Elements of Medical Genetics

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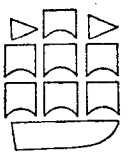

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Preface

In preparing this third edition, as in previous editions, no attempt has been made to cover all aspects of medical genetics but rather to indicate the ways in which geneticists approach problems in human disease and variation. More emphasis, however, has been placed on the role of genetics in clinical medicine particularly with regard to the prevention of genetic disease.

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I

The Development of Genetics

Early Beginnings

Ideas about heredity can be traced back at least 6000 years by means of stone engravings from Chaldea which depict pedigrees concerning the inheritance of certain characteristics of the mane in horses. With regard to human heredity, the inheritance of the bleeding disorder haemophilia was mentioned in the Talmud some 1500 years ago. However, despite this impressive historical record the nature of conception and explanations of heredity remained largely speculative until comparatively recent times. In fact certain primitive people still consider that sexual intercourse has nothing whatever to do with pregnancy and child bearing.

Aristotle in the third century B.C. suggested that male semen originated from the blood and possessed the ability to give life to the embryo which was formed in the uterus by the coagulation of menstrual blood. This idea was generally accepted for nearly 2000 years until the seventeenth century when William Harvey, who achieved fame for his studies of blood circulation, demonstrated that in deer killed at various times after mating there was never any evidence of coagulation of menstrual blood but that a small embryo developed which gradually increased in size and complexity throughout the whole period of gestation. The credit for first recognizing that the union of egg and sperm is the essential nature of conception is given to a Dutch scientist, Regnier de Graaf. In the latter half of the seventeenth century he described small protuberances on the ovaries of mammals. These protuberances, now called Graafian follicles, contain the unfertilized egg, or ovum. For the first time the idea was put forward that the sperm alone was not the sole hereditary agent thus explaining why the female parent as well as the male parent transmitted characteristics to their offspring. Nevertheless, it was many years before this concept was generally accepted.

Pierre Louis Moreau de Maupertuis was born in France in 1698. Through a fascinating study of him by Professor Bentley Glass we have a picture of a naturalist with views far in advance of his time.

He studied certain hereditary traits in man such as extra fingers (polydactyly) and lack of hair and skin pigmentation (albinism) and from pedigree studies showed that these two conditions were inherited in different ways. He firmly believed that both parents contributed equally to the make-up of their offspring and he provided experimental proof of this from animal breeding experiments. His conception of the structural basis of heredity was novel and in many ways resembled the ideas of Mendel formulated almost 100 years later. Maupertuis proposed that there were hereditary particles; each particle was destined to form a particular body part and each body part was formed by the union of two such particles: one from one parent and one from the other. One particle might dominate the other and so the offspring would come to resemble one parent more than the other.

MENDELISM

The story of our present ideas concerning genetics really starts with the work of the Moravian monk Gregor Mendel, in the latter half of the nineteenth century. Mendel made his far-reaching discoveries through careful and painstaking analysis of the results of crossing varieties of garden pea (*Pisum sativum*). At that time such experiments were not new. T. A. Knight in England in 1823 reported the results of crossing varieties of garden pea. He found that in the first generation, referred to as the *first filial* or F_1 generation, there was dominance of seed colour. That is, if a yellow-seeded plant was crossed with a green-seeded plant all the F_1 plants were yellow seeded, yellowness being dominant to greenness. If these F_1 plants were then self-pollinated (self-fertilized; inbred) the plants in the second generation (F_2) were of both parental colours, that is, green and yellow. Similar results were obtained by others but none of these earlier investigators recorded the actual numbers of the different types of progeny resulting from these various crosses. Prior to Mendel apparently no one thought in terms of inherited units which obeyed statistical laws. This was Mendel's great contribution.

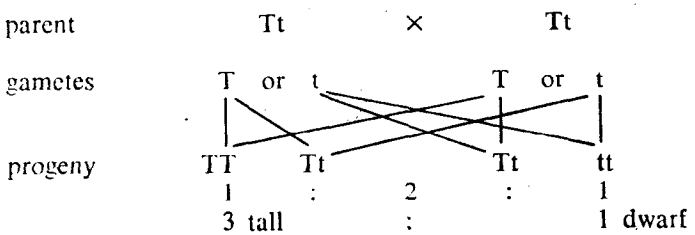
Johann Mendel was born July 22, 1822 in Heinzendorff in Moravia, then part of Austria but now part of Czechoslovakia. He adopted the name Gregor on entering the Augustinian Order in 1843. After becoming a priest he embarked upon the career of school teacher studying physics, mathematics, zoology, and botany at the University of Vienna, but failed to pass the qualifying examination. In 1853 he went to the monastery at Brunn (Brno, now in Czechoslovakia) where his classical experiments on garden peas were

carried out. His plant breeding experiments occupied most of his time until he was elected Abbot of the monastery in 1868. Thereafter his time was spent mainly in administrative duties and attempts to persuade the government to exempt monasteries from taxation. He died of Bright's disease (nephritis) on January 6, 1884.

