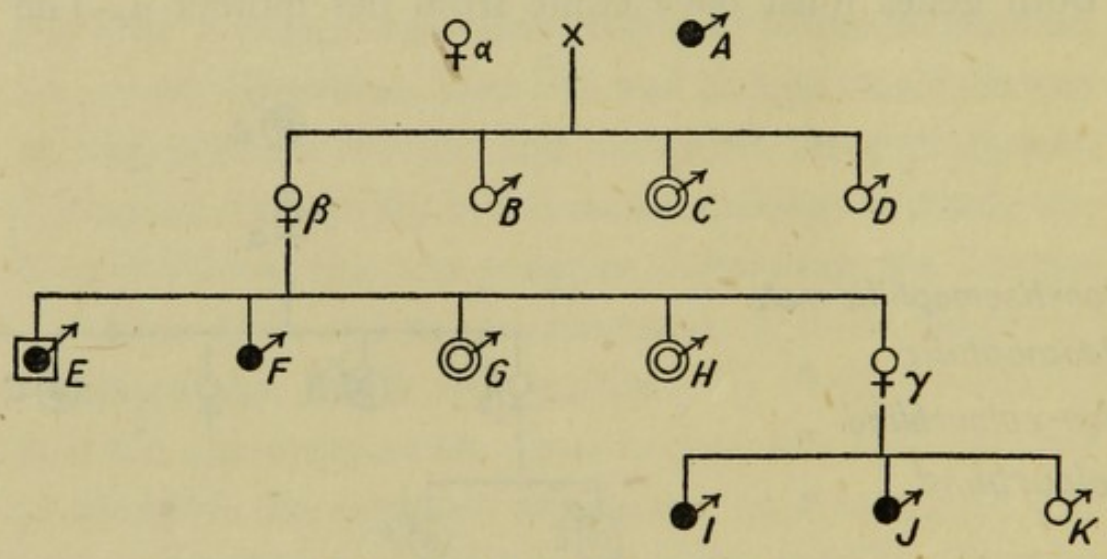


FIG. 13—BIRCH'S PEDIGREE

for her son C is colour-blind. Thus β, who transmitted both haemophilia and colour-blindness, must be $\frac{c+}{+h}$. Since E, G, and H were formed from her non-cross-over gametes, $P = y^3$. This value will have to be slightly modified when K, the only surviving son of γ, is tested for colour-blindness.

In these pedigrees everything is straightforward, and we can say, if we like, that Madlener tested six gametes

[1] Bell, J., and Haldane, J. B. S. (1937), "The Linkage between the Genes for Colour-blindness and Haemophilia in Man," *Proc. Roy. Soc.*, B, 123, pp. 119–50.

and Birch three, with no crossing over. But things are not so simple in the case of the pedigree of Fig. 14. This is the part of Bell and Haldane's pedigree A which is relevant to linkage. The total pedigree contains ninety-eight individuals, and gives fairly conclusive proof that

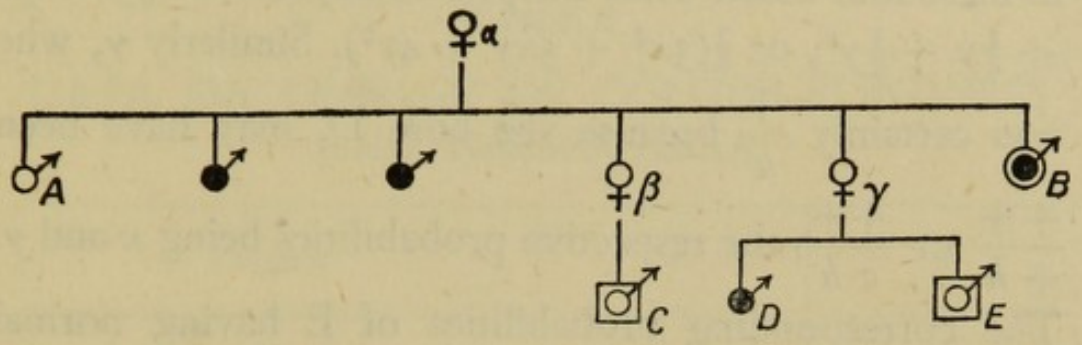


FIG. 14—BELL AND HALDANE'S PEDIGREE A

the haemophilia arose by mutation. Three of α's sisters have had colour-blind children, but there is no haemophilia save among her descendants. It may be asked why A was not tested for colour vision. I give the answer in his own words. "Though I bear at present the name of ....., I consider myself of no blood relationship to that family, and no useful purpose would be served by visiting me." It may be remarked that, even if A is a bastard, as his letter seems to suggest, information concerning him would be valuable, since the father is not responsible for the sons' sex-linked characters.

At first sight this pedigree might seem to give no information. But actually it does. Given that B is *ch*, we have two alternatives concerning α. (1) She is $\frac{++}{c\ h}$

with probability y. If so, the possible genotypes of β are $\frac{++}{++}$, $\frac{++}{+h}$, $\frac{++}{c+}$, and $\frac{++}{ch}$ with probabilities $\frac{1}{2}y$, $\frac{1}{2}x$, $\frac{1}{2}x$, and $\frac{1}{2}y$ respectively. The further probabilities of β bearing a son C who is not colour-blind are 1, 1, $\frac{1}{2}$, and y in these four cases. Thus the probability of C is $\frac{1}{2}y + \frac{1}{2}x + \frac{1}{4}x + \frac{1}{2}y^2$, or $\frac{1}{4}(3x^2 + 5xy + 4y^2)$. Similarly γ, who was certainly $\frac{+}{h}$ because she bore D, may have been $\frac{++}{+h}$ or $\frac{++}{ch}$, the respective probabilities being x and y. The corresponding probabilities of E having normal vision are 1 and y. Thus the probability of D is $x + y^2$ or $x^2 + xy + y^2$, and the overall probability of hypothesis (1) is $y \cdot \frac{1}{4}(3x^2 + 5xy + 4y^2)(x^2 + xy + y^2)$.

