SOME CONTRIBUTIONS OF MODERN GENETICS TO MEDICINE

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Modern genetics stems from the work, published in 1866, of the Augustinian monk Gregor Mendel, who occupied his leisure by growing edible peas in the monastery garden. Mendel's work went almost unnoticed by his contemporaries, and it was not until 1900, after the ground had been prepared by the great advances in cytology during the 'eighties and 'nineties, that its importance was recognized more or less simultaneously by de Vries, Correns, and Tschermak. For just half a century now genetics has made rapid and constant progress and has found application to the whole range of living organisms, from viruses and bacteria to man himself. It is with the latter that medical genetics has hitherto been mainly concerned, though the former will probably occupy an increasingly important place in the subject.

It is the purpose of this article both to indicate the scope and importance of medical genetics and to emphasize the unique opportunities which exist for doctors to collect and use genetical data. The main fields of application will be covered, with particular reference to the practical use to be made of genetical theory. Special attention will be given to methods of recording data so as to ensure that the maximum amount of information can be extracted from them; and some of the special uses of family pedigrees will also be mentioned.

There is no need to do more than make a passing reference to the elementary principles on which practically the whole of genetics is based. Both of Mendel's laws may be summarized under the single heading of "particulate inheritance," according to which the basic units of heredity are material particles—the genes—which are transmitted unchanged from generation to generation. The first law, the law of segregation, states that characters are controlled by pairs of genes which segregate or separate from one another during the formation of germ-cells and pass into different gametes, which contain only half the full (diploid) quota of chromosomes and are therefore termed haploid. The pairs are restored at fertilization. Thus the genes are shuffled by segregation and redealt to the next generation. Characters controlled by genes may also segregate, and different types will appear amongst the offspring in certain definite proportions. The second law, the law of independent assortment, states that when two or more pairs of genes segregate simultaneously they do so independently of each other. This law has had to be modified by the existence of linkage. Briefly, chromosomes, and therefore genes in different chromosomes, are shuffled independently; but genes in the same chromosome, in which they are arranged in a linear order, tend to be handed on together, segregating and recombining, however, to an extent which depends on their distance apart.

Owing to the random element introduced by the shuffling process the analysis of genetical data must

inevitably appeal to the ideas of uncertainty and probability associated, for example, with poker or bridge. With experimental plant or animal breeding the element of uncertainty can often be considerably reduced by using large progenies. In man, on the other hand, not only are families small but it is often difficult to find marriages between individuals of the appropriate genetic constitution. However, special methods are available for dealing with these difficulties, and a surprisingly large amount of useful information can often be extracted from apparently unpromising data.

There is another fundamental genetic phenomenon which must be mentioned; that is, the occurrence of mutations. Mutation is perhaps most satisfactorily defined as the beginning of a heritable variation. It can be applied to either genes or chromosomes. A gene may suddenly, though with extreme rarity, undergo a spontaneous change to a different form, and this change may be reflected in the characters which the gene controls. Again, chromosomes may be present in abnormal numbers, or a piece of one may break off and either be lost (deletion), or become reattached the wrong way round (inversion) or even joined on to a different chromosome (translocation). The word "mutation" should be applied only to the act of change in a hereditary unit. New genes which suddenly appear through mutation are called "mutant genes" and the characters to which they give rise "mutant characters."

Much of the early work on genetics was carried out by T. H. Morgan and his school, who bred the fruit-fly *Drosophila melanogaster* literally by the million. Though these studies may seem somewhat remote from medicine, the hereditary mechanisms thus elucidated have in fact proved to be of universal application.

Contributions to Plant and Animal Breeding

Substantial contributions have been made by genetics towards increasing the production of food, particularly in the cereal group. Considerable increases in the yield of maize were obtained by using breeding techniques designed to produce new varieties of "hybrid corn." Again, the manufacture of textiles has been aided by producing cotton plants with longer and stronger fibres, and by breeding sheep with heavier and finer fleeces. Useful work has also been done on the resistance of plants and animals to pests and disease. Further examples of advances in both plant and animal breeding could be given almost indefinitely.

