

sources we are increasing mutations, most of which are bad. We may therefore confidently predict that the human race will deteriorate unless we take steps to eliminate bad genes and preserve the good.

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### Clinical aspects of inborn metabolic defects

By P. R. EVANS, *Department of Paediatrics, Guy's Hospital, London, S.E.1*

#### *The clinical viewpoint*

Metabolic diseases involve interference with the use or disposal of nutritive material in vital processes that may affect the whole body or only certain cells. Many of the diseases that I shall mention are described in other chapters of medical text books than the one headed *Diseases of Metabolism*, for example, some in the haematological and some in the neurological sections.

The practitioner's viewpoint is quite different from that of the scientist. The aim of the scientist is to know fully, of the clinician to act successfully, even if he does not

really know why his treatment succeeds. Physicians have treated acute gout (one of the commonest of the diseases due to inborn error of metabolism) fairly successfully for centuries, although nobody knows how colchicine works.

The clinician, then, has four main objects, which he might place in this order:

- (1) To cure the patient, or to alleviate his condition.
- (2) To foresee the outcome of the illness—and in the branch of medicine we are discussing today that outcome includes the fate of children yet unborn.
- (3) To prevent disease or its worse consequences from occurring. We can prevent the occurrence of inherent disease only by genetic counselling, but the effects can sometimes be minimized by early treatment. If one detects galactosaemia in a young baby, blindness, mental defect and cirrhosis of the liver can be avoided by the omission of milk from the diet.
- (4) To understand the illness. We want to know the prime fault and how it throws physiological processes out of gear to produce the patient's symptoms and signs.

Underlying all these is a primary task, to make a diagnosis. Without that, the aims I have enumerated—treatment, prognosis, prevention and pathology—are hard to achieve although, contrary to popular belief, not always totally impossible. One can sometimes cure a patient before one knows what is really the matter with him, for example by a surgical operation to remove a lump. Pathology too can proceed in the absence of a categorical label.

As an example of clinical progress let us consider acholuric jaundice. Many years ago it was found that the recurrent jaundice which is a feature of this malady was caused by the production of excessive amounts of bile pigment due to the liberation of haemoglobin when red corpuscles were destroyed, particularly in haemolytic crises. As these cases occurred in families (in a manner indicating transmission as a Mendelian dominant) the illness was also called familial haemolytic icterus. The diagnosis was easily confirmed because the corpuscles were unduly fragile when suspended in hypotonic saline. Then it was observed that many of the corpuscles were more or less spherical and so had less room than normal biconcave corpuscles to accommodate water before bursting. This provided a new name, spherocytic anaemia or simply spherocytosis. Most of the cell destruction occurs in the spleen, and removal of that organ was found to cure the patient. So far so good; the practitioner could diagnose and cure his patient, give a prognosis for him and his family, and to a considerable extent understand what was going on.

Why the corpuscles should be spherical remained a mystery, but after all there were plenty of other examples of parts of the body being congenitally deformed. How much more satisfactory, nevertheless, to know as we now do from the work of Prankerd (1957) that the walls of the abnormal corpuscles lack high-energy phosphate bonds and so cannot maintain the biconcave form but become spherical and vulnerable. This is an exciting and enlightening step in the domain of congenital deformity but it makes no difference to well-established clinical practice. Fortunately this time no-one has had the nerve to coin a new name for the disease (e.g. anergo-phosphatozeugonerythrocytosis).

Instead of discussing inborn errors of metabolism in a rational chemical way I shall be preoccupied with the possibility of treating them. This may seem perverse, like looking through the wrong end of a telescope, but it has the advantage of projecting a large field in miniature. Garrod in 1909 described four inborn errors, by 1923 he had added two more (Garrod, 1909, 1923). Today we know of over 100. The first edition of Garrod's book weighed 11 oz and cost 3s. 6d.; one of the latest volumes on the same subject weighs nearly 5 lb and costs over £11. Nevertheless the printed word continues to sell at about 10 g for a shilling—scientific increase running parallel with monetary inflation.