The alternative (2) is that α is $\frac{c+}{+h}$. This has a probability x. The further probabilities that C and E are not colour-blind can be shown to be $\frac{1}{4}(2x^2 + 7xy + 3y^2)$ and $y(2x + y)$. Thus the overall probability of hypothesis (2) is $\frac{1}{4}xy(2x + y)(2x^2 + 7xy + 3y^2)$. So the sum of the probabilities of hypotheses (1) and (2) is:

$$P = \tfrac{1}{4}y(7x^3 + 17x^2y + 8xy^2 + 4y^3)$$

$$= y^2\left(1 + \frac{13x^2}{4y^2} - \frac{19x^3}{4y^3} + \frac{25x^4}{4y^4} - \ldots\right)$$

Since x is clearly small, this is nearly equivalent to y^2. In fact we are not far out if we neglect all the terms in P except the leading term y^2, and say that, effectively,

two gametes have been tested and found to be non-cross-overs. There is a further very small correction, involving p, for a possible secondary source of colour-blindness.

Bell and Haldane's pedigree B is a far more compli-

TABLE 6

DATA ON LINKAGE OF COLOUR-BLINDNESS AND HAEMOPHILIA

Pedigree	n	k
Madlener	6	0
Green	4	0
Bell and Haldane A ..	2	0
Bell and Haldane B ..	12·75	0
Riddell	2	1
Birch	3	0
Rath	4	2
Total	33·75	3

cated affair. It involved Dr. Bell in journeys to a number of towns, but gave a great deal of information. And here I should like to pay my tribute to her remarkable capacity for persuading patients that their case is of great interest and at the same time giving eugenical advice so tactfully as to cause no offence. This is quite as difficult as the logical analysis of the results, and much harder to teach.

The main data of all published pedigrees on the linkage in question are assembled in Table 6; n is the total number of gametes tested, k the number of cross-overs. So for all the pedigrees,

$$P = x^3 y^{30\cdot75}\left(1 + \frac{187x^2}{32y^2} + \ldots\right)$$

multiplied by a constant.

We can now choose the value of x which makes P a maximum. This is obviously $\frac{3}{33\cdot75}$ or 0·089 if we consider the leading term only. Thus we may take 8·9 per cent as the most probable cross-over value. This is a little misleading, as the distribution round the mode is far from symmetrical, and the standard error of 4·9 per cent is enormous. However, we may also ask what is the median cross-over value, that is to say, such a value that x is as likely to be above it as below it. That is to say, we must solve the equation $\int_0^x P\,dx = \frac{1}{2}\int_0^1 P\,dx$. We find $X = 10\cdot5$. The term $\frac{187x^2}{32y^2}$ raises the modal value to 9·2 per cent; the correction for a second source hardly lowers it appreciably. A small correction for the *a priori* probability again lowers X slightly. We conclude that the frequency of crossing over between the loci of haemophilia and colour-blindness in man is about 10 per cent, but may well be as high as 15 per cent or as low as 5 per cent. The interested reader is referred to Bell

and Haldane's paper for details of the calculation, but some more facts have accumulated, and in particular v. Rath has published his pedigree since Bell and Haldane wrote. Hence the results of the calculation are different.

It was lucky that the first search for linkage between two sex-linked genes gave such clear evidence. For the second did not. Its discovery was not due to systematic search, and was not made by a geneticist, but by a chemist, Dr. T. White.[1] While he was visiting a colleague's house, the colleague's father remarked that he was night-blind. He was also myopic, the myopia being due to the same sex-linked recessive which causes night-blindness of this particular type. "But," remarked the father, "my colour vision is very good. My wife calls things blue which are not blue at all." On his next visit White took one of the standard tests for colour vision, and discovered that his colleague's father was a deuteranope, or green-blind. He had correctly guessed that in a dispute on colour between a man and a woman, the woman is likely to be in agreement with 97·5 per cent or so of men, whilst the man displays the abnormality which we of the majority call colour-blindness, though colour-blind men can distinguish certain hues which normal people cannot.

A few further questions showed White that all the brothers of the original subject, marked with an asterisk in Fig. 15, had one or other of his two defects, but most

[1] White, T. (1940), *Journ. Gen.*, 40, pp. 403–37.

had only one. Some maternal uncles and cousins, but no women, were affected. The compresence of two sex-linked abnormalities excited his interest, and the hunt was on. With the aid of a grant from the Medical