In his plant breeding Mendel selected for study seven pairs of contrasting characters in the garden pea, for example, round or wrinkled seeds, tall or dwarf plants, violet or white flowers, and so on. For each experiment he crossed varieties differing only in one pair of these characters. He classified the hybrids in the F_1 generation and then allowed them to undergo self-pollination and studied the progeny in the F_2 generation. In each of the seven crosses, the plants in the F_1 generation always resembled one of the parental types. For example, when a tall plant was crossed with a dwarf plant all the F_1 offspring were tall. Those characteristics which were manifest in the hybrid were referred to as *dominant* and those which were not manifest in the hybrid were referred to as *recessive*.

The results obtained by allowing self-pollination of the F_1 plants were even more interesting. He found that in the F_2 generation there were individuals manifesting the dominant character but also others manifesting the recessive character. Not only was this true but the dominant and recessive characters in the F_2 generation occurred in a definite ratio of 3 to 1, and no transitional forms were observed. For example, out of 1064 plants in the F_2 generation, 787 were tall and 277 short; a ratio of 2·84 to 1. When the results of his experiments on all the different pairs of contrasting characters were added together the ratio of dominant to recessive was 2·98 to 1. If now the plants exhibiting the recessive character in the F_2 generation were self-pollinated all their progeny in the F_3 generation exhibited the recessive character, that is, short stature. However, if those exhibiting the dominant character in the F_2 generation were self-pollinated, two-thirds yielded offspring which displayed the dominant and recessive characters in the proportion of 3 to 1, and thus resembled the hybrid form in the F_1 generation. When the remaining one-third of the tall plants from the F_2 generation were self-pollinated they yielded offspring which displayed only the dominant character. As Mendel pointed out, the ratio of 3 to 1 in the second generation resolves itself into the ratio of 1:2:1 if the apparent dominant forms in this generation are analysed according to the type of offspring they produce when they are self-pollinated. It is possible to explain these results in the following manner. Each individual possesses two ' factors ' which determine a specific characteristic and, as Mendel emphasized, a parent transmits only one of a

pair of these factors to any particular offspring. It is purely a matter of chance which of the two factors happens to be transmitted at any one time. This is sometimes referred to as Mendel's 1st law, or the *law of segregation*. In the formation of the sex cells, or gametes, one contrasting character segregates or separates from another. The tall parent plants could be represented as TT, the dwarf parent plants as tt, and the tall hybrid plants in the F_1 generation as Tt. When the latter form gametes, each will contain either the factor T or the factor t. If the hybrid individuals are allowed to undergo self-pollination then union of the two different types of gametes might be expected to occur in the following way:



Alternatively the various gametic combinations can be obtained by drawing up what is sometimes referred to as a Punnett's square (after R. C. Punnett, a famous plant geneticist).

		Male gametes	
		T	t
Female gametes	T	TT	Tt
	t	Tt	tt

At this point it might be advisable to introduce a few terms. It has already been pointed out that for each physical characteristic or trait, each individual possesses two factors. If these factors are the same then the individual is said to be *homozygous*, but if these factors are different then the individual is said to be *heterozygous*

(for example Tt). In the heterozygous state a character which is manifest is dominant; one which is not manifest is recessive. Nearly 50 years ago Johannsen, a Danish botanist, coined the word '*gene*' for these hereditary factors. The genes responsible for contrasting characters are referred to as allelomorphs or alleles for short. Thus in garden pea there are two alleles for stature, one for tallness and one for shortness.

Before Mendel's time it was generally thought that conception involved the mingling of hereditary substances from both parents, each parent transmitting a little of all of its characteristics. But Mendel showed that this was not true. A tall plant did not necessarily transmit some of its tallness to all its progeny. If it were heterozygous then there was an equal chance of it transmitting either the gene for tallness or the gene for shortness. Similarly a person with polydactyly (a dominant factor in man) has an equal chance of transmitting to any particular child either the gene for polydactyly or the gene for normal hands. Each child does not receive from one parent a little bit of each. It is extraordinary that Mendel formulated these ideas without any knowledge of the nature of these hereditary factors or genes.

