Current Practice

GROWING POINTS

Genetics and Medicine—III*

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Linkage of Genes

Two genes are said to be linked when they do not segregate independently in gamete formation, and this indicates that they are situated on the same chromosome (Fig. 7). Two genes on different chromosomes will enter the same daughter cell in meiosis in 50% of cases, and different daughter cells in the other 50% of cases. If, however, they are close to each other on a chromosome free crossing over between them does not take place. They are then said to be *linked,* and they will enter the same daughter cell more often—the exact incidence of this depending on the distance between them. In this way, if the relative distance of pathological genes from marker genes—for example, those determining blood- and serum-group polymorphisms—can be determined, these linkage relationships can serve to identify and differentiate them. Thus "linkage" has a very specific genetical connotation, which is entirely different from its normal meaning of association, with which it is often confused.

In animals linkage studies are relatively easy, because controlled breeding is possible. In man, on the other hand, they are extremely difficult, and this has led to the development of intricate statistical techniques. Even so, these techniques cannot overcome the inherent difficulties of working with human beings, and progress in this field is very slow. One possibility which has recently been explored is to study linkage relationships and other aspects of human genetics in long-term cell cultures established from donors in the laboratory. This kind of approach is very promising, though it is still in its early stages.

Chromosomal Abnormalities

Dominant abnormalities may sometimes be due to larger rearrangements in chromosomes than point mutations, which concern a single base pair and lead to a single amino-acid substitution. It is now feasible to make preparations of chromosomes from human cells and study them under the microscope. This has made it possible to classify the more pronounced of these chromosomal rearrangements. This has been one of the fundamental advances of human genetics during the last decade.

Chromosomal aberrations may be of various types. There may be more or fewer chromosomes in number—with an extra chromosome (*trisomy*) or a missing chromosome (*monosomy*) (Fig. 8). Alternatively *translocations* of material from one chromosome to another (Fig. 9) may lead to the formation of abnormal gametes. After fertilization these gametes give rise to zygotes that are partially trisomic or monosomic for a part rather than a whole of a chromosome. Other possibilities of chromosomal rearrangements include *deletions,* where a piece of chromosome is lost ; *duplications,* where a piece is acquired ; and *inversions,* where a chromosome breaks in two places and the fragment between the breaks is reinserted the wrong way round (Fig. 9).

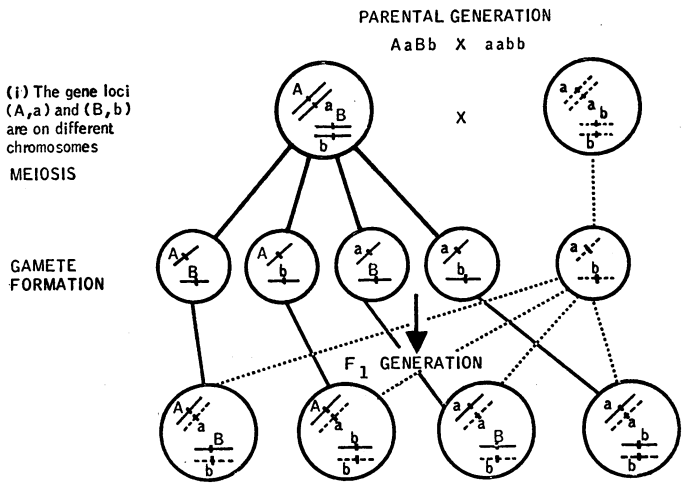

FIG. 7 (i).—Mendel's second law of independent segregation as modified by linkage. If the gene loci occupied by alleles (A,a) and (B,b) are on different chromosomes, independent segregation or assortment occurs. Thus gametes of all four possible types (AB, Ab, aB, ab) will be formed with equal frequency in the left-hand parent and in the particular cross under consideration progeny of all four possible types (AaBb, Aabb, aaBb, aabb) will also result with equal frequencies.

