Current Practice

GROWING POINTS

Genetics and Medicine—I

G. R. FRASER,* M.D., PH.D.

The basic importance of heredity in the aetiology of disease hardly needs to be stressed today. All our characteristics, whether physiological or pathological, and all aspects of our existence are determined by the interaction of genetical and environmental factors. In some cases either the genetical or the environmental factor may appear to be exclusively involved. For example, mongolism (Down's syndrome) is invariably associated with an abnormality of the chromosomes, and in phenylketonuria a gene is abnormal, leading to a gross impairment of the activity of a vital enzyme. In both cases pathological changes of the genetical complement or *genotype* have taken place. Nevertheless, the pathway between the genotype and its ultimate effects on the individual—the *phenotype* or overt manifestation of Down's syndrome or phenylketonuria—is a long one, and therefore subject to some extent to modifying influences, both genetical and environmental. On the other hand, it might be thought that involvement in a car accident or suffering a war wound are events that were purely determined by environment. Nevertheless, other considerations have to be taken into account. For example, the excess susceptibility of the deaf to traffic accidents is well known; on the other hand, they, and other persons handicapped by conditions with strong genetical determinations, are unlikely to find themselves in the front line in war.

Genes and Chromosomes

Hereditary influences on our existence are mediated by genes which are inherited from our parents. In order that this might be achieved, it is first necessary that male and female germ cells (or *gametes*) be produced which fuse to form the *zygote*, which develops into the new individual. The nucleus of every cell contains our genes arranged on linear structures, the *chromosomes*. The number and structure of the chromosomes differ according to species, and in man there are 46. These are arranged as one pair of *sex chromosomes* and 22 pairs of other chromosomes, or *autosomes*. In both sexes each autosome of a particular pair resembles the other, and the members of a pair are said to be *homologous*. In females this is also true for the sex chromosomes, these being designated as the XX chromosomes. In males, on the other hand, the sex chromosomes differ from each other and are designated as XY. Somatic cells that contain two sets of chromosomes are known as *diploid* cells; thus in man the diploid chromosome number is 46.

Meiosis

The process that gives rise to gametes (ova and spermatozoa) involves the halving of the diploid chromosome number in special cells known as oogonia and spermatogonia, and is called *meiosis* (Fig. 1). As a result ova and spermatozoa have the

haploid or single chromosome number of 23. Though there are differences between the formation of male and female gametes, basically meiosis is similar in the two sexes and occurs as one duplication of the chromosomes followed by two cell divisions. Each chromosome replicates to form two identical parts, known as *chromatids*, which are joined together at a single point, the *centromere*. Early in meiosis the two chromosomes (four chromatids) of each pair lie adjacent to each other. It is thought that at this time parts of the chromosomes are exchanged in a process known as *crossing over*. The physical basis for this exchange may be the X-shaped structures called *chiasmata*, which can be seen under the microscope during the early stages of meiosis. This process enables the genetical material to be recombined, so that the chromosomes in the gametes—and hence those handed on to the next generation—are not identical replicas of the parental ones, but each contains information from both the homologous chromosomes of the pair from which it is derived. This rearrangement (or recombination) is of vital importance in evolution, since it brings about new combinations of genes and increases the possibilities for variation in a species.

FIG. 1.—Schematic representation of one of the 23 pairs of human chromosomes during meiosis.

After the phase of crossing over, the first meiotic division is completed. This is done by the partner chromosomes of the 23 pairs separating from each other. Hence one member of each pair goes to each of the two daughter cells of the first meiotic division. Each daughter cell, therefore, now has 23 chromosomes each consisting of two chromatids.

During the second meiotic division each daughter cell again divides into two. During this process the chromatid pairs separate, so that each of the four resulting cells has a haploid

* Reader in Genetics, University of Adelaide, South Australia.

set of chromatids, or chromosomes. In the male all these four cells will be mature sperms, two bearing the Y chromosome and therefore male-determining, and two bearing the X chromosome and therefore female-determining. In the female, on the other hand, three cells are discarded, and the one that retains most of the originally available cytoplasm becomes the mature ovum, containing one X chromosome.