It has been argued that Mendel's results were almost too good. The numbers of the different types of progeny he obtained were extremely close to the values one would have expected on Mendel's theory. The late Sir Ronald Fisher, an eminent statistician, carefully analysed Mendel's data and concluded that Mendel's experiments were not discoveries but demonstrations of theories which Mendel had in mind when he made the experiments. Be this as it may, the point remains that Mendel's ideas were revolutionary in their day. The validity of his experimental findings has since been confirmed in countless organisms and Mendelism is now the basis of all genetic theory.

Mendel presented the results of his experiments before the Natural History Society of Brunn in 1865 and the following year they were published in the *Transactions* of the Society. However, his work remained largely unknown for nearly 50 years. The reason for this is not at all clear. One suggestion is that the *Transactions of the Natural History Society* of Brunn was an obscure journal, but the journal was at that time not so obscure as might have been expected for it was sent to at least 120 learned societies, academies, and libraries. It seems more likely that scientists in the mid-nineteenth century were simply not prepared for this work. Mendel's contemporaries were preoccupied with Darwin's theory of evolution and the nature of species. Possibly they misinterpreted Mendel's work as

a confused attempt to investigate their own problems. Even Carl Nägeli, a world authority on plant hybridization, failed to see the significance of Mendel's results and Nägeli was Mendel's close friend and advisor.

Mendel's laws of heredity remained largely unknown until 1900 when, within the space of a few months, they were independently rediscovered by three biologists: Hugo de Vries, Professor of Botany in the University of Amsterdam, Carl Correns, a botanist at the University of Tübingen, and Erich von Tschermak-Seysenegg, an assistant in the agricultural experimental station at Esslingen near Vienna. All three investigators quite independently arrived at the same conclusions as Mendel had. It is a matter of regret that Mendel died 16 years before his work became generally recognized as being among the most important scientific discoveries of all time.

The Chromosome Theory of Inheritance

As interest in 'Mendelian Inheritance' grew there was much speculation about its physical basis. It was well known that plants and animals were composed of millions of cells, and that each cell contained a nucleus and that within the nucleus were a number of minute threadlike structures called *chromosomes*, so called because of their affinity for certain stains (*chroma*=colour). But until 1903 when Walter S. Sutton and Theodor Boveri independently proposed the chromosome theory of heredity, the association between these minute structures and the phenomenon of inheritance had not been recognized. According to this theory the chromosomes carry the hereditary factors or genes, and the behaviour of the chromosomes at cell division provides the explanation for Mendelian inheritance. The chromosome theory of inheritance is one of the most important concepts in biology, and will be discussed in more detail later. It is interesting to note that Sutton made this major contribution while still a medical student. He later became a surgeon and died at the age of 39 from appendicitis, without ever returning to the field of study which had made him famous.

The Fruit Fly

Until 1905, most of the experimental work on genetics had been carried out on plants, but in that year Castle introduced to the laboratory an animal which was to be a major tool in genetic research for many years to come. This was the fruit fly *Drosophila*, which possesses certain distinct advantages for those interested in

studying genetics. First, it can be bred in the laboratory with ease. Second, the female produces thousands of eggs during her lifetime and because *Drosophila* develops so rapidly it is possible to study 20 to 25 generations in a year. In man, 25 generations would take about 750 years. Finally, *Drosophila melanogaster*, the species most often studied, has only four pairs of chromosomes, each pair having a distinctive appearance so that it is possible to identify individual chromosomes. In addition, the chromosomes in the salivary glands (and in a few other tissues as well) of *Drosophila* larvae are among the largest known in nature. They are at least 100 times bigger than those in other cells of the body. The reason for their phenomenal enlargement is still not clearly understood. The salivary gland chromosomes possess distinctive patterns of transverse bands which represent the sites of different genes. In some instances it has been possible to localize a particular gene to a very small group of bands or even to a single band.

At Columbia University, Thomas Hunt Morgan and his students Calvin Bridges and A. H. Sturtevant were amongst the first to study the genetics of *Drosophila*. They established the fact that hereditary units or genes were arranged in a particular linear sequence along the length of the chromosomes and cytological studies of the salivary gland chromosomes were often used to confirm the results of their breeding experiments. For his work on *Drosophila*, Morgan was awarded the Nobel Prize in 1934.