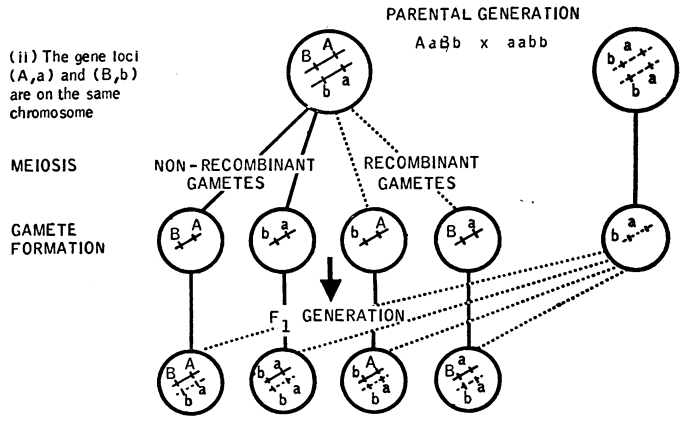

FIG. 7 (ii).—If now the gene loci are on the same chromosome, and close together, more progeny will be of the parental types (AaBb, aabb) than of the new or recombinant types (Aabb, aaBb). This is because segregation or assortment at meiosis is no longer independent and the combinations of alleles represented on the chromosomes of the left-hand parent (AB, ab) will tend to pass to the progeny together. They may, however, in the minority of gametes be separated by crossing over to form the recombinant chromosomes Ab, aB. The frequency of recombination will depend on the distance between the two loci. When these are very close together it will be very low and segregation will markedly lack independence. When they are far apart 50% of gametes may contain recombinant chromosomes and segregation may be independent with the same results as in (i).

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In 1959 it was discovered that mongolism (Down's syndrome) was associated with trisomy of one of the smaller chromosomes —conventionally known as number 21. Since then a whole series of diseases associated with abnormalities of chromosomal structure and number have been described. The mechanisms whereby these aberrations may arise and the more common results are shown in Figs. 8 and 9. The number of abnormalities of the sex chromosomes, including mosaic forms, which have been uncovered is truly remarkable. Possibly this is related to the fact that gross aberrations of chromosomes usually give rise to an inviable foetus and spontaneous abortion ; but in the case of the sex chromosomes this process may not be lethal so often because of the relative flexibility of the sex-determining mechanism. At the other end of the scale there are undoubtedly many chromosomal aberrations (especially small duplications, deletions, and inversions) that may be concerned in disease or malformation which cannot be seen because of the limits of present microscopic techniques. A whole spectrum of aberrations exists between the gross trisomy of Down's syndrome and the point mutation underlying sickle-cell anaemia.

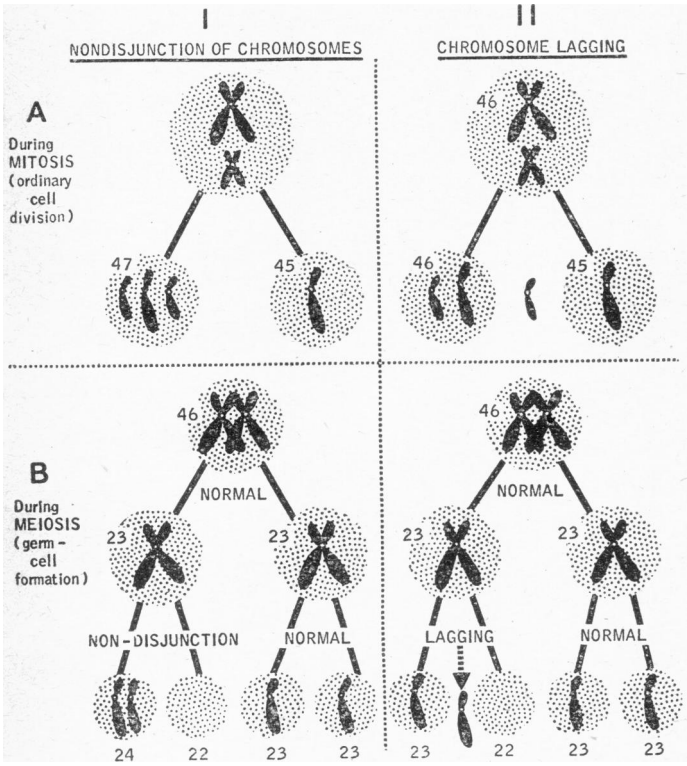

FIG. 8.—Some of the errors of chromosome behaviour which take place during meiosis and mitosis. Gametes which acquire an extra chromosome in meiosis may be responsible, if they take part in fertilization, for trisomic conditions (diploid chromosome number of 47) such as Down's syndrome (mongolism). If they lose a chromosome, monosomic conditions (diploid chromosome number of 45), such as Turner's syndrome, in which the sex chromosomes are represented by one X only, may result. If these anomalies of chromosome number arise during early mitotic divisions in the fertilized zygote, a *chromosomal mosaic* may result—an individual whose cells may be of two or more chromosomal types.

