Errant Genes

Few ideas have been more fruitful in the understanding of human disease than that of “inborn errors of metabolism.” Certain diseases are caused by deficiency of a particular enzyme, so that a particular reaction in one of the normal metabolic pathways cannot occur. The clinical features of the disease may result either from impaired production of a substance beyond the block or from accumulation of a substance which cannot be removed because of the block. Thus, in phenylketonuria there is a deficiency of the enzyme phenylalanine hydroxylase, so that phenylalanine cannot be converted to tyrosine. The resulting excess of phenylalanine in the blood is toxic to the growing brain, causing mental retardation and fits. In disorders of this kind the enzyme defect is genetically inherited.

The nature of the inborn errors of metabolism was clearly and almost fully worked out by A. E. Garrod 60 years ago in his remarkable Croonian lectures. 1 The principal advances since then have been made in the past 20 years, and they have been of two main kinds. Firstly, the number of disorders recognized as belonging to this category has changed from being too few and too obscure to be of any concern to practising doctors to being too many for anyone to attempt to remember them all. In many of these disorders—58 according to a recent count, 2—which must already be out of date—the actual enzyme deficiency has been demonstrated. Secondly, as Professor Harry Harris, F.R.S., shows in his Leonard Parsons memorial lecture at page 321 of this week’s B.M.J., the advances in molecular biology which have solved the genetic code 3-5 and clarified the mechanism of protein synthesis 6 have shown at a much deeper level than before how the inborn errors arise. It is now possible to relate the disorder to the actual biochemical structure of the gene.

One idea fundamental to understanding the inborn errors was originally formulated as “one gene : one enzyme” 7 but is now expressed in the more general form “one gene : one polypeptide chain.” This means that the function of certain genes is to control the synthesis of the whole or part of an enzyme or protein molecule. A simplified view of the genes concerned in inborn errors of metabolism is that each of them can exist in a normal and an abnormal (or mutant) form. If both genes of a particular pair—or an unpaired gene on the X chromosome in a male—are abnormal, then none of the corresponding enzyme is produced, and the inborn error results. This explains the pattern of recessive inheritance in these disorders. However, the true situation is more complex, for there are far more than two possible forms—or “alleles”—for a particular gene. Most mutations consist of a change of just one purine or pyrimidine base for another in the sequence of several hundred bases in the D.N.A. (deoxyribosenucleic acid) of a particular gene. In a typical gene of about 900 bases, which might code for the synthesis of a protein chain of 300 amino-acids, 2,700 possible alleles might arise...
from mutations each involving a single base. Not all these alleles would be abnormal; about a quarter of them would direct the synthesis of the same protein or enzyme as the normal gene. The remaining three-quarters would each direct the synthesis of a different protein. The term "genetic heterogeneity" includes the many variations possible in a single gene—and their biochemical consequences.

Not all genes direct the synthesis of enzymes. Some are concerned with the synthesis of other proteins or polypeptide chains, such as haemoglobin, whose structure is easier to study than that of most enzymes. Nearly a hundred variants of the alpha and beta polypeptide chains of haemoglobin A have been described, most of the variations consisting of a single amino-acid substitution, attributable to a single base change in the D.N.A. of the gene. Some of these variant forms of haemoglobin cause disease, but many do not, and many other harmless variants certainly remain to be identified. The genes which control the synthesis of an enzyme must undoubtedly show a similar heterogeneity: it is not simply that a normal gene directs the synthesis of enzyme and an abnormal gene does not. In most cases the abnormal gene will direct the synthesis of some form of polypeptide with different catalytic properties from the normal enzyme. The enzyme—substrate kinetics may be changed unfavourably, or the enzyme molecule may be unstable, or sometimes there may be a gross reduction or absence of enzyme synthesis. Clearly not all cases showing an apparent deficiency of enzyme activity have exactly the same defect, and Professor Harris quotes examples where such genetic heterogeneity is clinically important.

The Mediterranean form of glucose—6-phosphate dehydrogenase deficiency differs from the Negro form because the enzyme molecule produced in the former is more unstable and has a shorter half life than in the latter. In another example, methylmalonic aciduria, the effects of treatment vary according to the exact nature of the enzyme defect. Many of the doubts and confusions about the efficacy of dietary treatment in phenylketonuria might have been avoided by an earlier recognition of the differences in biochemistry and severity among patients with this disorder, which can readily be explained by genetic heterogeneity.

Another implication of genetic heterogeneity is that the pair of abnormal genes in a patient with a condition such as phenylketonuria may not be identical. One is derived from each parent, and they may therefore be the result of different mutations. The "homozygous" patient may thus, strictly speaking, be heterozygous for two abnormal alleles (this would be much less likely if the parents were consanguineous). This theoretically interesting idea may have practical application in assessing the treatment of metabolic disorders. Affected siblings whose parents are clinically normal must always have the same pair of alleles, even if the allele derived from one parent differs from the other. A disorder should therefore show less variation between siblings than between other patients. Studies like that of F. Hudson and colleagues on phenylketonuria, in which it has been possible to compare the outcome in treated and in older, untreated, affected siblings, are therefore of particular value. They may even have advantages over the controlled trial which some have advocated in phenylketonuria, but which few would be happy to undertake.

Biochemical genetics may sometimes seem remote from clinical medicine, and its terminology difficult and obscure. Garrod's contemporaries may well have thought the same of the "Inborn Errors." But Professor Harris's lecture gives a clear and readable account of some of the most exciting of all biological discoveries, and it shows their importance in medicine.

Unheard Voices

Traditionally, any complaints that a registrar had about his lot were met by contrasting it with the paradise inhabited by consultants; and indeed for many years hospital junior staff put up with long hours, poor pay, and little formal training because they thought a consultant post worth getting.

In the last year or two, however, there has been a steady growth of evidence of discontent among consultants. The publication of the cog-wheel1 and Godber reports and proposals for reorganization of the N.H.S. and medical education has brought this into the open. Many consultants in non-teaching hospitals clearly believe that their representatives are out of touch with the realities of their work, and that the proposals which are being discussed have little relevance to their everyday problems.

Busy clinicians have little time to spare for political meetings and little interest in the infighting of rival groups of committee-men. Some have given up attending committees because so little notice seems to be taken of the decisions reached, while others are daunted by the enormous volume of the documents and reports that are published each year. What they want is to be given adequate time, staff, and equipment to get on with the work they were trained for and to be paid a fair rate for it; their disenchantment stems from their growing conviction that the proposed reforms will not achieve this.

This week (p. 358) we start publication of a series of profiles of medical staff in non-teaching hospitals in which we hope to give a fair account of the way these doctors work and the major defects of the system as it affects them and their patients. Each of the articles is based on informal interviews with one or more doctors, given anonymity so that they could speak freely. Their complaints and criticisms may seem trivial or unrealistic to the planners and those at the centre of medical politics; but they should not remain unanswered. Nearly 90% of the work in the N.H.S. is done in regional non-teaching hospitals, and if consultant posts in these hospitals seem unattractive then improvements in postgraduate training will lead only to further frustration and higher emigration.

REFERENCES
10 Woolf, L. I., Developmental Medicine and Child Neurology, 1967, 9, 244.