MENDELISM AND MEDICINE.

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Every medical student knows that hæmophilia is one of the "hereditary" diseases. Most qualified doctors are aware that it is a disease which appears almost exclusively in males and it is transmitted through the female line. A few might be able to go further and state that its genetic behaviour was in accordance with Mendelian laws and that it could be classed as a sex-linked recessive. But I doubt whether many doctors could explain in detail the biological process which these terms imply. Not being a biologist myself I am conscious that my own efforts to do so lack authority and may be inaccurate in some of the minutiae; but I hope to be able to describe in broad outline the principles of what is known as Mendelism and their application to some of the problems of medical practice.

Historical.

In the year 1859 Darwin first published "The Origin of Species." Biologists were so preoccupied in discussing the revolutionary ideas contained in this astounding work that nobody noticed an insignificant paper in the Proceedings of the Natural History Society of Brunn published by Gregor Mendel in 1865. Had Darwin read this paper his views on certain aspects of evolution would have been materially altered. But apparently nobody read it until 1900 when it was independently rediscovered by the distinguished botanists de Vries, Correns and Tschermak. Subsequent workers have fully confirmed the fundamental truth of Mendel's discoveries and the modern science of cytology has provided a physical explanation of the facts which Mendel's experiments established.

Bateson wrote "The experiments which led to this advance in knowledge are worthy to rank with those that laid the foundation of the atomic laws of chemistry." What manner of man was he who made such a tremendous contribution to knowledge and whose work remained hidden until sixteen years after his death? Johann Gregor Mendel was born in 1822. His parents were prosperous peasants in what was then known as Austrian Silesia. At the age of 25 he became a priest entering the monastery at Brunn in Bohemia (now known as Brno in that unfortunate State Czechoslovakia) of which he ultimately became Abbot. For four years he studied science in Vienna returning to his monastery in 1853 where he spent his spare time making hybridisation experiments on the plants in the abbey garden. After eight years' work he published, in 1865, the paper which, had it been widely read, might have advanced the science of genetics by a generation. He died in 1884 with no position in the scientific world and no presentiment of the fame which was to be his in the twentieth century.

Mendel's Experiments.

Let me first describe briefly the nature of his experiments. He worked mainly with the edible pea. Experiments in hybridisation had often been made before but the distinctive character of Mendel's work is due to the fact that he had the wisdom to investigate hereditary characters singly. He discovered seven characters in the pea which had a consistent genetic behaviour. Instead of trying to find out how all these seven characters were transmitted to subsequent generations he concentrated on one at a time. As an example he investigated the factor of stem length. Some edible peas are tall, others are dwarf. What would happen to this particular character if the tall and dwarf were crossed (neglecting, of course, all the other hereditary characters)? The result of this experiment was

that the hybrids were all tall. They did not differ to the eye from their tall parent. But if these hybrid tall were allowed to self-fertilise a quite unexpected result appeared. The next generation consisted of both tall and dwarf types and when large numbers of these were counted it turned out that there were always three tall to one dwarf—i.e. 75 per cent. were tall and 25 per cent. dwarf. If the dwarfs of this second generation were crossed with each other they bred nothing but dwarfs. If the tall, however, were crossed with each other another generation of tall was produced, but with a difference concealed to the eye. For one-third of these tall, when crossed with each other bred true and produced nothing but tall; but two-thirds behaved exactly like the tall children of the original cross, producing tall and dwarf in the proportion of 3:1.

Now this all sounds rather complicated but it is essential to have the picture clear if the principles of heredity are to be understood. In Figure I the results are set out in the form of a genealogical tree the letters T and d being used for tall and dwarf. The original parent forms are referred to as P₁ and the subsequent "filial" generations as F₁, F₂, etc. (these are conventional terms used in all works on heredity and Mendelism).

FIGURE I.

The problem which Mendel set himself to solve was to find some sort of explanation of the curious mathematical behaviour of his hybrids, and for the equally odd fact (which has long been known as a characteristic of human pedigrees) that children may be exactly like their parents in one respect (e.g. a tall pea bred from another tall) or conversely unlike the parent but resembling one grandparent—in fact, "skipping a generation." Up to his time views of heredity had been quite unscientific. They either invoked spiritual intervention or postulated some sort of "mixture" theory. Black coffee and white milk make a brown mixture. If you mix more or less coffee or milk you get a lighter or darker mixture; or if you continue to dilute the mixture with one only of the two fluids you ultimately get back to the original colour. The old expression "mixed blood" implies some such explanation. Such a theory could account for certain of the observed phenomena of heredity especially in so complicated a genetic entity as the human species. Galton attempted to express the hereditary make up of succeeding generations in mathematical terms and his "Law

of ancestral heredity" contains a good deal of truth. Working on the colour of basset hounds Galton computed that if any individual's total heredity was unity the one-half came from the two parents (that is, a quarter from each), a quarter from the grandparents, an eighth from the great-grandparents and so on. Mendel, by confining his attention to single factors, had much more precise data to work on and he saw clearly that the germ cells of his original peas must contain some "factor," the physical nature of which he had no means of explaining, which was passed on to succeeding generations. When the tall factor met the short factor in the fertilised ovule the short "receded" so he called it recessive; the factor for tallness dominated the hybrid so he called this dominant. The production of a mixed F₂ generation from these tall hybrids he explained by "segregation" of hereditary factors in the gametes.