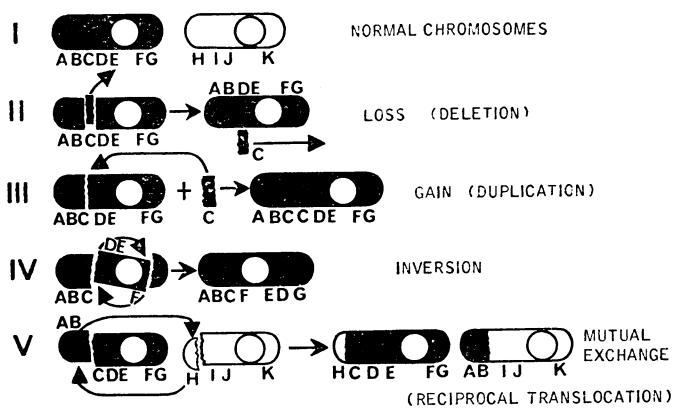

FIG. 9.—Some structural errors of the chromosomes. The letters refer to blocks of genes arranged in alphabetical order on the two normal chromosomes represented (I). In II–V the effects of various rearrangements on this original order are shown.

Genetical Counselling

Most of the diseases due to these relatively simple genetical mechanisms are rare, and many doctors will not see even one case of a particular condition in a lifetime. Yet there are so many of them that it is virtually certain even in a modestly sized general practice that one or two examples of molecular and chromosomal diseases will arise and present practical problems. Unfortunately, with rare exceptions, our knowledge about the aetiology of these conditions does not help in their treatment. Often all that can be provided is moral support to a family to enable it to bear its burden with fortitude ; though sometimes (as in the case of haemophilia, for example) more practical advice and treatment can be given.

Nevertheless, one immediate application of our knowledge lies in the field of gauging the prognosis for future children and of genetical counselling. Every doctor is sometimes faced with this problem, and the intense distress of the parents who have one or more handicapped child is known to all. Fortunately such advice can now be obtained at specialized institutes and clinics throughout the country. The principles underlying genetical counselling are very simple, and even in cases where no exact knowledge exists informed estimates of risk can be provided. For example, in the case of a couple who have had a single child with a recessive condition, such as phenylketonuria, the recurrence risk is 25%, but in the case of deafness of totally unknown cause it is rather less, since the deafness may not be inherited at all, but may be acquired owing to an undetected cause. When a genetical disease is simulated in this way the term *phenocopy* is used. Again, in the case of congenital malformations of complex and ill-understood aetiology—such as cleft palate—involving interactions of many genetical and possibly environmental factors, empirical recurrence risks can be given based on previous studies of large series of cases.

The function of such advice is simply to gauge the risk, and any decision must be left to the parents. Very often they can be reassured that their chance of bearing deformed or handicapped offspring is not much different from the not insubstantial chance that every parent takes. In some rare and very special circumstances, such as certain forms of chromosomal translocation or in families where congenitally deaf persons with the same type of recessive deafness marry, the risk is 100%. Between these two extremes there is an entire spectrum of risks. In each case it must be an individual decision whether such risks are acceptable, or whether recourse should be made to adoption or to other possibilities of circumventing them.

Prospects

Apart from his inherent disadvantages, man also has great advantages as a tool for genetical study. Thus the investigation of the complex chain of events between the genotype and the phenotype (between the gene and its final effects)—both in the case of point mutations and resultant inborn errors of metabolism and in the case of chromosomal aberrations—is made much easier in man because of the substantial background of knowledge (both of normal and disordered function) accumulated by medical science. Moreover, the human species has colonized much of the habitable area of the world, and has kept careful and, in some cases, long-term pedigree and historical records. This makes man particularly suitable for the study of the dynamics of gene flow and persistence in populations.

Though genetical studies can only be applied immediately to some rare diseases in man, such studies undoubtedly open wider perspectives in the treatment and prevention of human disease. The discoveries and methods described here will eventually be applied to the more common diseases and to the more universal aspects of human existence. Examples of these include the factors underlying resistance and sensitivity to infectious disease, to the degenerative diseases of old age, and to cancer, and also physiological attributes such as size, intelligence, fertility, behaviour, and social and psychological adaptation.

Impressive beginnings have already been made in these directions. Fields in which further advances may be expected in the immediate future include some of the following: the complex interplay of the genotypes of host and parasite, as modified by modern drugs, involved in infectious disease; the associations of the common polymorphisms, such as those concerned in the determination of the blood and serum groups with susceptibility to disease in general; the problem of autoimmunity in its relationship to the phenomenon of mutation in somatic cells; the elucidation of the basis of drug sensitivities on the lines of the relationship already established between suxamethonium sensitivity (with its great importance in anaesthesia) and serum pseudocholinesterase polymorphism; and the mechanisms whereby inheritance affects basic human attributes such as memory, behaviour, and intelligence.