THE BEGINNINGS OF HUMAN GENETICS

We might now turn to the work of some of the founders of human genetics. To be sure, interest in human genetics did not spring up overnight. We have seen how Maupertuis studied the inheritance of albinism and polydactyly in the eighteenth centry. Otto's account in 1803 of haemophilia in a New Hampshire family was apparently the earliest clear description of the clinical features and mode of inheritance of this disease: it was transmitted by healthy carrier females to their sons but never by an affected father to his son. A trait which is inherited in such a manner we call sex-linked. This will be discussed later.

Until the beginning of the present century most investigators of human heredity were mainly interested in tracing pedigrees. Other aspects of human genetics received very little attention, except for a few studies on the effects of cousin marriages (=consanguineous marriages). One of the first scientists to become interested in the effects of inbreeding was Charles Darwin, who himself married a

first cousin. The results of his plant breeding experiments led him to conclude that the progeny of crosses between unrelated organisms (outbreeding) were more vigorous than the progeny of crosses between related organisms (inbreeding). The French neurologist Ménière in 1856 suggested that in man deaf mutism was more common in the children of cousin marriages. All in all our knowledge of inheritance in man had progressed very little by the end of the nineteenth century.

Johannsen was the first to make clear the distinction between *genotype*, meaning the genetic constitution, and *phenotype*, meaning the appearance of an individual which results from the interaction of environment on the genotype. Thus a garden pea plant may have the genotype Tt but have a dwarfed phenotype because it grew in a shaded or poorly irrigated location. In man, the distinction between the effects of nature and nurture were made clear for the first time in 1875 by Sir Francis Galton who, like his eminent cousin Charles Darwin, began his career as a medical student but later on forsook medicine after being left a substantial legacy. Galton argued that since identical twins have the same genetic constitution, any difference between them must be due to environment, that is, identical twins have the same genotype but may have different phenotypes because of having grown up in different environments. Galton was especially interested in the inheritance of physique and special talents. In pursuing this interest, he studied families of wrestlers in the North of England. He realized, however, the unsatisfactory nature of qualitative estimates of such talents and the importance of quantifying the characteristics under study. As a means of estimating the degree of resemblance between various relatives he introduced to genetics the statistical concept of the regression coefficient. Galton's work formed a cornerstone for many future investigators interested in the more mathematical aspects of human heredity.

Galton had many interests and among them was the advancement of the idea of hereditary improvement of men and animals by such methods as selective breeding for which he coined the word *eugenics*. Over the years a eugenics movement developed which had fervent followers both in Europe and the United States. It seemed reasonable at the time that a desirable aim of human geneticists should be the improvement of the human species by selective breeding. For many years, therefore, human genetics and eugenics were linked in people's minds, but even today our knowledge of human genetics is too rudimentary to advocate drastic eugenic policies. What information we do have suggests that such measures would be largely inadequate anyway. This is not to say, however,

that there is no place for warning those who carry harmful hereditary factors of the risks of having affected children, and of explaining the importance of family limitation in such cases.

Genetics and Disease

One of the greatest proponents of Mendelism was William Bateson. The story is told that while he was on a train to London to present a paper before the Royal Horticultural Society on the results of his own plant breeding experiments, he read Mendel's paper for the first time and from then on became a fervent disciple of Mendelism. He translated the paper from German into English and had it published in the *Journal of the Royal Horticultural Society* of 1900. Immediately following the rediscovery of Mendelism in 1900 much effort was spent in attempts to apply these findings to man. Unfortunately many of the earlier investigators over-simplified things in order to make their observations agree with Mendel's concepts of dominance and recessiveness. For example, Davenport, who founded the Eugenics Record Office in the United States and was a prominent figure among human geneticists during the first quarter of the twentieth century, firmly believed that mental deficiency in general was inherited as a recessive trait. This is not true. There are many forms of mental deficiency, and although a few are inherited as Mendelian traits, most cases are due to the effects of many genes, so-called multifactorial inheritance. These early investigators not only believed that many human diseases were explicable in terms of the effects of single genes but that all disorders were either due to heredity or environment. This again was an oversimplification.

Nowadays we believe that both hereditary and environmental factors play a part in the causation of the vast majority of diseases, though in some cases one may appear to be more important than the other.