The germ cell is known as a gamete and, of course, may be either male or female. In the case of the peas they are represented by the pollen cells and the ovule. Mendel suggested that when the hybrids formed their pollen cells and ovules the "factors" for tallness and shortness separated and were segregated in separate cells. Thus half of all the pollen cells would contain a factor for tallness and the other half a factor for shortness; and the same would be true of the ovules. In ordinary self fertilisation, such as occurs in most plants there would be an even chance of any ovule being fertilised by a tall or short pollen cell; and the ovules themselves can only contain either the factor for tallness or the factor for shortness—never both.

A simple diagram will make clear what happens when this random system of fertilisation takes place. The type of diagram is one that can be used for determining the genetic constitution of zygotes (that is the cell resulting from the union of male and female gametes in fertilisation) with any number of factors so the method is worth studying carefully. As we are for the moment considering only two contrasted factors we require a square divided into four (Figure II).

T T	d T
T d	d d

FIGURE II.

The factor for tallness is represented by a capital T and that for shortness by a little d (the capital indicates dominance and the small letter recessiveness). In the two horizontal columns we write the constitution of the female gametes or ovules which will be alternately T and d; then we add in the vertical columns the constitution of the male gametes or pollen cells and the four combinations represent the possible resulting zygotes. These are TT, dT, Td, and dd. Actually dT and Td are exactly the same so that we can say that random self-fertilisation of gametes from a hybrid tall-dwarf pea should give rise to three sorts of zygotes in the proportion 25 per cent. TT, 50 per cent. Td and 25 per cent. dd. Now as tallness is dominant all the zygotes containing T will develop into tall peas so that we shall have 75 per cent. tall and only 25 per cent. dwarfs which is exactly the proportion Mendel found after self fertilisation of his F₁ generation. It should now be clear that if the peas resulting from the TT zygotes are bred together nothing but tall can result and, again Mendel found that 25 per cent. of his F₂ tall bred true for tallness. Similarly the dd dwarfs self fertilised can breed nothing but dwarfs for the factor T is absent from their constitution. Those which contain Td on the other hand will behave in exactly the same way as the F₁ hybrids whose gametes were half T and half d; they will breed 75 per cent. tall and 25 per cent. dwarfs, but the tall will similarly differ in their zygotic constitution and in the way they breed.

Inheritance of two characters.

This is the simplest example of "mendelisation" and illustrates the two fundamental principles which Mendel discovered—the law of segregation and the law of free assortment or random combination of the gametes. He also showed that his laws held good when two independent characters were watched through successive generations but in this case the mathematical combinations of the gametes are more complicated. Let us consider for a moment the case of a pea which is hybrid for two characters—stem length and seed colour. The seeds may be green or yellow, and, in crossing these, yellow is dominant to green. A hybrid yellow-seeded tall pea has, therefore, the constitution YgTd (Y for the dominant yellow and g for the recessive green). The two types can form four possible sorts of gametes, namely YT, Yd, gT and gd. There are sixteen possible resulting zygotes from random cross fertilisation of these two types and we shall need a "chess board" of sixteen squares instead of four only as in Figure II. The result is shown in Figure III. The four types of ovule are written

Y Y T T	g Y T T	Y Y d T	g Y d T
Y g T T	g g T T	Y g d T	g g d T
Y Y T d	g Y T d	Y Y d d	g Y d d
Y g T d	g Y T d	Y g d d	g g d d

FIGURE III.

horizontally across each of the four rows of four squares, the colour factor on top and the size factor below. Then the four types of pollen cell are written vertically downwards in the same way, care being taken to write them in exactly the same order. The resulting zygotes are thus obtained. Every one containing both Y and T will be yellow and tall—there are nine of these. Those containing gg and T will be green and tall—there are three of these. Those containing Y and dd will be yellow and dwarf—and there are also three of these. The final possibility is the constitution ggdd which will, of course, be green and dwarf and will only occur once in the whole sixteen.