Medical Applications

It is well known that the rare phenomenon of mutation can be considerably speeded up by x-ray irradiation. Various strains of the mould *Penicillium* were irradiated and a search was made for high-yield mutants. The process was then repeated, with the result that in less than a year a fivefold to sevenfold increase in the yield of penicillin was obtained under standard growth conditions.

Genetics has also something to say about another aspect of antibiotic therapy. The genetic study of bacteria indicates that strains resistant to penicillin, streptomycin, and sulphonamide drugs may originate through mutation. The antibiotic eliminates the susceptible bacteria and gives the resistant mutants a chance to survive and multiply. A thorough understanding of

this mechanism will make it increasingly easier to plan the clinical use of antibiotics in such a way as to minimize the risk of the development of resistant strains.

Although one of the essential ingredients of the evolutionary process is the variability provided by mutation, most mutations are deleterious for organisms which are fairly well adapted to a steady environment. Under ordinary conditions it can be shown that most fully recessive mutant genes that are capable of detection will lie latent for thousands of years before becoming manifest. However, heavy irradiation of the germ-plasm can occur through faulty technique in radiology and is an even greater danger with the use of atomic energy in peace and war. This may result in a very great increase in the natural mutation rate, producing an appreciable deterioration in human heredity. It is a sobering thought to consider that an atomic bomb falling in a highly populated region will probably cause more deaths in succeeding generations by genetic damage than it will at the time of the explosion by blast, heat flash, and irradiation.

A word should be said about the possibility of using experimental animals for the study of comparatively rare inherited defects. For example, canine haemophilia is a sex-linked recessive condition, as is human haemophilia, and it is also very similar clinically. Again, haemolytic disease of the newborn, due to incompatibility between the bloods of mother and offspring, also occurs in certain animals, notably mules, horses, dogs, and rabbits. But so far the analogy with man is not complete, injury in animals occurring only after birth through the absorption of maternal antibody from the colostrum. When genetic and clinical conditions are sufficiently close in both man and a suitable experimental animal, it is to be hoped that the far greater numbers of the latter available may simplify research and lead to substantial advances.

Much of the fascinating work in medical genetics has been done on rare abnormalities such as haemophilia or Huntington's chorea. The number of different conditions that have been studied is very large indeed, and it is most unlikely that the average student or clinician will ever personally encounter more than a small proportion of them. However, several characters, particularly serological ones, are by no means uncommon.

There are now eight main blood group systems: ABO, MNS, P, Rhesus, Lutheran, Lewis, Kell, and Duffy, which are apparently inherited independently of each other. Thus, with these and the attribute of sex and the ability or inability to taste phenylthiocarbamide (P.T.C.), we may have as many as 10 of the haploid number of 24 chromosomes of man distinctly marked. In searching for linkage these are the characters most worthy of examination. It is difficult to over-emphasize the importance of genetics in serology, and the extreme relevance of this field to everyday problems confronting practitioner and specialist alike. Common applications are to problems of relationship and disputed paternity.

Medico-legal Work

One of the best-known elementary cases is that of Mrs. W, who found on returning home from hospital that her baby had on its back a piece of adhesive tape bearing the name "B." The baby at the "B" house was labelled "W." Had the babies been interchanged

or had someone been careless with the labels? The bloods of the six persons involved were as follows:

	Group	Genotype		Group	Genotype
Mr. B.	AB	GAGB	Mr. W.	O	gg
Mrs. B.	O	gg	Mrs. W.	O	gg
Baby "W"	O	gg	Baby "B"	A	GAGA or GAg

In this table G denotes a dominant gene and g a recessive one. When the pair are identical, they are said to be homozygous, when different (as GAg) they are called heterozygous. A recessive gene is one which cannot make its influence felt in the individual when present with a dominant, but which after segregation (separation from its dominant partner) may have the chance to manifest itself in the offspring.