Lastly, an example may be given which shows one such development in actual progress. Blood-group genetics brought about a revolution in surgery in this century by making blood-transfusion a safe procedure. Today extensions of these advances are being applied to the relief of one of the most common diseases of the late foetal and early neonatal period—haemolytic disease of the newborn, due to blood-group (usually rhesus-group) incompatibility between mother and foetus. Two methods are being used with promising results. First, the foetus can now receive intrauterine blood-transfusion instead of waiting till after birth, with all the dangers which such delay involves. Secondly, when incompatibility exists the mother can be desensitized immediately after pregnancy, so that the antigenic stimulus from the incompatible foetal red cells is minimized. In this way antibody formation may be delayed for several pregnancies or even avoided altogether.

The perspectives for genetics in medicine for the next century are vast indeed; but they are no vaster than the knowledge which has already accumulated in the century which has elapsed since Mendel's discovery.

I would like to thank Dr. M. J. Mayo and Dr. U. Mittwoch for their advice regarding certain aspects of this paper.

ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Paroxysmal Tachycardia in Pregnancy

Q.—*Are attacks of paroxysmal tachycardia in pregnancy likely to affect the foetus? Should quinidine, digoxin, or morphine be avoided in such cases?*

A.—Paroxysmal tachycardia is relatively rare in association with pregnancy[1] and the opportunities for observing the effect of this condition on the foetus are correspondingly few. However, there seems to be no evidence that the foetus is adversely affected.

There is no reason why any of the drugs mentioned should not be used in the treatment of paroxysmal tachycardia during pregnancy.[2]

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Drawing Blood

Q.—*Is arterialized venous blood, arterial blood, or capillary blood the most satisfactory for tests for pH, P_{O_2}, and P_{CO_2} in the assessment of pulmonary disability in patients who are not in serious respiratory failure? Are there any fixed relationships in the respective accuracies of measurement between these three types of blood? Is arterial puncture too hazardous for routine use? If not, which artery is it safest to use—the radial, brachial, or femoral?*

A.—Lilienthal and Riley[1] showed that capillary blood obtained by puncture of a well-heated lobe of the ear could be used to measure arterial oxygen *saturation*. Since then a number of papers have appeared to show that capillary blood can equally be used for the direct measurement of oxygen *tension* and of the P_{CO_2} and *p*H. One such recent paper by Langlands and Wallace[2] gives a comparison of these measurements on blood from the heated lobe of the ear with those on arterial blood taken concurrently from the brachial artery.

From all this work there is no doubt that, with skilled and careful operators, blood from ear-puncture is satisfactory provided that the lobe is most energetically warmed by heating it with a heater giving radiant heat from small bulbs inside an anaesthetic mask covering the lobe. One method of getting the sample from the lobe of the ear is to rub in histamine cream, heat with the electrical "ear warmer," and then make a scalpel cut in the lobe so that blood drips freely into a small funnel placed on the end of a syringe with dried heparin in it.[3]

I do not think arterial puncture is too hazardous for routine use provided, again, that great care is taken with the technique. The brachial artery seems to be the most satisfactory. Plenty of local anaesthetic is infiltrated round the artery, a Riley needle is then inserted through the skin, with the arm held rigid at the elbow, until the needle is felt to pulsate on the artery. It is then advanced and held, when arterial blood should squirt freely. Sometimes the artery goes into spasm on puncture, so that it is important to wait for 2 to 3 seconds after advancing the needle.

There have been many opinions on the safety of arterial puncture, and the general impression is that it carries negligible risk, though with catheterization there is a small risk of haemorrhage and thrombosis. After any attempt a pad must be held tightly against the artery for a full 5 minutes after the puncture. The lobe of the ear is probably satisfactory for routine use provided the patient is not in circulatory failure and that full vasodilatation is obtained. However, errors can be made, and it seems to me reasonable to use direct puncture. The femoral is best avoided, as there appears to be greater chance of accident. Moreover, in some patients it can be difficult to differentiate between femoral venous and femoral arterial blood.

The questioner would be well advised to visit a centre where arterial punctures are being routinely made and to learn the technique.

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Autoimmune Disease in Animals

Q.—*Have any of the diseases now designated "autoimmune" ever been reported in animals in their natural state or in captivity?*

A.—The putative autoimmune diseases have, with few exceptions, not been reported in animals either in their natural state or in captivity. There are three main exceptions, as follows:

(1) Lesions experimentally induced by autoimmunization—e.g., thyroiditis[1] and experimental allergic encephalomyelitis.[2]

(2) A Coombs-positive haemolytic anaemia in certain strains of mice, notably New Zealand blacks and New Zealand whites. Renal