INBORN ERRORS OF IODINE METABOLISM

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Garrod,⁴ in 1908, introduced the term 'inborn errors of metabolism' to describe biochemical abnormalities which were genetically determined, present throughout life and relatively non-lethal. He suggested that it would ultimately be possible to attribute the biochemical aberrations found in these conditions to specific enzyme defects. Recent work⁵ has confirmed the validity of Garrod's ideas to a remarkable extent, and has extended them to a considerably greater range of conditions than the four originally considered by him (albinism, alcaptonuria, cystinuria and pentosuria). One of the most fruitful of these extensions has been to certain types of thyroid disease.¹⁶ These defects (collectively known as 'sporadic goitrous cretinism') conform extremely well to Garrod's definition, for they are hereditary, congenital, persist through life, and are relatively non-lethal. The fact that they are accompanied by gross structural changes (goitre, cretinism) does not by any means exclude them from the group defined by Garrod, for these structural changes are merely anatomical reflections of the underlying biochemical defect. Although existing evidence cannot be regarded as conclusive, most authors are agreed that the biochemical defects consist essentially of absence or inadequacy of one or more of the enzyme systems which collectively enable the thyroid gland to produce its hormones (thyroxine and triiodothyronine).

Clinical Aspects

It is easy enough to deduce from physiological principles what the clinical effects of a block in thyroxine synthesis will be. The first effect of the resulting low levels of circulating thyroxine is stimulation of the anterior pituitary to produce more of its thyroid-stimulating hormone (T.S.H.). This causes hyperplasia and hypertrophy of the thyroid, and a goitre is formed. Hence the goitre may not unreasonably be regarded as an attempt to compensate for the block in thyroxine synthesis. In the cases described as sporadic goitrous cretins, this attempt at compensation has clearly failed, and the usual manifestations of hypothyroidism

during the growing period can be plainly seen. When the degree of hypothyroidism is severe the child's whole development, physical and mental, is drastically slowed down; and the characteristic puffy face, thick lips, large tongue and dry, coarse skin appear. The extent to which thyroxine synthesis is interfered with may, however, vary within wide limits in this group of cases. Occasionally one of the less severely affected cases may escape detection during childhood, and present during adult life with the evidence of past hypothyroidism clearly shown by the infantile proportions, distorted femoral head and enlarged pituitary fossa.¹⁷

The cases with the grossest metabolic errors were naturally enough the first to be studied and described.¹⁶ More recently, however, it has become apparent that the biochemical defect need not be severe enough to cause manifest hypothyroidism. In fact, the compensatory hypertrophy and hyperplasia of the thyroid may enable the gland to produce normal quantities of thyroxine. In that case, the only manifestation of the inborn error is a goitre which is not clinically distinguishable from any other type of simple goitre. Like other goitres it is initially diffuse, but with the passage of time it becomes nodular. The best example of this type of euthyroid goitre, caused by an inborn error of metabolism, is to be found in the group of cases in which it is associated with congenital deafness. The first cases of this type were described by Pendred¹⁰ in 1896 and are most conveniently referred to by his name. Persons afflicted with Pendred's syndrome are usually euthyroid, but may be hypothyroid. The goitre usually appears in middle childhood, histologically shows marked hyperplasia and has an inveterate tendency to recur after a partial thyroidectomy. The deafness is present from birth, usually symmetrical and most marked for high tones, and may be severe enough to cause deaf-mutism.

It is extremely probable that there are other types of defect capable of causing goitre without hypothyroidism. Pendred's syndrome is unusually

FIG. 2.—Effect of an oral dose of 400 mg. of potassium perchlorate on thyroid counting rate, when given to a patient with Pendred's syndrome one hour after an oral tracer dose of ^{132}I . The counting rate falls steeply as perchlorate ion discharges unbound labelled iodide from the thyroid.

later by 400 mg. of potassium perchlorate or by 1 g. of potassium thiocyanate. If the concentration of labelled iodine within the thyroid is measured by serial counting over the gland, a sharp fall in thyroid counting-rate following the administration of perchlorate indicates that an appreciable proportion of the radio-iodine was in the form of iodide (Fig. 2). This in turn shows that the thyroid's capacity to oxidize iodide to iodine is severely limited. When this defect occurs naturally it is generally presumed that the oxidation enzyme ('peroxidase') is absent or inadequate. In the cases described as goitrous cretins by Stanbury and Hedge¹³ it seems likely that the enzyme was entirely missing, for all the radio-iodine could be discharged from the thyroid. However, incomplete defects of the same type (without cretinism) are much more common; a partial discharge of radio-iodine following perchlorate is a characteristic feature of Pendred's syndrome.^{3, 8, 9} It should be noted that the same type of biochemical defect can be induced temporarily in any type of subject by thiourea derivatives, or other anti-thyroid drugs with a similar action.^{2, 9, 17} Hence it is possible that the inefficiency of the oxidative enzyme in Pendred's syndrome might be the result of a circulating

metabolite, having a thiourea-like action, rather than to an actual deficiency of the enzyme itself. This hypothesis is not as yet supported by any direct evidence.