There had clearly been an accidental interchange of babies before the mothers went home. This is doubly proved, for Mr. B could not have had an O child, nor could Mr. and Mrs. W, both of group O, have produced an A baby. In this extreme case no recourse to any other group is necessary. The same kind of principle applies to disputed paternity. Although a decisive result is by no means always the case, the use of as many blood groups as possible makes such a result very much more likely. In this country extensive use of the available knowledge about the inheritance of blood groups has not yet been made, although considerable steps have been taken towards this in the United States. Only recently a court refused to accept quite definite evidence which clearly disproved paternity. It seems likely that about 50% of the men against whom affiliation orders have been made have been wrongfully accused. It can be shown that by recourse to the full series of eight blood groups now available about 62% of those wrongly accused could be exonerated. As about 7,200 affiliation orders are made every year and 2,000 men go to prison for non-payment, it seems that preventable injustice is occurring on an appreciable scale.

It is usual for most textbooks to say that paternity tests can only be negative—that they can only on occasion disprove paternity, and can never provide positive evidence in its favour. This was the case when knowledge of blood groups was in its infancy, but is no longer true with the existence of rare antigens or combinations of antigens. For example, suppose a woman of rhesus constitution cde/cde has a baby with the extremely rare genotype C^wde/cde, while the putative father is also C^wde/cde. The conclusion would be irresistible—though perhaps not in a court of law. In a similar manner a number of rare abnormalities might occasionally give positive evidence of paternity. In 1921 there was reported in Norway a paternity case in which a normal mother had given birth to a brachyphalangic child. Brachyphalangy is inherited as a rare simple dominant, and the court accepted the fact that the putative father was brachyphalangic as evidence of his paternity.

Now evidence concerning blood groups may be required by either party in divorce or kindred proceedings, and a doctor called as an expert witness may find himself exposed to the following criticism. He may be asked, "Is it not true that genetic factors are subject to sudden and unpredictable changes, called mutations, and is not evidence depending upon their inheritance therefore suspect? Can it be asserted that the genetic factor in question has not in fact changed in this way?" It is essential to be prepared for such opposition, and it is worth while giving a correct reply here in some detail. It would run something like this.

The hereditary mechanism of all higher organisms is of the particulate or Mendelian type, which depends for its

operation upon the extreme permanence of the hereditary factors themselves. Were these to change or mutate in as many as one individual in even a few thousand, the system would break down. A study of such mutations throughout the widest selection of living organisms demonstrates that a mutation rate of as high as 1 in 50,000 individuals is extremely rare, and this frequency is hardly ever exceeded. Inheritance in man is of the same type, and these conclusions are strictly applicable to him. However, it is unnecessary to depend on mere analogy for a knowledge of human mutation rate. It has been possible to study this in several instances in which it proved to be, when most frequent, of the same order of rarity as in other animals. The error introduced into blood grouping by mutation is very unlikely to be greater than 1 in 50,000, and is probably less.

Few legal cases can have been decided in the present century in which the possibility of mistake was not considerably greater than this.

The Rhesus Group and Haemolytic Disease

The importance of avoiding serological incompatibility in blood transfusion is well known. With the ABO group one merely has to ensure that the transfused erythrocytes are not agglutinated by the recipient's antibodies. With the rhesus group, on the other hand, the danger is that a rhesus-negative woman may become immunized by transfusion or pregnancy, with the consequent risk of haemolytic disease of the newborn in her offspring. The practical implication that every female requiring transfusion, or who has or who may become pregnant, should be rhesus-tested does not of itself involve genetics. But in the case of a rhesus-negative woman for whom one wishes to assess possible risks the invocation of genetical principles is essential.

It should be noted that the great majority of cases of rhesus incompatibility are in connexion with the antigen D, although the others (C,E ; c,d,e, etc.) may very occasionally stimulate the production of antibody.

When a rhesus-negative woman marries a rhesus-negative man there is no danger, as all the children will be rhesus-negative. (The mating is of type $dd \times dd$.) Even if she marries a rhesus-positive man ($dd \times Dd$ or $dd \times DD$) the risks are still small, in spite of the contrary assertions of newspaper articles. Provided the woman has never been transfused or injected with even minute amounts of rhesus-positive blood the chance of the first child suffering from haemolytic disease is almost zero, and the chance for the second child still extremely small. The combined chance of disease in the first four or five children is uncertain, but is perhaps no greater than 5% if the husband's genotype is unknown. With homozygous (DD) husbands this chance would be about 9%, and with heterozygous husbands (Dd) it would be only 2%.