Such an experiment, therefore, gives rise to 9 yellow-seeded tall plants, 3 green-seeded tall plants, 3 yellow-seeded dwarf plants and one green-seeded dwarf. Nevertheless it will be seen by studying their zygotic constitution that these four varieties can be further sub-divided if we do not only consider their outward appearance. The actual hereditary potentialities of their cells will be as follows:—4 will be YgTd; the combinations YgTT, YYtd, ggTd and Ygdd will each occur twice; and the ggTT and ggdd combinations once. If the system of working out the constitution of the zygotes from the gametes has been understood the reader should now be able to forecast the result of crossing any of these different types. In order to know what will be the result of a cross between, say, a tall green-seeded pea and a dwarf yellow-seed one it is necessary to know their respective zygotic constitutions. And it should by now be clear that, if this is not known, it would be possible to discover it by crossing the doubtful plant with one of known constitution.

A "pure" dominant—that is one in which the dominant character is doubly represented as TT of Figure II and the TTYy in Figure III—can, when self-fertilised, only produce its own kind and such an experiment proves its constitution. Such a plant can be used to find out the zygotic constitution of another by cross fertilisation.

Homozygotes and Heterozygotes.

Before giving an actual example to make this perfectly clear two commonly used terms must be introduced and briefly explained; these are homozygote and heterozygote with the corresponding adjectives homozygous and heterozygous. A homozygote is a zygote formed from two gametes bearing the same factor for two contrasted characters. In the illustrations previously given a TT or a dd zygote is a homozygote and the resulting individual can be said to be homozygous for the dominant or recessive character respectively. On the other hand the Td zygote and resulting pea are heterozygous. The usual way of determining the constitution of the individual's zygotes for any particular character is to cross it with the recessive—which, under all circumstances, can only be homozygous. If we have a tall pea we cannot tell by looking at it whether it has the constitution TT or Td. If we cross it with the recessive dd we shall get different results according to whether the tall is heterozygous or homozygous. It should not need elaborate diagrams or calculations to show that crossing a TT with a dd can only give rise to Td plants; and self fertilising the latter will at once show their zygotic constitution as they will produce the usual 3:1 tall and dwarfs. If our unknown tall has the constitution Td the result of crossing with dd will be different. We shall get 50 per cent. Td and 50 per cent. dd; the latter can be distinguished by their form and the former by self fertilisation.

Human eye colour.

Having got so far we might make a brief excursion into human genetics and see a simple example of the application of these principles to a common human character—eye colour. The subject is actually not so simple as in the example I propose to give but it is broadly true and will afford the reader an opportunity to test his understanding of the simple forms of mendelism which have so far been described. Let us assume two basic eye colours, brown (B, because it is dominant) and blue (b, because it is recessive). An homozygous brown-eyed man marries an homozygous blue-eyed woman. I suggest that the reader thinks out the result of this mating (if necessary, with pencil and paper) before reading further.

The father is BB; the mother bb. The only possible gametes are B and b so that all the resulting zygotes must be Bb, that is heterozygous brown-eyed children.

If we consider an incestuous union between the males and females of the F₁ generation we shall get a result which, again, the reader is invited to think out. We now have both male and female gametes of different sorts, B and b. The resulting zygotes will be BB, Bb, bB and bb. In our new terminology 25 per cent. homozygous brown-eyed, 50 per cent. heterozygous brown-eyed and 25 per cent. homozygous blue-eyed children. On this assumption two blue-eyed parents cannot have a brown-eyed child; but brown-eyed parents may have blue-eyed children provided they are both heterozygous. This illustrates a most important point in inheritance with special reference to the inheritance of certain human diseases, for it shows how a recessive character may be carried through many generations before actually appearing. In our illustration brown-eyed parents might give rise to many generations of brown-eyed children before a blue-eyed one appeared. For the latter event to happen both the parents must be heterozygous and, even so, the chance of a blue-eyed child is only one in four; as human families are small compared with those of plants and animals the blue-eyed child of brown-eyed parent will be a relatively rare occurrence.

Dominance.

In all the foregoing examples great prominence has been given to the phenomenon of dominance. Nevertheless it must not be assumed that dominance of one character over another is always displayed. In crossing a red snapdragon with an ivory-coloured one the 50 per cent. heterozygotes will be pink, that is intermediate between the two pure homozygous forms. In human eye colour the evidence available tends to show that individuals with light brown, medium brown and greenish-hazel eyes are really heterozygous hybrids and that the basic colours are black and grey; of these the former may include the dark browns and the latter the blues and violets.