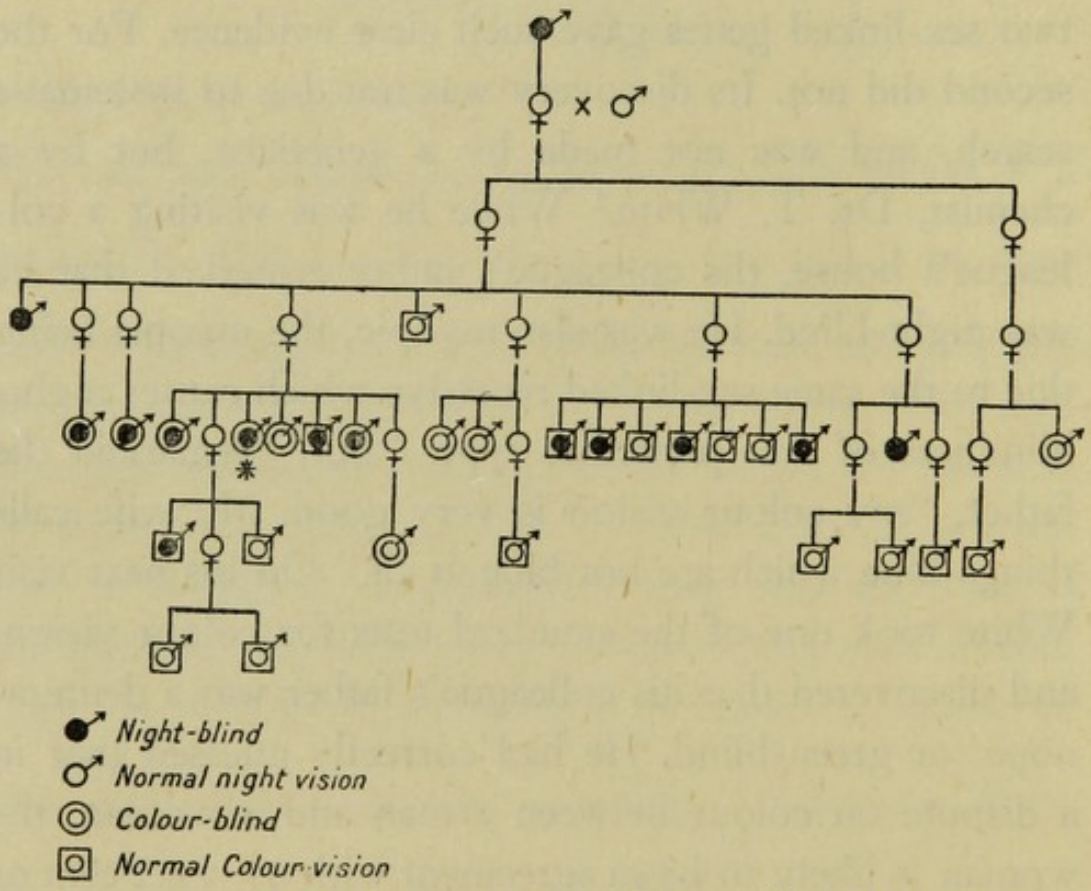


FIG. 15—WHITE'S PEDIGREE OF MYOPIC NIGHT-BLINDNESS AND DEUTERANOPIA

Research Council, White visited a number of English towns. He discovered branches of the family which had lost touch with the rest for forty years. Professor MacArthur of Toronto tested a branch of the family located there, and the final result was a pedigree of two hundred and seventy-three members, of which Fig. 15

summarizes those parts which are relevant to the problem of linkage. It is at once clear that crossing over is very frequent. In the family first observed, assuming the mother to have been $\frac{++}{c\ \ n}$, where n is the gene for night-blindness with myopia, three sons with both defects were non-cross-overs, three sons with one defect were cross-overs, and the two daughters, who transmitted one defect only, were probably cross-overs. As the mother apparently received both genes from her mother, she was almost certainly $\frac{++}{c\ \ n}$, so in this family there is an excess of cross-overs.

The evaluation of P is an intricate and bewildering problem. Unless I have made a mistake in my appendix to White's[1] paper, it is:

$$2^{-15}x^4y^3(x+3y)(5x^3+14x^2y+13xy^2+8y^3)$$
$$[y^4(3x^4+24x^3y+38x^2y^2+28xy^3+3y^4)$$
$$(3x^5+15x^4y+42x^3y^2+64x^2y^3+51xy^4+17y^5)$$
$$(1+x^3y^4)+2x^2(x+y)^2(9x^4+25x^3y+35x^2y^2$$
$$+21xy^3+6y^4)(12x^5+23x^4y+28x^3y^2+18x^2y^3$$
$$+12xy^4+3y^5)(1+x^5y^2)]$$

Putting unity for the terms $(1+x^3y^4)$ and $(1+x^5y^2)$ of which the variable parts symbolize the remote probability that the mother of seven non-colour-blind sons may yet have been heterozygous, and putting $z=2x-1$,

[1] White, T. (1940), *Journ. Gen.*, 40, pp. 403–37.

we have as the condition that P should be a maximum,

$$\frac{9}{1+z} - \frac{6}{1-z} - \frac{2}{2-z} - \frac{2-6z+3z^2}{10-2z+3z^2-z^3} - \frac{22-34z+27z^2-20z^3+5z^4}{74-22z+17z^2-9z^3+5z^4-z^5}$$
$$+ 2(1{,}026 - 8{,}849z + 4{,}671z^2 + 13{,}282z^3 + 8{,}475z^4 - 1{,}200z^5 + 5{,}831z^6 + 864z^7 + 1{,}143z^8 - 125z^9 + 66z^{10} - 6z^{11})$$
$$+ (1{,}440 + 2{,}124z - 8{,}849z^2 + 3{,}114z^3 + 6{,}641z^4 + 3{,}390z^5 - 400z^6 + 1{,}666z^7 - 216z^8 + 254z^9 - 25z^{10} + 12z^{11} - z^{12}) = 0$$

This reduces to an algebraic equation of the twenty-second degree with integral coefficients, and I think I am probably safe in saying that this is the first occasion on which such an equation has arisen in the course of scientific work. The real root lying between $+1$ and -1 is $z = 0{\cdot}2956$, whence $x = 0{\cdot}648$. In fact, the most probable value is $64{\cdot}8 \pm 12{\cdot}7$ per cent. Presumably the true value is under 50 per cent, though my colleagues Rendel and Spurway[1] appear to have observed slightly over 50 per cent crossing over in *Drosophila subobscura*, so women may also produce more than 50 per cent. But we may be quite sure that the true value of this particular human cross-over frequency will not be known within 5 per cent within our lifetimes, and perhaps not for some centuries.

The human X chromosome, then, will have a long

[1] Rendel, J. M., and Spurway, Helen (unpublished data).

map, like those of the *Drosophila* species and poultry, whereas Bell and Haldane's work left it possible that the map would be short, like those of the *X* chromosome in the fish *Lebistes* and other Cyprinodonts, or in the beetle *Phytodecta variabilis*. Work like that described above could and should be carried out in all civilized countries. But it will not, by itself, give us a chromosome map. If we desire to make a "map" of the stations on the railway from London to Plymouth, we can do so provided we know their distances from two stations on it, say Reading and Exeter. But distances from a single point leave the order of the stations ambiguous. It is hopeless to look for families showing the simultaneous segregation of two rare genes such as haemophilia and myopic night-blindness. There may not be a dozen on the whole planet. The most hopeful prospect is the discovery, in the field either of immunology or of sense physiology, of a pair of sex-linked genes of which both allelomorphs are fairly common. Schiff, who discovered several antigenic differences due to autosomal gene pairs in Germany, is a Jew, and has therefore had to cease his work. Blakeslee, who discovered that inability to taste phenyl-thio-urea is due to an autosomal recessive, is still at work. Perhaps he will discover a sex-linked gene in this field. If so, a rough map of the human *X* chromosome will become possible.