If, however, the woman has already given birth to an affected infant, further rhesus-positive children are very likely to be diseased and only rhesus-negative children will be healthy. If the father is heterozygous, then there is an even chance of a healthy child at each subsequent pregnancy. On the other hand, if the father is homozygous, all future children are likely to be affected; but, even so, there is still some chance that a child diseased at birth will respond to treatment and eventually be healthy.

Collecting Data and Preparing Pedigrees

It is a peculiar characteristic of genetic data that they are often collected only incidentally during the course

of work primarily concerned with some other department of medicine. More pedigrees of rare inherited abnormalities have been placed on record by physicians in the course of their ordinary work than have been amassed by research workers making special efforts to obtain such material. A lot of information of a genetical nature normally arises in clinical, pathological, and socio-medical investigations.

Carefully and properly collected genetic data have a certain permanence about them which is not so characteristic of other branches of medicine where new methods of observation and experiment frequently make older work obsolete. Although the systematic and detailed construction of pedigrees is of fairly recent origin, it is likely that they will be of immense value for centuries to come.

Desiderata for Good Family Record

Let us consider some of the special points to be observed in keeping a good family record. Clinical histories of individuals are usually perfectly adequate for their immediate purpose. But when their information on hereditary factors is later extracted and collated it is only too common to find that vital links in the chain of inference are missing because their relevance was not apparent at the beginning.

While there is already in existence a vast but relatively untapped mine of information in the records of general practitioners which could be made to yield valuable results if systematically investigated, it is also certain that a great deal of promising data would in fact be found to be of little use because of the failure to observe one or two elementary precautions in the original compilation.

Obviously, in reporting an abnormality or disease of any kind it is essential to have a full clinical description, including such items as the age and sex of the patient, age at onset of the disease, variations in severity and frequency of attack, and so on. Some indication of the patient's social background should also be given; his social and economic status, the type of work he does, etc. It is also important to have this sort of information about near relatives, especially parents, brothers and sisters (sibs), and children. It is these near relatives that are the most important—data should always be obtained about more distant relatives if available, but this is not quite so essential.

The usefulness of a family history is naturally dependent on the firm establishment of the clinical diagnosis, and in the case of the patient through whom the pedigree first comes to be noticed (called the "propositus") this will normally have been obtained at first hand. It often happens that the doctor will be able to see the close relatives himself and record his own direct impressions—this is much the most satisfactory state of affairs. But sometimes it is possible to secure quite good second-hand information from the patient himself or other relatives—for example, about members of the family whom the doctor is unable to see himself. In an extensive study it might be useful to classify the individuals in some such grouping as: "certainly affected," "almost certainly affected," "possibly affected," "almost certainly unaffected," "certainly unaffected," "unknown," etc. But in any event there should always be notes on each individual giving the exact evidence itself. Should it prove impossible to obtain information about any particular relative of the generations and degrees of

kinship studied, the reason for the failure should always be stated.

When collecting together data on several related persons in this manner one should clearly indicate who is the *propositus*—the individual who first brings the family to notice, or primary case in the genetic sense. Failure to do this may seriously affect the interpretation of genetical data, particularly in the sib method of analysis, which is discussed below.

Another vital piece of information which must not escape the record is the existence of a consanguineous marriage. Positive or negative information on this point is equally valuable. In many cases it is not sufficient merely to state that husband and wife are related, that they are cousins, for example: one wants to know in greater detail, for instance, whether the mother of the husband and the father of the wife are brother and sister. Cases of twins should also be carefully noted, together with any positive or negative information on whether they are identical or not.

It is useful to be able to lay out an interesting pedigree so that the salient characteristics may be seen at a glance. There are various ways of doing this, and some of the main symbols in common use are shown in the accompanying Table. In complicated pedigrees, especially

experience of only a certain proportion of all the available cases. If one collects consecutive cases of a condition, then the correct proportion of affected individuals among sibs (which is the most informative figure) is obtained by calculating the proportion among the remainder of each sibship, ignoring the *propositus*. If two members of a single sibship present themselves independently then that sibship must be counted twice over. For example, if a sibship consists of four normal and three affected individuals, of whom two of the affected persons appear for examination independently while the third is found only as a result of a family inquiry, then that sibship is counted twice, each time as four normal and two affected.