Let us for a moment consider the case of two mendelian characteristics in a human being which do not show complete dominance—straight and curly hair and black and grey eyes. Take the case of an F₁ generation from the mating of a black-eyed straight-haired person with a grey-eyed curly-haired one. Inasmuch as we are assuming the absence of dominance these two individuals must be homozygous or pure for the two characteristics; otherwise they would be intermediate in appearance. Their offspring will be heterozygous for both features and intermediate in appearance; they will be brown-eyed with wavy hair. The effect of interbreeding these can be worked out in exactly the same way as was done in Figure III for the peas with two characteristics. They can form four sorts of gametes. Black eye—straight hair (BS); Black eye—curly hair (BC); Grey eye—straight hair (GS); and grey eye—curly hair (GC). Of the sixteen zygotes formed from free assortment of these gametes we shall find (Figure IV):—

B B S S	B B C S	G B S S	G B C S
B B S C	B B C C	G B S C	G B C C
B G S S	B G C S	G G S S	G G C S
B G S C	B G C C	G G S C	G G C C

FIGURE IV.

“pure”—in other words they are heterozygous and will not breed true. Reversions will occur and spoil the pedigree.

- 4 BGSC brown and wavy like the parents.
- 2 BBSC black and wavy.
- 2 BGSS brown and straight.
- 2 BGCC brown and curly.
- 1 BBSS black and straight like one of the grand-parents.
- 1 GGCC grey and curly like the other grand-parent.
- 1 BBCC black and curly.
- 1 GGSS grey and straight.

It will be noticed that the last two are homozygous for both factors and will breed true in future generations. In other words, a new true-breeding type has been evolved from the original cross and this is a method used by stock breeders. The other new varieties are not

Chromosomes and genes.

It was about 1883 that Van Beneden discovered that the germ cells contained half the number of chromosomes contained in the somatic cells. It will be remembered that this halving occurs in the so-called maturation division and applies equally to male and female germ cell. In the early part of the present century, soon after the rediscovery of Mendel's work, it gradually dawned on biologists that here might be the physical explanation of segregation. What if

the mendelian factors were carried in the chromosomes, the pairs of contrasted characters (allelomorphs as they are called) separating from each other in the splitting of the chromosomes and being segregated by the act of reduction which ensures that only a half of each "diploid" outfit of chromosomes enters each germ cell? Without going in detail into the work which has been done on this particular branch of the subject in the past 30 years it may be said that such a mechanism is now generally accepted as being the true physical basis of mendelism. To Thomas Hunt Morgan, Professor of Zoology at Columbia University, in particular we owe this important development of Mendel's work. Using the fruit fly, *drosophila melanogaster*, as his experimental animal he has illuminated the darkness of genetic theory in the most astonishing manner. This is not the place to describe in detail the processes of spermatogenesis and oögenesis; for those who wish to refresh their memory works on biology should be consulted. It will be sufficient to recall that the chromatin of the nucleus, which normally appears as an irregular network, forms itself into pairs of "strings" when each cell divides; it is these latter which are known as chromosomes and which undergo reduction in the maturation division. Now it has been found that the number of chromosomes is constant for each species. Man has 24 pairs and his germ cells 12 each. *Drosophila* has only four pairs and each pair is sufficiently different to be recognisable under the microscope. In studying the behaviour of mendelian characters in *drosophila* it was found that many of them appeared to be linked together; and further investigation of the different linked groups showed that they fell naturally into four groups—in fact that there are as many groups as there are pairs of chromosomes. From these facts Morgan has built up the theory of the "gene"—which is only another word for one of each allelomorphic pair of mendelian characters. We must regard each chromosome as made up of a number of these genes arranged in a linear fashion like beads on a necklace. It has been estimated that these genes are comparable in size with some of the larger protein molecules. From observations on the phenomenon of "crossing over" it has actually been possible to give definite positions to the genes in the chromosomes of *drosophila*. By "crossing over" is meant an exchange of genes between two homologous pairs while they lie intimately connected during cell division. An elementary picture of the process may be conjured up by imagining two strings of beads, red and green, lying side by side. Four or five of the red beads get entwined with the four or five corresponding green ones and both strings break; the green ones then exchange places with the red ones and the strings join up again. In this way a dominant gene from the maternal half of the chromosome may take the place of its recessive allelomorph in the paternal half of the chromosome. Such crossings over naturally upset the expected Mendelian behaviour. But they have been tremendously useful in that they have enabled Morgan actually to prepare a map of many of the genes in the chromosomes of *drosophila*. The map may take many years to complete as it is calculated that this small insect with only four chromosomes possesses probably several thousand genes. Man with his 48 chromosomes must possess a startlingly large number, and the possible combinations of these, even allowing for linkage, is almost infinitely great.

Let us take stock for a moment of the position as far as we have got. The tallness of Mendel's peas was due to a gene for tallness situated in one of the chromosomes. Side by side with the tallness gene was a gene for dwarfness.