### *The variety of inborn errors*

There are probably as many errors of metabolism as there are steps in a metabolic succession, for each is a vulnerable point. It is convenient to think of these steps or stages in metabolism, although Garrod (1909) was nearer to temporal actuality when he wrote:

'It may well be that the intermediate products formed at the several stages have only momentary existence as such, being subjected to further change almost as soon as they are formed; so that the course of metabolism along any particular path should be pictured as in continuous movement rather than as a series of distinct steps. If any one step in the process fail the intermediate product being at the point of arrest will escape further change, just as when the film of a biograph is brought to a stand-still the moving figures are left foot in air'.

When we define diseases in terms of aetiology the variety increases, for several causative factors may impinge on one point. For instance, favism is an acute haemolytic anaemia due to sensitivity to broad beans which occurs in Mediterranean people, whether living in Sicily or Soho. It is said that walking over a field of beans in flower may induce an attack. A similar acute haemolytic anaemia occurs in some negro children who happen to eat naphthalene moth balls. Haemolysis may also take place in some individuals who take primaquin to suppress malaria. These anaemias were all described separately, but Beutler (1957) showed that in the people who were sensitive to primaquin there was diminution of glutathione in the blood, due to deficiency of glucose-6-phosphate dehydrogenase. The situation was similar in favism and in moth-ball anaemia (Zinkham & Childs, 1957; Childs, Zinkham, Browne, Kimbro & Torbert, 1958). As a result of their work and that of others (reviewed by Beutler, 1960) we now know that there is a type of acute haemolytic anaemia which is due to abnormality of the red blood corpuscles caused by deficiency of a particular enzyme. Those at risk may be detected by finding decreased glutathione in their blood or by examining red corpuscles for Heinz bodies after incubating them with one of the haemolytic substances. These include drugs such as pamaquin, sulphanilamide, acetanilide, phenacetin, sulphacetamide, probenecid, nitrofurantoin and aminosalicic acid. This is by no means entirely a list of drugs of simple historical interest; I take one of them myself every day and prescribe two of the others frequently.

The method of destruction of the cells is not known, and there are differences in severity and in time of onset after ingestion of different drugs. The abnormality has been shown to be due in all probability to a sex-linked gene with incomplete dominance (Childs *et al.* 1958).

Most inborn errors of metabolism that we know are hereditary, and this may be true of those we do not know, although it is the multiple cases occurring in a family which are liable to attract attention and stimulate the curious mind. We must not, however, forget that many inborn errors of morphology are not hereditary but are due to antenatal mischances, and the same may be true of chemical anomalies.

Although a variety of agents may affect one step in metabolism, disturbance at several steps may have only one clinical consequence. There are many severe calls on the body but its repertoire is limited. All cases of hypothyroidism are basically similar and respond to treatment with thyroxine or tri-iodothyronine. Endemic cretinism with goitre is due to lack of iodine in the environment, and thus until recently in the food. Familial goitrous cretinism may be due to inability to combine iodine with tyrosine (Stanbury & Hedge, 1950), but in other cases there is a block in the conversion of tyrosine to thyroxine which in different families has occurred at two separate points (Hutchison & McGirr, 1956; McGirr, Hutchison & Clement, 1956; Hutchison, Arneil & McGirr, 1957.) In the usual cases of sporadic cretinism there is no goitre, for the thyroid gland is absent or small and perhaps displaced. It is not known whether the failure of development is due to local chemical failure of induction or to something else, such as deficiency of oxygenation at a critical time.

In these conditions five pathological faults are equally well bypassed by giving thyroxine, just as in acholuric jaundice the haemolysis is sufficiently diminished by removal of the spleen.

#### *Methods of therapy*

In other conditions a simple bypass is not enough. Thus with hypoglycaemia, giving glucose will overcome the immediate crisis but the sugar is rapidly destroyed. Polysaccharides will persist longer, but to last through the night protein is better. In certain cases Cochrane, Payne, Simpkins & Woolf (1956) noticed that hypoglycaemic attacks were more instead of less likely to occur when protein food was given. They found that in these patients leucine or isovaleric acid induced a fall in blood sugar. Strict reduction of food containing these amino-acids was needed if such patients were to be maintained in health, particularly mental health, for prolonged hypoglycaemia causes irreversible cerebral damage. In another family there was a similar sensitivity to ingestion of fructose (Froesch, Prader, Labhart, Stuber & Wolff, 1957; Dormandy & Porter, 1961) and hypoglycaemia may be the cause of the mental changes in galactosaemia, for as the galactose rises in the blood the glucose falls. There is also an idiopathic group in which hypoglycaemia is kept within bounds by the injection of adrenocorticotrophic hormone (ACTH), an empirical treatment (McQuarrie, 1954). Insulin-producing tumours cause hypoglycaemia in adults but rarely occur in children. It is interesting that a patient with an insuloma may be leucine-sensitive—a tumour with an allergy (Marrack, Marks & Rose, 1960). So we

see that to treat hypoglycaemia one may decide to give one sugar or omit another, to feed with protein or to remove certain amino acids from the diet, to administer a hormone or to remove part of an endocrine gland surgically.