Two points stand out. First, that the right method of analysing the data must be employed. Second, that useful information can be obtained from a study of sibs only. It follows, therefore, that there is no need to be discouraged because of the difficulty of seeing or gaining information about distant relatives. It is worth making a special effort to obtain detailed information about parents, sibs, and children, but less than this can be of use. The same thing is true of data which are collected in the hopes of finding a genetic linkage. There is not space to go into these methods now; suffice it to say that the general principle is to test the *propositus*, together with his sibs and parents if available, for the possession of suitable characters other than the one used for selection—say, the individuals' blood groups or their ability to taste P.T.C., etc.

Eugenic Prognosis

A few comments on the practical value of a knowledge of linkage may be mentioned here. Unfortunately such knowledge is still somewhat rudimentary in man, but with the increasing number of marked chromosomes, especially those due to the discovery of new blood groups, quite extensive data on human linkage are potentially within our grasp.

Many serious human defects are heterozygous conditions, and some of them do not become apparent until

after the normal age of marriage, as in Huntington's chorea. Children whose father or mother has developed that disease may wish to marry. Though they are apparently healthy it is probably undesirable for them to do so if between the ages of 30 and 40 they are destined to develop a progressive mental deterioration leading to insanity, which they will moreover transmit to half their offspring. At present such individuals can only be told that the chances are exactly equal: they may be afflicted in this way, or they and their descendants may remain perfectly normal. If, however, we knew of a number of genes controlling ordinary characters, such as eye colour, blood groups, P.T.C. tasting, attached ear lobes, etc., which were linked with Huntington's chorea, then the situation would be much clearer. We could say perhaps whether the chances of developing the disease or not were very remote or very considerable, and this might have far-reaching effects on the decisions of the patients concerned. Similarly, in families with sex-linked disease it would be invaluable to know whether a woman was carrying a recessive gene or not.

Pedigree Symbols in Common Use

Part of a pedigree of polydactyly

those involving the inheritance of two or more characters, special symbols may have to be employed. For further suggestions, reference may be made to Ruggles Gates's *Human Genetics*, vol. 1, p. 4.

Ascertainment

The modern methods employed for interpreting genetical data normally involve some kind of statistical analysis. The reliability of these analyses depends on a knowledge of the way in which the material was collected—what is usually called the “method of ascertainment.” Uncertainty about ascertainment will affect the validity of the results. Sometimes it is possible to make some allowance for ignorance of the method of ascertainment, but naturally there is an inevitable loss of certainty.

One might in theory collect all the cases of a particular condition in a given neighbourhood or district. Such a procedure would readily lend itself to simple interpretation, but would in general be exceedingly troublesome to carry out. It is usually possible to gain

It is commonly said that in families harbouring a serious recessive defect no one should marry a near relative, that marriages between cousins should be prohibited. While the ethics of this sort of problem are by no means easy, an assessment of the probabilities involved may well provide useful guidance. If there is any doubt about how to do this the advice of a competent geneticist should be sought.

Suppose, for example, a man has had a brother who died of juvenile amaurotic idiocy, which is due to an autosomal recessive gene (one not on a sex chromosome), and that he wishes to marry his first cousin. If there are no other cases of the disease in the family then the chance that both the man and his cousin are heterozygous is 1 in 6. The chance of a single child from such a marriage being an idiot is therefore 1 in 24. The couple may be prepared to accept this risk, but it is desirable that they should know what it is. The chances of having an affected child are greater if they have more than one; and the probability of producing a heterozygous child, which though itself unaffected is capable of transmitting the gene, is considerably higher. In any case a consanguineous marriage always increases the likelihood of bringing to light an undesirable recessive gene.

To take another case, consider a woman who has a brother who dies of true haemophilia, which is a sex-linked recessive. What are the prospects both for her and for another brother who is unaffected? The unaffected brother cannot carry the gene at all and his descendants will all be free of it. The woman, on the other hand, has a 50% chance of carrying a gene for haemophilia. If this is so she will transmit the disease to half her sons, and half her daughters will be carriers.