(It might be mentioned, in passing, that it has been considered by many biologists that a recessive gene really means the absence of the dominant gene from the pair of homologous chromosomes—the so-called "presence and absence

theory." On this theory (which is not, by the way, supported by Morgan) the gene we have described as *d* would mean absence of *T*—if *T* is completely absent (*dd*) the plant is dwarf.)

In maturation of the ovules and pollen cells this chromosome split longitudinally separating the tall gene from its allelomorph the short gene. As only one-half of the chromosomes could be present in the gamete this would contain either one or other of the genes, not both. In fertilisation the two allelomorphs looked for their proper partners and joined up with the results which have been stated. In the illustrations of two independent characters, whether in pea or human being, the genes concerned must have been in different chromosomes for there was no linkage. In other words, the free assortment postulated by Mendel refers to chromosomes and not to genes. If the genes for two characters are in the same chromosome there cannot be real free assortment. It follows that every gene must have a partner or allelomorph with a contrasting potentiality; that genes will be linked in as many groups as there are chromosomes; and that the expected genetic behaviour of any organism may, from time to time, be upset by crossing over.

The determination of sex.

Now let us consider why it is that some zygotes develop into males and others into females. In practically all organisms who reproduce sexually there is found in the males one pair of chromosomes of unequal size; the larger of the two is called *X* and the smaller *Y*. The females have no unequal pair the *X* being partnered not by a *Y* but by another *X*. As far as these two chromosomes are concerned, therefore, the male constitution is *XY* and the female *XX*. There must obviously be a difference in the germ cells of the two sexes in respect of these chromosomes. The ova can only contain *X* while half the sperms will contain *X* and the other half *Y*. In fertilisation *X* and *Y* sperms are trying, in equal numbers, to enter ova containing only *X*. It follows that, other things being equal, there is an equal chance of any ovum being fertilised by an *X* or a *Y* sperm. If *X* wins the race the zygote will grow into a female (*XX*). If *Y* wins it will be a male (*XY*). This mechanism is an established fact and finally disposes of the numerous unscientific theories which still flourish amongst expectant parents and are occasionally encouraged by medical men who should know better. The *Y* chromosome is very small and can contain few, if any, genes. There are a few organisms in which genes in the *Y* chromosome have been found, but for most species (including, probably, the human race) it is of no importance except for its sex determining capacity. In some cases it appears to be absent altogether, the male cell simply having an odd unpaired *X* chromosome. The *X* chromosome is of normal form and there is no doubt that it contains genes for many other characters besides sex. Such characters being carried in the sex chromosome are known as "sex-linked" and are of importance in medicine since the genes which cause colour blindness, hæmophilia and certain other conditions are of this sort.

Hæmophilia and sex linkage.

As so many erroneous ideas are prevalent about hæmophilia it may be as well to explain its genetic behaviour in more detail. The man with hæmophilia has, in his *X* chromosome a factor (*A*) which prevents the proper clotting of the blood (it is more probable that his *X* chromosome *lacks* a gene which normally causes clotting but, for the sake of clarity, we will represent the abnormality by adding

the letter A to the X which represents the chromosome). The factor A is recessive to the normal condition. As the Y chromosome has no dominant gene to balance it the males which contain it will be affected, but most of the females will possess a contrasting dominant gene in the other X chromosome. A male hæmophilic has the constitution AXY. He marries a normal woman (XX). The sperms will be half AX and half Y; the ova all X. In the next generation (F₁) all the daughters must be AXX and all the sons XY. The latter are free from the taint and cannot transmit it. The daughters are free from the taint but the ova they form will be half AX and half X. If these are fertilised by normal sperms, as when one of the F₁ daughters marries a normal man, there will be four possibilities; AXX, AXY, XY and XX. In other words, one-half of the sons will be affected and half the daughters will be carriers; the remaining 50 per cent. of the children (sons and daughters) will be neither affected nor carriers.

If a carrier female marries an affected male (AXX = AXY) the female gametes will be AX and X and the sperms AX and Y. The next generation will be AXAX, AXX, AXY and XY. Therefore half the daughters will be homozygous recessives and therefore affected; the remaining daughters will be carriers and half the sons affected; the remaining half of the sons will be free. It is, therefore, possible for a woman to be affected with hæmophilia (contrary to popular belief) but such an event is rare because it requires an affected father. Hæmophilics rarely survive to maturity and consequently hardly ever have children. If they do the male can transmit the disease but, of course, only indirectly through his daughters. If, however, an affected male marries an affected female (AXY = AXAX) it is obvious that all the children will be affected irrespective of sex.

Mutation.