Fructosuria and pentosuria are errors of metabolism but not diseases. Moving up the carbohydrate scale, we come to glycogen storage disease in which glycogen cannot be mobilized and hypoglycaemia may result. There are several chemical forms of this condition and there are clinical differences. In the commonest form glycogen is stored mainly in the liver and kidneys, but in other cases it infiltrates the brain, the skeletal muscles or the heart, with grave effects on function. One family has now been observed for a long time. A brother and two sisters were described as examples of familial cirrhosis of the liver in the first article of the first volume of a new journal—*Archives of Disease in Childhood*—in 1927 (Poynton & Wyllie, 1927). After von Gierke (1929) had described the post-mortem findings in a similar case the children were reinvestigated and appeared with the correct diagnosis in the *Quarterly Journal of Medicine* (Ellis & Payne, 1936). Through the kindness of Dr E. W. Holling I came across them again a few years ago. The least severely affected patient, one of the sisters, seemed to have completely recovered. The boy had grown up, married and had an unaffected child. The other sister was somewhat stunted and her liver was a great hard block. She was full of energy and attributed her health to physical training. Later she married and had an unaffected child but she developed gout—a most unusual event in a young woman.

In other instances illness is caused by lack of an essential substance. Congenital hypogammaglobulinaemia is a good example, a sex-linked anomaly in which globulin is produced in only minute amounts, the infant therefore suffering from lack of antibodies. This cannot be detected at birth, for the newborn infant's  $\gamma$ -globulin is acquired from its mother, but as her antibodies are gradually destroyed in its body its own  $\gamma$ -globulin production increases. In an affected infant the deficiency can usually be demonstrated between the 4th and the 6th month and the patient enters on a course of infections from which he may not recover. He can be given injections of  $\gamma$ -globulin, which may protect him, but the antibodies in it are those of the adults who provide the plasma from which the active material is obtained and may lack the specific antibody which he needs in order to overcome his own particular infection. This seems to be almost the rule with pneumocystis carinii, which causes a long-lasting pneumonia. Many epidemics in Middle European newborn babies have been described, but in Britain, Canada and the United States it is almost restricted to hypogammaglobulinaemic infants. In them it is as a rule fatal; I have been fortunate in seeing one child recover when treated with Pentamidine. What other trouble this boy will run into is difficult to foretell. Regular globulin injections may prevent him from being unduly susceptible to bacterial infections, and  $\gamma$ -globulin seems to be less important in virus infections. Vaccination is often successful but it may be followed by generalized vaccinia which progresses to death (Gitlin, Gross & Janeway, 1959 a,b).

Another example of substitution therapy is seen in Hartnup disease. It was originally described under the title *Hereditary Pellagra-like Skin Rash with Temporary*

*Cerebellar Ataxia, Constant Renal Amino Aciduria, and other Bizarre Biochemical Features* (Baron, Dent, Harris, Hart & Jepson, 1956). Chemically and clinically it is a disease of varied manifestations, but one of the clinical features is pellagra, which seems to respond to treatment with nicotinic acid. Here one of the abnormalities in the syndrome was picked out because it seemed amenable to treatment by a readily available medicament, and this almost symptomatic therapy has been effective. I treated one girl before the disease had been described—an example of treatment without diagnosis to which I referred earlier.