Before the work described above, I attacked the problem of linkage from another angle. I may have been

the first to map a human chromosome. Some of my colleagues think so. I am not, however, completely convinced by my own argument. It runs as follows. The human *X* and *Y* chromosomes possess a homologous segment. Otherwise they would not pair at meiosis, and about half the spermatozoa would contain both an *X* and a *Y*, or neither. The homologous segment probably includes most of the short *Y*. During the pachytene stage of the first meiotic prophase in males one or more chiasmata are formed in the homologous segment, and these hold the *X* and *Y* chromatids together during metaphase. They have a further effect. Genes in this segment will cross over between the *X* and *Y* chromosomes. Thus if a man inherits such a gene from his mother, it will be in his *X* chromosome. In meiosis it will occasionally cross over to the *Y*, so the man will transmit it to most of his daughters, but a few of his sons. Similarly, if he inherits it from his father, he will transmit it to most of his sons and a few of his daughters. More accurately a large group of men will do so.

When this not very profound idea first occurred to me, I spent a number of hours of my spare time looking for evidence of such a gene among the dominants recorded in the *Treasury of Human Inheritance*. A gene of this kind would at first sight be classed as an autosomal dominant, and only careful study of the pedigrees would demonstrate its true nature. I soon found what I thought was a gene of this kind in the case of Hunting-

ton's chorea. But further consideration (see p. 192) showed that I was wrong, and I gave up the search, except as a diversion for leisure hours. A year later I hit on the only case which I have so far found, and, stimulated by my success, put in two months of hard work, during which I discovered, or claim to have discovered, five recessive genes of the same type. In 1940 I discovered

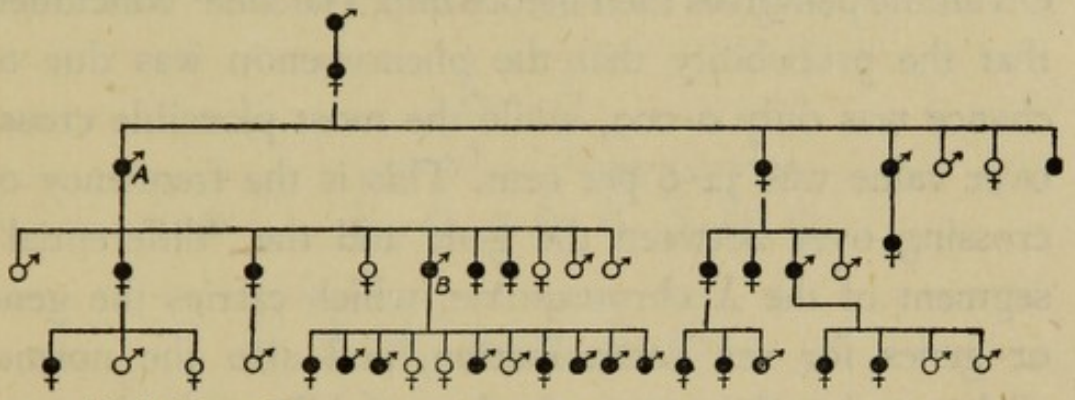


FIG. 16—PEDIGREE OF DOMINANT RETINITIS PIGMENTOSA
(After Snell)

a sixth. Such genes are described as incompletely or, better, partially, sex-linked.

Fig. 16 is a pedigree of retinitis pigmentosa, due to Snell. Clearly it is what might be expected if the gene in question were partially sex-linked. A got the gene from his mother, and of his ten children only three, the affected son and two unaffected daughters, are cross-overs. B got it from his father, and there are three cross-overs among his eleven children. Altogether there are six cross-overs out of twenty-six children of affected males in the pedigree, or 23 per cent. This pedigree,

taken alone, is strong evidence for an abnormal type of inheritance, though not quite conclusive by itself. Such a deviation would be expected as a result of chance once in about two hundred and fourteen cases. However, the pedigree does not stand alone. Nearly half the pedigrees of dominant retinitis pigmentosa so far published show the same phenomenon and none show the contrary one. On all the pedigrees then before him, Haldane[1] concluded that the probability that the phenomenon was due to chance was only 0·009, while the most plausible cross-over value was 32·6 per cent. This is the frequency of crossing over between the gene and the "differential" segment of the *X* chromosome, which carries the gene or genes for sex determination, and also the normal allelomorphs of the genes for haemophilia and other sex-linked abnormalities, or more rarely the genes themselves which cause these conditions.

Just as a partially sex-linked dominant is at first sight taken for an autosomal dominant, so a partially sex-linked recessive is reported as an autosomal recessive. It can, however, be detected in two different ways. Where the parents of one or more recessive children are relatives, it may be presumed that they derive the recessive gene from their common ancestors. So, unless they are uncle and niece or nearer relatives, or double first cousins, we can say that the father derived the gene either from his father or his mother. Fig. 17 is a pedigree of achro-

[1] Haldane, J. B. S. (1936), *Ann. Eug.*, 7, pp. 28–57.

matopsia. In this disease the cones of the retina do not function. There is no colour vision, and during daylight the patients are perpetually dazzled, as if they had just come out of a dark room. Since foveal vision is poor or absent, they cannot see a thing at which they look closely. Thus there is nystagmus.

Now if, as in this case, the father of the abnormals is related to their mother through his mother, the gene is

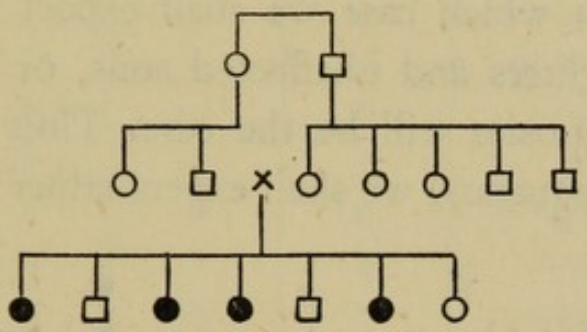


FIG. 17—PEDIGREE OF ACHROMATOPSIA
(After Komai)

in his *X* chromosome, and he will transmit it, apart from crossing over, to half his daughters. Thus most of the affected children will be of the same sex as the paternal grandparent through whom the parents are related. There is, I think, only one drawback to this method, but it is a serious one. A good many cases of cousin marriage are drawn from inbred rural, Jewish, or royal communities. So when parents are related in one way they are often related in another as well. This does not matter in the case of autosomal recessives, but it may dilute the effect in the case of partial sex-linkage.