Alkaptonuria is a very rare condition in which affected persons excrete dark-coloured urine. The disease is usually recognized in infancy because the napkins are dark stained and in fact washing with soap tends to make these stains even more intense. The dark colour is due to the presence of homogentisic acid which in normal people is broken down and so does not appear in the urine. The disease is not serious and apart from arthritis, which may ensue as a complication later in life, the disorder is harmless and not incapacitating. In 1901, in a paper read before the Royal Medical and Chirurgical Society in London, Sir Archibald Garrod described four families in which 11 persons had alkaptonuria and no less than

three affected individuals were the offspring of first cousin marriages. In each case the parents of affected individuals were apparently normal. Bateson suggested to Garrod that alkaptonuria was probably a rare recessive disorder because, he argued, since first cousins are more likely to share the same genes inherited from a common grandparent, so a high frequency of consanguineous marriages would be expected among the parents of individuals homozygous for a rare gene. This is exactly what Garrod had found in the families with alkaptonuria. In general terms, the rarer a recessive disorder the more often it will be found that the parents of affected individuals are cousins.

Until Garrod's discoveries, genetics had been largely concerned with the inheritance of structural or other obvious abnormalities such as polydactyly in man or flower colour in peas. The novel and important point made by Garrod was that in alkaptonuria there was an inherited disorder involving a chemical process or, as Garrod preferred to call it, an *inborn error of metabolism*. This was the beginning of biochemical genetics and the idea that genes control the synthesis of enzymes, which in turn are responsible for carrying out specific biochemical processes. Beadle and Tatum provided experimental evidence for these ideas from breeding experiments with the bread mould *Neurospora crassa*. Their work was of such importance that they were awarded the Nobel Prize in Medicine and Physiology in 1958.

At about the same time that Garrod was making his important observations on the inheritance of alkaptonuria and certain other biochemical abnormalities in man, Karl Landsteiner discovered the ABO blood groups. This discovery was the prelude to an important branch of human genetics, namely blood-group genetics.

Finally in 1956, Tjio and Levan, and independently Ford and Hamerton, clearly demonstrated for the first time that the number of chromosomes in man was 46 and not 48 as was previously believed. The great contribution made by these investigators was the introduction of improved methods for studying chromosomes. Until then it had been very difficult to study human chromosomes because of their small size. With the new techniques it was possible to separate them and observe them more accurately. This was largely the reason for the ' chromosome breakthrough ' in 1959 when Lejeune in Paris and Ford and Jacobs in Britain demonstrated that in patients with Down's syndrome (mongolism) and in those with various abnormalities of sexual development there were clearly recognizable, specific, chromosome aberrations.

This historical introduction of necessity has been brief and rather

sketchy, but nevertheless certain basic ideas should now be evident. First, the general principles of heredity as discovered by Mendel in garden peas, are applicable to all living creatures, including man. Second, unlike animal genetics, the study of human genetics is inherently difficult because we cannot carry out breeding experiments. On the other hand we know more about the biochemistry and physiology of man than we do about any other organism. Third, some of the most profound observations in human genetics have been made on rare and obscure diseases.

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II

The Chemical Basis of Inheritance

How does a gene determine a particular characteristic? For example, how does one gene determine eye colour and yet another determine whether a person will have extra fingers? What is the chain of events which leads from the gene to the final product? These are difficult questions to answer and are the main concern nowadays of much biological research. The purpose of this chapter is to answer some of these questions but it should be realized that our understanding of gene action is still very far from being complete.

The Nucleus

Within each cell of the body are located the cytoplasm and a dark-staining body, the nucleus (fig. 1). The cytoplasm used to be considered merely a fluid which bathed the nucleus but this is now believed to be an oversimplification. The cytoplasm certainly is semifluid in consistency but it has within itself a complex arrangement of very fine tubes which open onto the surface of the cell (= *endoplasmic reticulum*). These tubes are probably involved in conducting nutrients from the outside to the inside of the cell and are

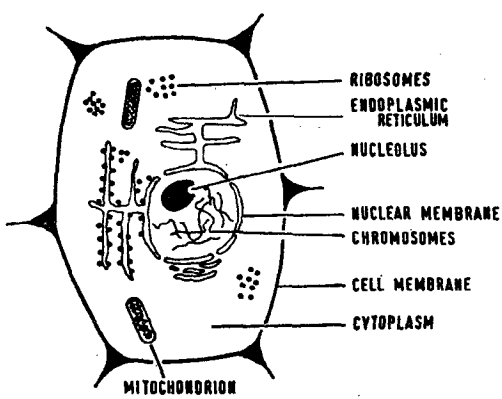

Figure 1. A schematic diagram of an animal cell.