In other conditions the deficiency cannot be made good, for example in thalassaemia, another anaemia that occurs mainly in Mediterranean peoples. In it the child cannot produce enough haemoglobin. There is congenital deficiency of polypeptide chains in the adult type of haemoglobin (Ingram & Stretton, 1959). In one type the missing polypeptide is  $\beta$  so adult (A) haemoglobin cannot be formed (Table 1) and it is replaced by foetal (F) and alternative adult (A<sub>2</sub>) haemoglobin, but unfortunately they cannot be produced in large enough quantities. In the other type  $\alpha$  chains are lacking and there is deficiency of all types of haemoglobin. All we can do to make

Table 1. *Polypeptide chains in haemoglobins*  
(Lehman, 1961)

Haemoglobin	Polypeptide chains	
A	$\alpha_2$	$\beta_2$
F	$\alpha_2$	$\gamma_2$
A <sub>2</sub>	$\alpha_2$	$\delta_2$

good the deficiency is to give blood transfusions. It is amazing how well some of these infants manage to live for long periods on haemoglobin of their own manufacture; they may run on for months with a haemoglobin level of 40%, with gross enlargement of liver and heart, and yet remain active until an infection upsets the balance and blood transfusion is essential.

I mentioned bypassing a defect when I spoke of giving thyroid to cretins. There the natural product can be used. In other cases one can use an alternative mechanism to produce a satisfactory clinical effect. For instance, a boy, B.P., was born 11 years ago. When he was 2½ years old he started having convulsions. Anticonvulsant drugs did not help. At 5½ years his serum calcium level was found to be 6.6 mg/100 ml. It did not rise when he was given parathormone injections and he had some characteristic physical peculiarities so a diagnosis of pseudohypoparathyroidism was made and it was assumed that his end-organ for calcium regulation was hormone-resistant. He was given 50 000 i.u. daily of ergocalciferol—more than fifty times his daily need as an antirachitic agent—and the calcium level soon rose. On this dose it has remained between 8.4 and 11.4 mg/100 ml for over 5 years and he has had no fits, even without anticonvulsants (Fig. 1). His intelligence quotient rose from 42 to 71 over a period of 2½ years, and there it has remained. If only the diagnosis had been made 2 years earlier perhaps his IQ could have been brought up to average, but even as it is he has recently been able to move from a special to an ordinary school and he is holding his own there.

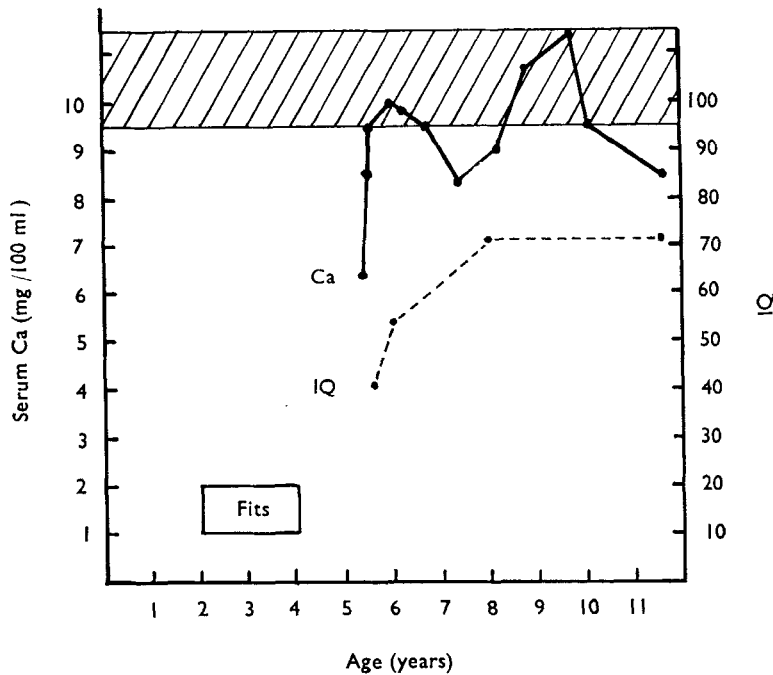


Fig. 1. Serum calcium level and intelligence quotient of a boy diagnosed as having pseudohypoparathyroidism, given 50 000 i.u. daily of ergocalciferol from the age of 5½ years.

Another therapeutic method is to utilize a feed-back mechanism, and this is done to suppress overactivity of the adrenal cortex. The adrenogenital syndrome is a familial condition due to autosomal recessive inheritance, in which the adrenal cortex forms excess male hormone and causes virilism in girls and precocious sexual development in boys. In girls the effect is usually noticeable at birth, for the masculinization has occurred during prenatal development. It may be difficult to decide whether a baby is a female pseudohermaphrodite or a boy with defective development of the external genitalia (hypospadias). An affected boy will not show signs of precocious development until a year or two have passed, although he may be excreting large quantities of 17-ketosteroids. In either sex, growth will be much accelerated. The child is very tall, but bony growth is overtaken by skeletal maturity before adult height is reached and the gigantic child becomes a stunted adult.