At this point it may not be inappropriate to discuss how such a hereditary disease first arises. This is so closely associated with the larger problems of variation in general, evolution, and the origin of species that only a very superficial discussion can be allowed. Before the days of Darwin, Lamarck had postulated a mystical urge which led living things to improve on the work of their creator and to develop variations useful in the struggle for existence. Darwin proposed the view that use and disuse were the main causes of variation. The hand developed from the foot because through countless generations certain types of animals had tried to use their feet for holding things and climbing trees; similarly disuse of a limb might lead to its ultimate disappearance. Such a theory demanded that acquired characteristics should be inherited and although, even in Darwin's day, there was a good deal of evidence to negative such an idea no theory could be found which better fitted the facts of evolution. Weismann in 1885 dealt the death blow to the possibility of acquired characters being transmitted and since his day evidence has accumulated in support of his view.

Even before Morgan's theory of the 'gene' was known, the idea that hereditary variations occurred by "mutation" had been put forward. De Vries, in the closing years of the last century, published his studies on the variations of the evening primrose and showed that new varieties with the capacity to mendelise always arose suddenly and not by any gradual process. The modern theory of variation, excluding those that are purely environmental in origin and consequently not transmissible, is that mutations (probably chemico-physical changes) occur in the genes and, once present, follow the ordinary laws of genetic transmission. Evolution, therefore, becomes a matter simply of periodic mutations

combined with natural selection; the advantageous mutations survive and the others tend to die out. But harmful mutations do not by any means always disappear and, even if they do, they may recur. The mutation must have some natural cause and as long as the cause is in existence the same mutation may be expected to turn up at fairly regular intervals. Hæmophilia is a harmful mutation and natural selection limits its propagation through the high death rate of the affected males. If it behaved like a simple dominant it would soon be eliminated from any given pedigree—although it might crop up again in another from a fresh mutation of the “clotting” gene. But its recessiveness and the linkage to the sex chromosome give it a chance of survival although opposed to the interests of the race.

Environment.

An important factor in the survival of variations is environment. A favourable environment may perpetuate a variation; but place it in a different environment and it will rapidly die out. Thus a “natural” environment leads to “natural” selection; but an artificial environment may select variations which nature would reject. One effect of the advance of medicine is thus to prevent the operation of natural selection, for we continually strive to keep the defective genes going. There has been much controversy over the question of whether there is a hereditary factor in pulmonary tuberculosis. Not a few observers have denied it altogether and attribute the common familial incidence solely to the increased exposure to contact. There is at least an equally good case to be made out for the view that variations in immunity to the disease are inherited. This explains the relative immunity of the civilised and urbanised communities compared with the uncivilised and primitive races. The former, by natural selection, have improved the stock and the gene or genes responsible for defective immunity have tended to die out. Advances in the treatment of the disease should now ensure a reversal of the process. Our artificial selection perpetuates the hostile gene. The obvious remedy is sterilisation but even this cannot have any effect upon the incidence of mutations. It is not likely, for example, that the compulsory sterilisation of mental defectives (even if it were practicable) would entirely eradicate mental defect from the race. If the original defect was due to a mutation (and since it is transmissible this is likely) the same mutation may be expected to arise from time to time. Nevertheless sterilisation should prove racially beneficial.

Having introduced the word “environment” it is tempting to embark upon a discussion of the relative rôles of heredity and environment in forming the sum of individual characteristics which we call constitution. It is, however, such a big subject that the temptation must be resisted. It is obvious that, to a greater or smaller extent, environment fashions the individual from the genetic clay. And in so complex an organism as the human being it can never be easy to allot full responsibility to either factor. The most interesting observations on this subject are those which deal with the differences between what are known as “identical” twins. Such twins are formed from the union of the same gametes—one sperm and one ovum—and it might be assumed that they would be, genetically at any rate, the same individual doubled. If this were so any differences would be due only to changes in the environments. It is certainly true that such twins in their early years, when the environment is as nearly identical as it can be, usually show a most remarkable similarity, physical mental and emotional. But I am not aware that any pair of twins has yet been investigated in which no physical differences could be found. The finger prints, although much more akin than those of other sibs (the word used for the brother-sister relationship), always display recognisable

variations and it is thought that the degree of difference depends upon the stage at which the embryo divides into two. If it divides early, say at the first cell division after fertilisation, the likeness will be great; if the separation occurs late greater differences will appear and the latest of all will give rise to the different varieties of conjoined twins. But these are matters which can only be mentioned; there is not time to discuss them fully.

Practical applications.