In the case of achromatopsia there were, in the three

families where the parental relationship is known, eight recessives of the same sex as the paternal grandparent through whom their parents were related, and one doubtful case of the other sex. This evidence is not conclusive by itself, but it is backed up by a great deal of indirect evidence. If the parents are not related, or their relationship is not clearly stated, we can still argue as follows. In any given family the gene will come from the father's X, in which case we shall expect an excess of affected daughters and unaffected sons, or from his Y, when the opposite will be the case. Thus if x be the cross-over frequency, we shall expect either

♂	♀
$2 + x : 1 - x$	
or $1 - x : 2 + x$	
$7 : 3$	
or $3 : 7$	

♂	♀
$x : 1 - x$	
$1 - x : x$,	
and if $x = 0 \cdot 1$	
$1 : 9$	
$9 : 1$	

We cannot say what ratio of normals to abnormals is to be expected; for the reasons discussed in the last chapter it is certainly less than 3 : 1. But we shall expect to find far too many families with all or almost all the affected members of one sex, as compared with what might be expected on a basis of random sampling. Table 7 shows all the recorded families segregating for

achromatopsia and containing five or more members. It will be seen that in a large number of cases most or all

TABLE 7

♂*a*	♀*b*	♂*c*	♀*d*	*u*	*k*
1	4	3	0	+ 112	776
1	2	0	2	+ 4	276
2	3	1	1	— 22	362
2	3	2	0	+ 26	362
2	1	2	0	+ 4	276
3	1	2	1	— 30	714
0	2	6	0	+ 344	2,648
2	2	1	4	— 8	1,992
1	3	0	1	— 12	84
2	1	3	0	+ 34	654
2	0	1	4	+ 74	1,802
3	2	0	1	+ 2	110
2	1	2	1	— 26	654
0	4	2	1	+ 18	714
5	3	1	0	— 16	200
28	32	26	16	+ 504	11,624

of the affected children are of one sex, often with a shortage of this sex among the normals.

Fisher[1] has shown that we can estimate x from the "score" $u = (a - b - 3c + 3d)^2 - (a + b + 9c + 9d)$ which is tabulated in column 5. In the case of normal

[1] Fisher, R. A. (1936), *Ann. Eug.*, 7, pp. 87–104.

recessives the algebraic sum of the values of u is near to zero. In this case it is positive. To find out whether the positive value is significant we compare it with the sum of the values of k, or $(s + 9t)^2 - (s + 81t)$, where s and t are the number of normals and abnormals in the family. If there is no linkage, the standard deviation of Σu from its mean value of zero is $\sqrt{2\Sigma k}$. Here the positive deviation is 3·3 times the standard, and therefore significant. We can obtain an estimate of x from the equation $(1 - 2x)^2 = \frac{9\Sigma u}{\Sigma k}$. This gives $x = 0{\cdot}188$. A better value, obtained by considering small families as well, is $x = 0{\cdot}1415$. Perhaps a further refinement of Fisher's method would give a still better value.

From such arguments as these I have deduced that the following genes are partially sex-linked:

Dominant retinitis pigmentosa, in some families.
Recessive retinitis pigmentosa, when not associated with deafness.
Oguchi's disease of the retina (recessive).
Epidermolysis bullosa dystrophica (recessive).
Xeroderma pigmentosum, a condition in which the skin is light-sensitive, and the lesions produced in it generally become cancerous; there is also photophobia (recessive).
Spastic paraplegia (recessive).
Achromatopsia (recessive).

A provisional map can be made, but the data are not good enough to make it worth reproducing, though

their significance is in little doubt. Thus in the case of spastic paraplegia, Σu is just five times its standard error. Burks[1] has criticized my treatment of recessive retinitis pigmentosa. I can accept some, but not all, of her criticisms, to which I hope to reply in detail. It is a striking, and possibly significant, fact that five of the seven conditions are concerned with light sensitivity. Perhaps the first two, and possibly some of the others, are allelomorphic.

This work, if correct, is important, for it locates a number of genes in the small section of the sex chromosomes between the centromere and the differential segments responsible for sex determination. But apart from Burks' paper, it has been little criticized. I should like to suggest some possible methods of disproof. For one cannot prove a scientific hypothesis as one can a mathematical one, unless indeed Milne's work presages the introduction of deductive logic into physics. On the other hand, a good scientific hypothesis is capable of disproof. Thus the hypothesis that the planet Mercury obeys Newton's laws can be (and has been) disproved, though it is a very good approximation to the truth. On the other hand, the hypothesis that it is carried about by an angel cannot be disproved, because no one knows what an angel would do with a planet, and therefore the hypothesis is useless for prediction.

In the first place much more numerous data are needed.

[1] Burks, B. (1937), *Eugen. News*, 22, pp. 33–42.

I recently read a German paper on retinitis pigmentosa in which a dozen or so cases were described among children of first cousins. In no case was the exact relationship given. The data doubtless gave strong evidence for the recessivity of the character. Had full pedigrees been given they would have proved or disproved its partial sex-linkage. It is most important that as many details as possible should be published, not merely details sufficient to verify or disprove the genetical hypotheses which are fashionable at the moment of publication. I would particularly commend the work of Usher and other colleagues of the late Karl Pearson, who, just because they did not accept Mendelism, gave fuller information than many workers who did so.