The abnormality of growth and superficial sexuality causes embarrassment and unhappiness. Surgical treatment would appear to be indicated, but to remove the whole of one adrenal gland and most of the other in order to cut down production of male hormone (androgen) would inevitably also remove tissue producing other hormones which are essential for life. One of them is cortisol, and its production is under the control of ACTH of the pituitary. So is the production of androgen by the adrenals. It was found in January 1950 by Lawson Wilkins that giving the patient

cortisone caused a reduction of androgen production (Wilkins, 1957). Presumably the high cortisone level in the blood causes the pituitary gland to cut down production of ACTH which is no longer needed for one purpose, but in so doing the gland also removes the stimulus to production of androgen.

In more than half of these patients the adrenal cortex is abnormal in another facet of its behaviour, for overproduction of androgen goes with underproduction of salt-retaining hormone and in that sense the child suffers from adrenal insufficiency, just as an adult whose adrenals have been destroyed suffers from Addison's disease. Very severe vomiting with collapse, hyperkalaemia and hyponatraemia used to be fatal before evidence of sexual precocity declared itself, but treatment with NaCl and cortisone by mouth saves these children if the diagnosis is made in time. It usually is in females since their external genital abnormality draws attention to the possibility. Cortisone is then in this disease being used for replacement therapy as well as acting to suppress one of the activities of the neurohypophysis.

Other conditions find us powerless to affect the primary abnormality, yet life may be made more tolerable and prolonged by the correction of some secondary aberration of physiology which has been produced. The bizarre disorder (Fanconi-de Toni-Debré-Dent syndrome) of the renal tubules which produces defective growth with aminoaciduria, deposition of cystine crystals in the cornea, slight glycosuria and rickets will ultimately be fatal because of malnutrition or renal failure. Yet great benefit accrues from correction of the accompanying acidosis by giving citric acid and sodium citrate, and the rickets is amenable to heavy dosage with vitamin D. As the kidneys become more severely diseased, potassium loss in the urine may become serious, but it can be countered by the administration of potassium salts.

In other aberrations we are virtually impotent to affect the outcome, and this is especially so in neurolipidoses like the cerebromascular degenerations or the familial dystrophies of cerebral white matter like metachromatic leucodystrophy or sudanophilic leucodystrophy (Schilder's encephalitis periaxialis diffusa). The disease progresses, and at his own rate the patient deteriorates. The same applies in the general mucopolysaccharide infiltration which produces gargoylism (Hunter-Hurler syndrome).

The clinical detection of these varied syndromes may be easy but often it amounts only to suspicion. We depend on chemical pathologists for the diagnosis. They use methods which are not always very precise but which are ingenious and informative, and have increasingly illuminated the dark places of disease. New chemical aberrations are discovered year by year and relatively old ones become more readily understood. Great strides have been made by the application of ready minds and neat techniques to those available fluids—blood and urine. What an advance it would be if neurons could be studied like red blood corpuscles.

### *Summary*

At each stage in a metabolic succession there is an opportunity for one or more errors of metabolism to occur. Many of these errors cause disease.



The clinical response of the body to calls on its integrity is, however, somewhat limited, so that what appears to be one disease may be produced in several ways. This means that there may also be several ways of treating rather similar illnesses. In other errors the pathological disturbance may be bypassed acceptably as in the treatment of some diseases of the endocrine system, or less successfully as in chronic anaemia or deficiency of plasma proteins.

Treatment is hardly ever aimed at the fundamental error as it cannot usually be influenced. There are other ways of bringing about clinical improvement—surgical removal of an overactive organ, for example, or elimination from the diet of sugars or amino acids to which the patient is sensitive, giving a vitamin to bypass end-organ resistance to a hormone, using a feed-back mechanism to control overproduction of hormones, and so on.

In some errors therapy is incomplete—it may amount to no more than correcting electrolyte disturbance—and in many diseases, especially all but one or two of those affecting the central nervous system, it is only symptomatic. Prognosis is important even in these cases, for the family as much as for the patient.

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