Conventionally it is assumed that each parent makes an equal hereditary contribution to the next generation, but this is not entirely true. The mother contributes more in three ways. Firstly, and directly, she contributes initially the entire cytoplasm of the fertilized cell (or zygote), since the sperm consists almost wholly of the nucleus and the requisite apparatus and energy stores to enable it to migrate through the female genital canal. Second, the mother provides the environment in which the zygote develops for the first nine months of its existence. Though this contribution cannot be regarded as a direct hereditary one it can greatly influence the subsequent course of post-natal existence. Third, in the case of male offspring the X chromosome from the mother contributes substantially more to their genetical material than the much smaller Y chromosome from the father.

Mitosis

During the growth of the zygote, and throughout life, cell division in somatic cells takes place by a different mechanism known as *mitosis* (Fig. 2). During mitotic division no halving of the chromosome number takes place, and a diploid cell gives rise to two daughter diploid cells. The first event in this process is for each of the 46 chromosomes to make a copy of itself by the formation of two chromatids, which, as before, are attached only at one point, the centromere. The chromatids then separate fully, with longitudinal splitting of the centromere, and migrate to the opposite poles of the dividing cell.

Fig. 2.—(1) Two chromosomes (from different pairs) of the 46 which constitute the diploid number are represented. (2) The two chromosomes have replicated, each to form two chromatids, joined at the centromere. (3) Division of the cell to form two daughter cells. (4) After separation each daughter cell has 46 chromosomes, the full diploid number, as has the parent cell.

Genetical Variation

Division, recombination, gamete formation, fertilization, growth—these are the steps by which the individual is determined. Each stage represents a lottery, which may lead, on the one hand, to the formation of a successful and creative person, or, at the other extreme, to one who is cruelly malformed and who is throughout life unable to play any effective part in society. Between these two extremes there is an infinite number of gradations, which are due to two forms of variation—the continuous and the discontinuous. The continuous type is considerably more important, though it is more difficult to define and to analyse. Examples of continuous variations

occur in characters such as height, intelligence, the shape and size of the eye—to mention only a few of the more important ones. All of these are under the control of a great many genes, each of which has a small effect on the final result (*multifactorial* or *polygenic* inheritance). Because of the way in which these multiple genes are inherited the relatives in a particular family tend to resemble one another with respect to these characters. These resemblances are influenced by the degree of relationship of one person to another, by the relative importance of genetical and environmental factors in the determination of the particular trait under consideration, and by the degree of dominance involved in the genetical components.

Dominance and *recessivity* are terms that are particularly useful in understanding genetical mechanisms. A gene has a definite position or *locus* on a chromosome, but since chromosomes exist in homologous pairs each gene must exist in duplicate. Furthermore, the genes of each pair may either be identical or different. Differences probably reflect small changes, or *mutations*, in the chemical constitution of the genes, and such alternative forms are known as *alleles*, or *allelomorphs*. Hence a person may either be *homozygous* at any chromosomal locus—that is to say, the two alleles occupying that locus are identical—or he may be *heterozygous*—that is to say, the two alleles are different. Authorities differ about the proportion of loci (in man or other species) which can be *polymorphic*—that is, which can harbour common alternative or allelic genes. Possibly this proportion is small, in which case homozygosity is the general rule; or it may be large, in which case individuals would normally be heterozygous at a great number of loci.

At loci where heterozygosity exists each of the two alleles may exert its individual effect. The resulting effect on the individual may be just a summation of the impacts of the two alleles separately. Thus, in the case of quantitative traits such as height or intelligence, if the effect of homozygosity for the allele A at a certain locus (genetical constitution, or genotype, AA) is 2a and the effect of homozygosity for the allele A' (A'A') is 2a' the effect of heterozygosity for the two alleles (AA') will be a + a'. In this case dominance is said to be absent. If, on the other hand, the allele A is completely dominant, A' will have no effect when it occurs together with A, and the genotypes AA and AA' will have effects equal to 2a. Varying degrees of dominance may occur, and the effect of the genotype AA' may be anywhere between a + a' (no dominance) and 2a (complete dominance). There is even a condition of over-dominance. This occurs when the effect of the heterozygous genotype is actually greater than that of either homozygous genotype instead of being intermediate. This condition may partially account for the phenomenon of hybrid vigour, which is of so much importance in plant and animal breeding.