Secondly, the hypothesis would become much less credible if it were found that, in dominant conditions where there is no evidence for sex-limited modifiers (see p. 192), there was a tendency for the sex of the affected children of females to agree with that of the affected maternal grandparents. A glance at Fig. 16 shows that there are only five out of fifteen "cross-overs" for this type of "linkage," which if it occurred would have no known physical basis. However, so large a deviation would occur in 15 per cent of cases by chance, and it is not shown by the grouped pedigrees. Similarly, if significantly large negative values of Σu can be found, this will show that some unknown cause is at work, and if it can lower u, it may also be able to raise it. Finally,

some other biological explanation of my results may be suggested. If so, a criterion for distinguishing between this and my own hypothesis will have to be found. At the risk of being obvious, I must point out that a significant value of such a score as "*u*" does not prove the hypothesis which it is designed to test. It merely proves that there is some causal relation between sex and the recessive abnormality, which may be the one suggested by myself. So whilst I hope that I have established in man the existence of the partial sex-linkage which Aida[1] established in fish, I am not convinced that I have done so. What is certain is that a small group of genes behave in a peculiar manner. It remains to be seen whether my explanation of their behaviour is correct.

Burks[2] has produced evidence for the linkage of two autosomal genes, one for defective teeth, the other for hair colour. The tooth defect was congenital absence of teeth, notably third molars (wisdom teeth). This is thought to be due to an irregularly dominant gene, producing more extensive deficiencies when homozygous, and particularly lack of permanent upper lateral incisors. The hair colour is thought to be due to a series of allelomorphs. It may be added in parenthesis that these, if they exist, are very likely allelomorphs of albinism. Just as chinchilla is incompletely dominant over albinism in rabbits, the heterozygote being rather dilute, so we

[1] Aida, T. (1921), *Genetics*, 6, pp. 554–73.
[2] Burks, B. (1939), *Proc. Nat. Ac. Sci.*, 24, pp. 512–19.

find a striking frequency of "platinum blondes" among the parents, children, and sibs of albinos. Probably, then, a normal colour gene found in some blondes is an allelomorph of the gene for albinism, and incompletely dominant over it.

To return to Burks' work, she compared one hundred

TABLE 8

EVIDENCE FOR LINKAGE OF GENES FOR HAIR COLOUR AND TOOTH DEFECT

		Teeth	
		Like	Unlike
Hair	Like ..	51	14
	Unlike ..	72	57

and six sibs in twenty-nine families. Sixty-four had deficient teeth, forty-two a full set. If the genes were completely linked, and if no other genes were controlling hair colour, we should expect every pair of sibs whose teeth were in agreement to agree in hair colour if the gene for tooth deficiency was recessive. If it were dominant there would be a less complete coincidence. Crossing over and segregation of other colour genes would still further lessen it. But any agreement points to linkage. Burks' totals are given in Table 8. Each entry

refers to a pair. Thus fifty-one pairs of sibs were alike both in hair colour and in lacking some teeth. If these two kinds of likeness were independent, the table would read $\frac{41 \mid 24}{82 \mid 47}$, to the nearest unit. The χ^2 test gives $\chi = + 3{\cdot}13$ in the expected direction. The probability that this should be due to chance is 0·0009, and Burks' estimate of the cross-over frequency is about 10 per cent.

As in my own case, Burks has almost certainly got hold of something, and I for one hope that it is the first case of human autosomal linkage. Nevertheless, there are grounds for caution. The genetic bases of tooth defect and hair colour are equally uncertain. It is not inconceivable that the gene or genes for tooth abnormality may also, like Grüneberg's gray lethal, affect hair colour. If this is so, Burks' results do not necessarily indicate linkage. Again, eye colour is known to be moderately correlated with hair colour, doubtless because, as in other mammals, some of the genes controlling eye colour also control hair colour, while some do not, or some of the hair colour genes do not influence eye colour. It will be very interesting to see whether eye colour is in any way related to tooth deficiency. Doubtless the full account of Burks' work will deal with this matter. The account published so far is rather condensed, and it seems to me not unreasonable, while admitting that Burks has made out a very strong *prima facie* case, to suspend judgment until all the details are available. The

fact that I have suggested a similar suspension of judgment regarding my own work will, I hope, show that I am in no way hostile to Burks' claims. All her data are American, and her work represents a challenge to European geneticists to confirm or disprove it, if, indeed, genetical work continues in Europe.

Hogben and Pollack[1] published data for the segregation of Friedreich's ataxia and the blood group genes which led them to regard these genes as independent. However, Fisher[2] pointed out that one of their families shows strong evidence of linkage, whilst eleven others do not. This is entirely plausible if Friedreich's ataxia is due to several genes (see p. 191). It is thus possible that Hogben and Pollack may have discovered an autosomal linkage without knowing it. If so, they have priority over Burks. Since the above was written, Finney[3] has subjected the data of Wiener, Zieve, and Fries[4] on the linkage relations of allergic disease and blood groups to a closer analysis. They had obtained a suggestion of linkage. Finney finds that the probability that the observed results could be due to chance is about 4 per cent. The most likely value for the cross-over frequency between the two loci is about 23 per cent. As in Burks' case, there is some doubt as to the genetics of allergic

[1] Hogben, L., and Pollack, R. (1935), *Journ. Gen.*, 31, p. 353.
[2] Fisher, R. A. (1936), *Ann. Eug.*, 7, p. 17.
[3] Finney, D. J. (1940), *Ann. Eug.*, 10, p. 171.
[4] Wiener, A. S., Zieve, I., and Fries, J. H. (1936), *Ann. Eug.*, 7, p. 141.

disease. The evidence is not quite so strong, nevertheless it seems likely that the genes are linked. And it is, I think, almost certain that one of the three alleged cases of human autosomal linkage will prove to be genuine. Other authors have published results which cannot be said to be more than suggestive of linkage.

We are still a long way from the chromosome maps which will perhaps enable our descendants to trace recessive genes through many generations, and prevent or encourage their reunion. That need not trouble us. Galileo with his home-made telescope was a long way from the modern 200-inch diameter mirror, and daguerreotypes were a long way from modern high-speed films. The important point is that we are moving in the right direction, the direction which will ultimately permit us to control human heredity.

As a further example of the power of statistical methods, let us consider the question of modifying genes. The results produced by a gene may depend to a greater or less extent on modifiers. Thus in *Drosophila melanogaster* every male carrying the gene *w* has white eyes. But the eye colour of flies carrying its allelomorphs such as eosin (w^e) depends on other genes. Some of these have an effect on normal eyes. Others are specific modifiers. That is to say, they have no effect on the eye of otherwise normal flies, but only on flies which carry w^e or some other allelomorph of white.