As this article has been written for the benefit of doctors we must now turn from the more biological aspects of the subject, superficial as these have been, and consider for a moment some of the practical applications of the science of genetics to medical practice. A complete review of all the hereditary diseases is out of the question and, indeed, most of those which show a well marked Mendelian inheritance are rare. Hæmophilia and colour blindness have been mentioned. Their genetic behaviour is fairly clear cut because they are sex-linked. Any disease which is due to a single dominant gene will be expected to turn up in every generation, although cases of dominant pedigrees in which the disease skips a generation have been recorded; this is explained by assuming a temporary reversal of dominance, but it may be due to the fact that the disease is present in so modified a form that it escapes recognition.

On the other hand the disease which is caused by a single recessive gene may be very irregular in its appearance. As long as heterozygous carriers mate with normals the defect will be passed down the generations without appearing. Then one of these mates with another heterozygous carrier and the resulting homozygous recessive displays the disease. This is really the only disadvantage of consanguineous marriages. Mere inbreeding is not in itself undesirable. Stock breeders use it freely and human inbreeding to a high degree has been known to occur without harmful results. The Pharaohs of ancient Egypt inbred for religious reasons but continued to produce rulers of high mental and physical qualities. Inbreeding tends to produce homozygosity. If all the genes are desirable nothing but good can result. The harm comes when some undesirable gene is concealed in a heterozygous individual. If this individual mates with a near relative there is naturally a fair prospect that he or she too will carry the same gene and that some of the offspring will be homozygous for it. If the doctor is consulted about a prospective cousin marriage he need not necessarily condemn it out of hand. In cases where there is a bad family history in the common ancestry there would be real risk of the children of such a union being affected. But where the family history is good the chances of some hereditary defect appearing in the offspring is only slightly greater than in a similar marriage of unrelated parties. One can never absolutely exclude the noxious recessive gene.

In human beings many normal inherited characters are controlled not by a single gene but several interacting ones. If, for example, skin colour was due to a single gene and black was dominant to white we should find that the children of a pure black—pure white marriage would be all black; and interbreeding of these would give three blacks to one white. If dominance was not marked the hybrid F₁ children would be brown and their offspring would conform to the pattern of any heterozygotic mating—25 per cent. pure black, 25 per cent. pure white and 50 per cent. hybrid. In actual practice these results do not appear for, although the F₁ generation tends to be a coffee coloured hybrid, the F₂ generation displays all grades from pure white to pure black. This can be explained on the assumption (which is probably true) that a number of different genes in different chromosomes

are concerned with the production of skin colour. Such a mode of transmission is called "multifactorial."

The genetics of disease is somewhat simplified by the fact that a large number of them seem to depend on a single gene. As they were presumably due in the first place to mutations this is not surprising. We have, therefore, a number of different types of mendelian inheritance of pathological conditions. The simple dominant will, if the generations are sufficiently numerous, turn up regularly. The simple recessive, on the other hand, may be concealed for many generations; its chance of showing itself will depend (except in consanguineous unions) upon the incidence of the recessive gene in the general population. A nation such as ours, being, until recent years, an island race with little contact with the outside world is necessarily to some extent inbred; the Norman genes introduced in 1066 must have had a considerable influence upon the genetic make-up of the race. In the animal world most mutations are recessive to the normal condition and one might expect diseases and malformations which are hereditary to follow the same rule. In man, however, not a few of these are dominant. The explanation lies in the fact that natural selection eliminates the dominant mutation which is disadvantageous to the animal. Man alone has the power of survival in spite of disadvantageous mutations and so tends to preserve a number of the abnormalities which show a dominant form of inheritance.

It had been my original intention to devote more space in this article to a discussion of actual diseases which are known to be hereditary. Space, however, forbids any detailed description of these and my main purpose will have been served if the reader with little or no previous knowledge of the biological aspects of heredity feels that he could now inspect a human pedigree with intelligent interest. As already indicated it must not be expected that all diseases and abnormalities can easily be shown to have a simple Mendelian behaviour. "Multifactorial" transmission leads to a very complicated picture when the pedigree is traced and some knowledge of mathematics is needed to attribute a variation to a two-factor mendelian inheritance. It has, for example, been suggested that certain pedigrees of diabetes could be accounted for by the presence of two dominant unlinked genes both of which must be present if the disease is to develop; and other conditions may depend upon an even more complicated method of transmission.

It must also be borne in mind that the diathesis or constitutional liability to certain diseases is likely to be the hereditary factor in quite a number of cases (tuberculosis for example) and in this case the disease will only develop in a favourable environment. The diathesis might follow the rule of dominant inheritance (unifactorial) and yet skip a generation because the environment was unfavourable. And it must also be remembered that family tradition, which is an external form of inheritance quite independent of genes or mendelian mechanism, often determines the environment.