Because of the great number of genes concerned, any analysis of the inheritance of quantitative traits (such as height or intelligence) is bound to be extremely complex. This is even more true for traits that reflect many of our most vital attributes—such as behaviour patterns, social adaptability, susceptibility to common diseases (infectious or otherwise), and reaction to ageing.

Discontinuous Variation

Discontinuous variation, on the other hand, may be defined as the inheritance of characters that show marked qualitative differences between individuals. Mendel, who founded the science of genetics a century ago, worked with such discontinuous contrasting characters in peas—such as tallness or shortness of the stem, colour of the seeds, smooth or wrinkled appearance of the pods.

Fig. 3 illustrates some of these points regarding discontinuous inheritance, and is based on some of Mendel's original experiments with peas—though he did not, of course, employ all the

terms in use today. Two allelic genes (A, a) at a certain locus of the pea plant are responsible for determining the yellow or green colour of the cotyledons. If a pure-breeding homozygous (AA) yellow plant is crossed with a pure-breeding homozygous (aa) green plant only yellow heterozygous (Aa) plants result in the F_1 generation. These are not pure-breeding, however, and if two of these are crossed then both yellow and green plants result in the F_2 generation, in the Mendelian 3:1 ratio. The yellow plants are not, however, homogeneous, since they include not only pure-breeding homozygous (AA) plants but also heterozygous plants (Aa), which, as in the F_1 generation, do not breed true. The green colour is recessive to the dominant yellow, since AA and Aa plants, though genotypically (according to gene content) distinct, are phenotypically (according to appearance) indistinguishable, both being yellow. The parental green colour is hidden in the F_1 generation, to reappear again in the F_2 generation; this "concealment" is the basis of the term recessive.

FIG. 3

It cannot be sufficiently emphasized that it is the phenotypic character (greenness) which is recessive and not the gene. It may well be in the heterozygotes that both the A and the a alleles are producing a characteristic protein product, but that only the one formed by the A allele gives rise to the cotyledon colour, the green colour being suppressed by the dominant yellowness.

Continuous Variation

Intermediate situations between continuous and discontinuous inheritance occur. Thus continuous variation of a particular character, determined by multiple genes (polygenic or multifactorial inheritance), often leads to a normal (or Gaussian) distribution of the character in the population. But once a certain threshold is passed this pattern may cause a discontinuous characteristic to appear. This concept will be clearer if we take one possible example—that of cleft palate. The effects of multiple genes (to some extent modified by environment) on such traits as the width of the skull or of the palate shelf will tend to produce a normal, or Gaussian, distribution

of these traits in the population. If, through some unfavourable combination of genetical or environmental factors, or both, the width of the palate shelf exceeds a certain threshold the normal mechanism of palate closure during embryogenesis becomes impossible. Thus cleft palate, which is a discontinuous character, may in fact reflect an extreme of continuous variation in which a threshold has been passed.

Such threshold effects have been studied in mice, and the whole phenomenon has been described as "quasi-continuous" variation. This type of mechanism may have a very important role in the aetiology of many congenital malformations in man besides cleft palate. It is undoubtedly important where susceptibility to common disease is concerned. The genes involved may not all have equal effects; some "major" genes will influence skull width to a far greater extent than others.

Fig. 4 illustrates some of the points regarding continuous and discontinuous variation mentioned in this section. It shows a normal, or Gaussian, curve, representing the population distribution of such quantitative characters as intelligence, height, or the axial length of the eyeball, determined by multiple genes, each with a small effect. Most individuals will have values near the average; only a few will have extreme values. Beyond the right-hand vertical line (threshold 1) very high values may lead to genius, gigantism, or short sight (myopia) respectively; values less than the left-hand vertical line (threshold 2) may be responsible for imbecility, dwarfism, or long sight (hypermetropia). In such cases these attributes are not discontinuous but reflect an extreme of natural continuous variation.

FIG. 4

Sometimes, however, such an extreme value can lead to an appearance of a discontinuous character, as in our example of cleft palate. True discontinuous variation is very different from such "quasi-continuous" variation, and is due not to multiple genes but to single genes—such as those determining phenylketonuria or sickle-cell anaemia. In such cases the population distribution cannot be represented by a Gaussian dumb-bell-shaped curve but falls into two or more discrete classes—that is, normal-phenylketonuria, or normal-sickle-cell-trait-sickle-cell-anaemia.

(This article will be continued in next week's issue.)