In men and women we say that lobster-claw is a

dominant, haemophilia a sex-linked recessive, and phenylketonuria an autosomal recessive. Nevertheless, all cases of these conditions are not equally severe. Sometimes this is due to the environment. Thus a baby is obviously more likely to die of haemophilia in infancy if he is circumcized than if he is not. But the environment is not always responsible. One of Penrose's phenylketonurics was an imbecile, another an idiot. The difference is considerable, and can hardly be due to environment. It may be that had these children had a normal metabolism, but the other genes the same, the imbecile would have been a bright child and the idiot a dull one. If so, the modifying genes are not specific, but would have similar effects on normal children. The modifiers may, however, be specific. Or the truth may be somewhere between these two alternatives.

But there is still another possibility. It may be that haemophilia and phenylketonuria are due, not to one gene, but to a number, which cause abnormalities which are clinically indistinguishable, or at least so alike as to be classified together. Further, these different genes may be at different loci, like the numerous genes for white cotyledons in maize, or at the same locus, that is to say, allelomorphs.

In some cases we can say with complete certainty that many genes are responsible for one condition. Thus in some pedigrees of retinitis pigmentosa the condition is dominant, in others a sex-linked recessive, in others an

autosomal or partially sex-linked recessive. The recessive form is invariably associated with deafness in some pedigrees but not in others. Finally, some of the dominant genes show the behaviour which I have attributed to partial sex linkage, while others do not. Thus there seem to be at least five different genes which may cause the development of retinitis pigmentosa.

We can be sure that there are a number of different genes in another case. We can often grade the severity of a condition. For example, we can estimate the mental age or intelligence quotient in mental defect, or the area of retina which is functionless in retinal disease. Above all, in many cases the age of onset is very variable, and this makes a great practical difference. It does not much matter if a man develops the first symptoms of "creeping paralysis" at the age of sixty. A life is wrecked if a child does so at the age of six. Bell[1] has studied the age of onset in seven diseases, namely glaucoma and optic atrophy, which affect the eyes, and Huntington's chorea, peroneal atrophy, Friedreich's ataxia, spastic ataxia, and spastic paraplegia, which affect the nerves and muscles. The distinction between Friedreich's ataxia and spastic ataxia does not seem to be very sharp. In the last four diseases there are both dominant and recessive forms. The data are sufficient to yield correlation tables for the age of onset in sibs or in parent and offspring, of which Table 9 is an example. The first entry means that, in

[1] Bell, J. (1934–39), *Treas. Hum. Inher.*, 4, *passim*.

TABLE 9

DOMINANT FRIEDREICH'S ATAXIA. AGES OF ONSET IN PAIRS OF SIBS

(From Bell)

Years	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	Total
0–4	40	—	—	—	—	—	—	—	40
5–9	—	22	6	3	—	—	—	—	31
10–14	—	6	10	8	—	1	—	—	25
15–19	—	3	8	—	3	2	—	—	16
20–24	—	—	—	3	2	—	2	—	7
25–29	—	—	1	2	—	6	—	—	9
30–34	—	—	—	—	2	—	2	—	4
35–39	—	—	—	—	—	—	—	12	12
Total ..	40	31	25	16	7	9	4	12	144

sibships containing more than one affected member, there were a number of cases where the age of onset was under five years. In every case all the affected sibs developed the disease before they were five years old. There were forty sib pairs. Thus two sibs would count as two pairs, three as six pairs, four as twelve pairs, and so on, for each pair of sibs is counted twice.

A glance at this table shows the very high correlation between pairs, the coefficient of correlation being 0·925. This is far higher than the correlations found between sibs for any ordinary measurements such as stature, or for graded qualitative characters such as eye colour. It is as large as the organic correlations found between the lengths of neighbouring bones in the same hand. Nor does it stand alone. Table 10 summarizes Bell's results. Further, although the populations are not very large, there is no doubt that the high values are significantly greater than the values in the neighbourhood of 0·5 which are generally found for correlations between parent and offspring, or sib and sib.

The explanation is, I believe, a simple one. If in the case in question there were three or four different genes, each determining an age of onset, we should have a correlation of one. In one family the age would be four, in another forty. Actually environmental variations and other genes have some effect, or all the figures would lie in the diagonal column. We can also see that such high correlations cannot be due to modifiers. For both parents

TABLE 10

COEFFICIENTS OF CORRELATION OF AGES OF ONSET, AND NUMBERS ON WHICH THEY ARE BASED

(After Bell)

Diseases	Sib-sib		Parent-offspring	
	n	*r*	*n*	*r*
Sex-linked recessive optic atrophy ..	812	0·510	—	—
Dominant Huntington's chorea	442	0·465	153	0·593
Dominant glaucoma	256	0·897	113	0·813
Dominant peroneal atrophy	164	0·803	86	0·764
Dominant Friedreich's ataxia	144	0·925		
Dominant spastic ataxia	198	0·812	135	0·743
Dominant spastic paraplegia	154	0·884		
Recessive peroneal atrophy	108	0·840	—	—
Recessive Friedreich's ataxia	500	0·694	—	—
Recessive spastic ataxia	164	0·845	—	—
Recessive spastic paraplegia	218	0·852	—	—

must contribute these modifiers equally. Now a correlation of 0·8 between parent and offspring means that when we know the parent's age we have eliminated 64 per cent of the variance in the age of the offspring. This only leaves 36 per cent to be accounted for by the other parent and the environment. The only exception to this argument would be if all the modifiers were very closely linked with the main gene. This might occur in one case, but could not do so as a principle.

In most of these cases of high correlation the different main genes may be in different chromosomes; indeed, we saw reason to suspect this in the case of recessive Friedreich's ataxia. But recessive spastic paraplegia is partially sex-linked, so here it is pretty sure that the different genes are in the same locus, that is to say, are multiple allelomorphs at least three in number. For similar reasons it is fairly sure that there are at least two multiple allelomorphs of haemophilia, while there are certainly four of colour-blindness. But so far the only proved cases of multiple allelomorphism in autosomes are those of the genes for blood agglutinogens. Here all the allelomorphs are so common that they can be observed segregating in different combinations. Given these facts, it is highly probable that some of the genes for other diseases showing high correlation will turn out to be multiple allelomorphs.