In conclusion, I propose to give a few examples of human pedigrees and briefly indicate the points they illustrate. It would prove a useful exercise for the reader if he were to attempt to analyse these before reading the explanations; with the knowledge gained by the general description of heredity he should be able to determine which types of mendelian inheritance are at work in each case. In all the pedigrees males are indicated by squares and females by circles; the affected individuals are shown black and the normals clear. Each generation is numbered on the left in roman figures and the individuals are numbered in ordinary numerals

—this facilitates reference and one can refer to an individual as for example, III 7. Where an individual is a healthy carrier of the defect the square or circle contains a dot.

The first pedigree is one of feeble mindedness showing dominance of the defect. It will be noticed that I 2 married twice. By his normal wife he had all normal children but when he married an affected wife he had one normal and one affected. The wife must, therefore, have been heterozygous. Had she been homozygous all her children would have been affected. Actually the expected proportion (50 per cent.) showed the defect but with so small a number she might easily have had two children of the same sort. The fact that one was normal, however, proves her to be heterozygous. Her son, having a normal father, must also be heterozygous. He (II 2) marries a normal and we should expect half his children to be affected; actually he has three normals (III 5, 10 and 11) out of seven. Three of the abnormals marry. III 3 who must be heterozygous, marries another feeble minded woman and has one normal child (IV 6) out of eleven. This proves that the mother is also heterozygous and we should, therefore, expect their children to mendelise in the proportion 50 per cent. heterozygous, 25 per cent. homozygous (i.e. 75 per cent. affected) and 25 per cent. homozygous for the pure recessive (normal) condition. With only eleven offspring the result is sufficiently near to what we expect. III 6, a feeble minded girl, marries a feeble minded man and has one normal out of three children. This shows the father to be heterozygous and the expected ratio from the union is the same as in the III 2—3 union. III 8 marries but the condition of her husband has not been ascertained; as they have one normal child the chances are very strongly that he is normal; but he might have been affected and the one child might represent the one pure recessive we should expect in every four children (assuming the father to be heterozygous). Conversely III 11 is normal but has one affected child out of two so we may safely assume that she married a feeble minded man who was heterozygous—this is proved by the fact that he had one normal child.

Pedigree I.—Feeble-Mindedness (after Goddard) : from Crew's "Organic Inheritance in Man."

The second pedigree is from an allergic family displaying the defect of asthma on exposure to rabbit fur. No particular comment is necessary. It is presumed that the marriages were all to normal individuals but the pedigree does not show this. If this is so, some explanation is required of the fact that IV 4 had two affected children, for a dominant defect cannot be "carried." This may be an

example of temporary reversal of dominance. A less likely explanation is that she was never exposed to rabbit fur and so never displayed the defect which was present in her genetic make-up—or, as the genetecist would say, her genotype did not correspond with her phenotype.

Pedigree II.—Allergy ("Rabbit" Asthma). Fantham's pedigree (1925) from "The Chances of Morbid Inheritance."

In pedigree three we have a case of a simple recessive defect (Freidrich's ataxia) which appears in the fifth generation as the result of a consanguineous marriage. IV 1 and 2 both marry their second cousins (3 and 4). Although no case of the disease has been known in the family for three generations back, it duly appears in the next. We have no means of telling whether I 1 or 2 was responsible for introducing the guilty gene into the family. It must have been one or other of them but only by tracing the pedigree further back could we determine which; even then we might have to go back for many generations before we found another case of the disease. As a result of the two marriages in generation IV—in both cases, of course the two partners are heterozygous—we should expect only 25 per cent. of the children to be pure recessives and so affected. In the larger family the incidence works out very approximately according to expectations; but in the other, simply by the operation of the laws of chance, half the children are affected.

Finally we have a pedigree of a sex-linked recessive defect (in this case red-green colour blindness). It will be noticed at once that all the affected members of the family are males, which immediately suggests sex linkage. Only one male in the family marries (II 2) and all his children are normal. II 4 and 6 are females. They marry normals and transmit the defect to a proportion of their male offspring (on an average to a half) and some of their daughters (again on an average half) must be carriers. We know nothing of the daughters of 6 because they were not

married at the time the pedigree was traced. At least one of them would be likely to be a carrier. The only daughter of II 4 is obviously a carrier as one of her two sons is affected.

Pedigree III.—Freidreich's Ataxia (after Hanhart) from Crew's "Organic Inheritance in Man."

Pedigree IV.—Red-Green Blindness (after Groenouw) from Crew's "Organic Inheritance in Man."

If perforce I leave the subject there I hope my readers will not think that I have attempted to do more than scratch the surface of this complex but fascinating field of study. If I have succeeded in giving an intelligible introduction to the subject my aim has been achieved. Below will be found a bibliography of the works which I have found most useful. I owe a debt to their authors which it would be ungrateful not to acknowledge.

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