It is interesting to note that the linkage of the loci (gene positions) for haemophilia and colour-blindness has already been used for eugenic prognosis in families exhibiting both these defects. In a certain Dutch family it was possible to say that the colour-blind daughter had a 90% chance of carrying a haemophilia gene, where her normal sisters had only a 10% chance. Probabilities like these are clearly of much greater value than the more usual 50% chances, as in the previous example. No doubt when the human germ-plasm is as well charted as that of *Drosophila melanogaster*, this kind of argument will be used as a matter of course in the prevention of congenital abnormalities.

Aids to Diagnosis and Preventive Medicine

The discovery of a hereditary factor in the aetiology of a disease by no means implies that further medical progress is impossible. Heredity and environment interact and determine jointly the condition of a person. Thus an ailment which depends to some extent on heredity may be ameliorated, cured, or even entirely avoided by suitable treatment or alteration in living conditions.

There are occasions when a knowledge of hereditary background can be used as an aid to diagnosis. For instance, a man was admitted to hospital having lost considerable blood by haematemesis. The diagnosis lay between gastric ulcer, cirrhosis of the liver with oesophageal varices, and Banti's disease. One physician, however, happened to know that the man's father had suffered from a mild telangiectasis and had had the typical spider's-webbing of the nasal mucous membrane. Now, multiple telangiectasis, or Osler's disease, is due to

a dominant gene, and it was suggested that perhaps the patient in question also had the disease—with a telangiectatic spot in the gastric mucosa. The surgeon explored, found a large telangiectatic focus and excised it. Symptoms disappeared and there was no recurrent haemorrhage. If a dominant gene always has full expression then it is true that no treatment will prevent the bearers from exhibiting the abnormality; nevertheless some form of treatment may be available, as in the surgical treatment of polydactyly.

In other circumstances genetic knowledge may help to detect hereditary diseases in their preclinical stages, when full advantage can be taken of preventive measures to forestall the appearance of manifest disease. Thus familial acholuric jaundice is a dominant condition for which splenectomy is a common prophylactic measure. Moreover, it can always be recognized preclinically by certain laboratory tests. Although it would not be feasible to examine whole populations of individuals, special examination can be made of the relatives of known sufferers. When laboratory tests show an individual to be carrying the gene, the spleen can be removed, if indicated, and clinical disease probably averted.

Conclusion

It can be said with full justification that a deeper understanding of the genetical basis of a disease will often help to fill in the gaps in a purely clinical approach and may make material contributions to both treatment and prevention. The field of application of genetics to medicine is a wide one. There is the study of mutation, which has been applied to the advancement of antibiotic therapy and which has also emphasized some of the dangers attached to x-ray irradiation and the use of atomic energy. There is the study of the inheritance of blood groups and other common characters as an aid to identifying individuals, particularly in paternity cases. The rhesus blood groups are of special interest, and genetical theory is particularly valuable in estimating the risks run by rhesus-negative mothers. The possibility of gaining new insight into various diseases in man by an investigation of closely similar diseases in experimental animals is also worthy of consideration. Genetics can be used as an aid to diagnosis, and for suggesting certain procedures in preventive medicine. Another important application is to eugenic prognosis, when one wishes to assess some of the dangers attached to parenthood where there is the possibility of heritable disease.

There can be no doubt that medical genetics has a very real contribution to make to the cause of suffering humanity, and that its power and scope will greatly increase and spread in the years ahead.

In his annual report for 1949 Dr. Hugh Paul, medical officer of health for Smethwick, writes: "It is unfortunate that many of these [investigational] facilities are only available to the practitioner through a senior member of the hospital staff; for example, the general practitioner may find great difficulty in getting the result of an examination of the patient's blood, a bacteriological examination, or a radiograph, except by making an appointment with the appropriate consultant in the hospital. This may be excellent hospital etiquette, but it is deplorable medical practice, and the technical facilities of the hospital, particularly those associated with bacteriology and biochemistry, should be immediately available to the general practitioner without the intervention of a third person except when the general practitioner asks for an opinion as well as for a test."