In one of the cases of low correlation, namely, Huntington's chorea, there is good evidence for the existence

of modifiers. The age of onset is very variable, and as its mean is 35·5 years and its standard deviation 12·4, it follows that in any pedigree some individuals who carried the gene may be omitted because they died before it showed its effect. Now Bell[1] found the following distribution of the affected progeny:

	Male	Female	Sex Unknown
Fathers affected ..	232	163	16
Mothers affected ..	153	173	7

The difference is highly significant for the children of affected fathers. This can be explained if there are one or more sex-limited modifiers tending to lower the age of onset in males. A man carrying such a modifier would be more likely than the average man carrying the main gene to develop the disease, and his sons would also, on the average, develop it before his daughters. Both allelomorphs of the modifier must be fairly common, or alternatively there must be a number of not very rare dominant modifiers. They cannot have any conspicuous effect on normal people, but may have some.

Let us consider the effect of selection in these cases. Dominant genes are exposed to selection in each generation. Many of these diseases are sub-lethal. Thus the

[1] Bell, J. (1934), "Huntington's Chorea," *Treas. Hum. Inher.*, 4, 1.

average time of survival after the onset of the ataxias is about sixteen years, whatever the age of onset. Hence genes causing early onset will soon be wiped out. But the recessive genes are not so exposed, except in the course of thousands of years; and unless they are in equilibrium we should expect to find a larger proportion with early onset. This is the case. Bell finds the mean age of onset in Friedreich's ataxia to be twenty-three years in the dominant and twelve in the recessive type. The corresponding figures for spastic ataxia are thirty-seven and sixteen, for spastic paraplegia nineteen and eleven. In such cases as these, where modifiers are unimportant, selection will do little to improve the race. It will merely keep mutation at bay.

Where, on the other hand, modifiers are important, as in Huntington's chorea, we may expect that selection will cause them to spread. The present age of onset of that disease may merely mean that primitive men and women seldom lived much beyond forty, so postponement of onset beyond this age had no selective advantage. If the unfavourable modifiers are not disadvantageous, they will spread until the disease becomes one of old age. Then the gene frequency will be increased by mutation until unions of persons carrying it become fairly common. The homozygous form will be a severe and perhaps lethal disease, and then perhaps other modifiers will be selected. This is Fisher's[1] theory of dominance. (I have

[1] Fisher, R. A. (1931), *Biol. Rev.*, 6, p. 345.

assumed that no eugenic measures are taken against the disease, which is unlikely. Of course Fisher's theory refers to the past.) It may well be that the genes which Penrose found to cause insanity in old age when heterozygous and mental defect in the young when homozygous upset the rudimentary minds of young *Pithecanthropus* even when heterozygous. But only much more prolonged research will decide whether Fisher's process is undergone by the majority of dominant genes, or only by a few.

In this chapter I have tried to show how, in the study of human genetics, statistical methods replace the various technical devices, such as milk bottles and etherizers, which are familiar to the *Drosophila* worker. These statistical methods owe much to the genius of Karl Pearson. He developed them in connection with a theory of heredity which is not now accepted. But they are essential adjuncts to any study of human genetics which goes beyond the mere accumulation of pedigrees. I have personally been fortunate in securing the advice, if not always the agreement, of his distinguished successor, Professor Fisher, until, as the result of a brutal assault by employees of University College, London, whilst attempting to enter his laboratory, he was compelled to leave London. He and I have frequently disagreed, but I think that any reader of *The Annals of Eugenics* will realize that our controversies have been far from sterile, and that, on the contrary, some of them have led, by a dialectical method, to the advancement of genetics.

It may be argued that such abstract investigations as I have described in this chapter will be useless for many generations, and that we should be better employed in collecting data of more immediate applicability; for example, as to the proportion of blind people whose parents are also blind, or the incidence of mental defect in different classes. I believe that this is wrong for two reasons. Science has progressed largely because scientists interested themselves in problems which the practical man scorned. The seventeenth-century scientist

> "Who made an instrument to know
> If the sun shine at noon, or no,"

was the pioneer of photography. Above all, I believe that in the present state of prejudice concerning human genetics any investigations which demand the most accurate possible observation and thought on this topic are of value. The late Pope wrote of "conjectures" concerning heredity. It is true that there is almost always an element of uncertainty in predictions concerning individuals. But when we deal with millions, probability becomes certainty, and conjecture accurate prediction. And when Herr Hitler writes of the evil effects of race crossing it seems worth while to point out that a race is nothing homogeneous, but a collection of very various individuals who have something in common which can only be accurately described in terms of the statistical methods which we are working out. Before we can speak

accurately of the evil effects of so complicated a process as a racial cross it would be well to investigate the evil effects of a single gene substitution.

We geneticists who are working on the accurate description and analysis of human genetics stand between two extremes, the conservatives who do not wish to see scientific method applied to human affairs, and the reactionaries who would apply half-baked science to them in the interests of a particular class or nation. Unlike conservatism and reaction, progress demands clear thinking. If this book can help towards clear thinking on human genetics it will not have failed.

ADDENDUM

Since this book was written Bell's important paper on human inbreeding, referred to on p. 154, has been published (*Ann. Eug.* 10, pp. 370–391). So have my own on the partial sex-linkage of spastic paraplegia (*Journ. Gen.* 41, pp. 141–147, 1941), referred to on p. 178, and on modifying genes (*Journ. Gen.* 41, pp. 149–157, 1941), summarized on pp. 185–194. I have also found reason to doubt the validity of Fisher's argument for linkage between Friedreich's ataxia and the blood groups (p. 184). Dr. Grüneberg has discovered new facts concerning the congenital mouse anaemias (pp. 105–108) which make the nature of these diseases clearer, but probably do not actually controvert any of the statements made concerning them. If I could have modified Chapter 3 after reading Waddington's *Organizers and Genes* I would gladly have done so, if only to use his terminology, which, in some respects, is clearer than my own. But I do not think that our views on any of the questions there treated are in serious disagreement.

J. B. S. HALDANE

May 1941

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