A defect at site B in the diagram is much more difficult to identify by current techniques. Here it is supposed that mono- and di-iodotyrosines are formed in the normal way, but are unable to couple together to form tri-iodothyronine and thyroxine. A fundamental difficulty is that we do not know whether a specific enzyme is required for this step or not; the coupling of di-iodotyrosine derivatives can occur *in vitro* in the absence of enzymes.¹¹ It will be obvious from the diagram that a defect at site B will be revealed by a 'build-up' of mono- and di-iodotyrosines within the thyroid. This indeed occurred in the two cases in which site B defects have been postulated.^{15, 18} Unfortunately, a similar build-up of iodotyrosines is also seen in site C defects. There is therefore no critical test available now for the identification of site B defects.

Site C defects, due to absence of the de-iodinating enzyme, are more securely established, but some puzzling features still remain unexplained. The existence of an enzyme which specifically de-iodinates mono- and di-iodotyrosine

TWO INTERMARRIED FAMILIES CARRYING THE PENDRED GENE.

FIG. 3.—Pedigree of two unrelated cases of Pendred's syndrome who married each other, showing the characteristic recessive mode of inheritance. Assortative mating is not uncommon in deaf populations.

is well established (deiodinase, dehalogenase). It can be seen from Fig. 1 that the coupling of iodotyrosines to form iodothyronines occurs within the thyroglobulin molecule. However, not all the iodotyrosines are actually converted into iodothyronines; when the thyroglobulin molecule is hydrolysed by thyroid protease, much free mono- and di-iodothyronine is released within the gland. The deiodinase acts on these free iodotyrosines and liberates their iodine as iodide. This iodide then re-enters the synthetic cycle. Absence of deiodinase obviously has two effects: it diminishes the amount of iodide available for hormone synthesis, and it floods the gland with free iodotyrosines, which also appear in excess in the blood and urine. It is not clear which of these effects is the more important from the point of view of hormone production; one would not expect that iodine deficiency induced in this way would be severe enough to cause hypothyroidism. Proof that a patient lacks deiodinase can only be afforded by direct demonstration that his excised goitre cannot deiodinate iodotyrosines; this has been shown to be so in two cases.^{7, 8, 12} However, lack of thyroid deiodinase can be inferred if

exogenous labelled mono- or di-iodotyrosine is not deiodinated by the tissues generally, so that substantial proportion of the administered material appears unchanged in the urine.^{7, 8, 14}

It is obvious from Fig. 1 that there are other possible sites at which enzyme blocks might occur. For instance, before hormone synthesis can begin iodide must be held within the thyroid at a considerably higher concentration than in blood. This process must require energy, and probably the help of an enzyme. No defect of this mechanism has as yet been identified. Similarly, the final step in hormone production is the enzymic proteolysis of thyroglobulin, with the release of thyroxine and triiodothyronine into the blood. Defects of this enzyme have not yet been found either.

Another biochemical aberration, not as yet related to any known or suspected enzyme system, has been described by DeGroot and Stanbury.¹⁵ They described five patients with goitrous cretinism, and referred to reports of probably similar cases in the literature. This variety, which also seems to be genetically determined, is characterized by the presence in the serum of an iodine

containing substance, probably a polypeptide, which is insoluble in butanol. The existence of this substance may indicate a defect in thyroglobulin synthesis resulting in the formation of a precursor or variant which is metabolically inert, and which leaks out readily into the circulation. Iodine is thus diverted from the normal pathway leading to thyroglobulin into a metabolic blind alley.

Genetic Aspects

Site A defects are inherited in a strictly recessive fashion.^{3, 9, 13} Cases occur only in single generations, and (after allowing for inadequate ascertainment) the ratio of affected : unaffected sibs is very near to the expected 1 : 3. There seems to be an excessive consanguinity rate among the parents of cases. There is no evidence of sex linkage and the abnormal gene is able to manifest itself with equal facility in males and females. In Pendred's syndrome it is probable that a gene defect at the same locus is responsible for both deafness and the thyroid enzyme defect. Heterozygotes for the defective gene cannot at present be identified. A typical pedigree of two families with Pendred's syndrome is shown in Fig. 3.

Nothing useful can be said about the inheritance of site B defects because insufficient cases have been described.

Site C defects are inherited in the same manner as site A defects, i.e. as an autosomal recessive.¹⁶ Hutchison and McGirr⁶ have described no less than ten goitrous cretins in a group of intermarried Scottish tinkers, and subsequent studies confirmed that the underlying biochemical defect was a lack of deiodinase.^{7, 8} This highly inbred isolated community provided an ideal setting for the manifestation of a gene of recessive type. Although heterozygotes carrying the defective gene could not be identified clinically, McGirr *et al.*^{7, 8} think they have been able to recognize them by their slightly impaired ability to deiodinate an oral dose of labelled mono-iodotyrosine. Stanbury *et al.*¹⁴ found that some relatives of a Dutch goitrous cretin (with the same type of biochemical defect) had goitres and also were unable to deiodinate iodotyrosines as completely as other people.

Discussion

When goitrous cretins were first shown to belong to Garrod's group of inborn errors of metabolism, they were regarded as extreme

rarity. It is indeed clear that genetically-determined defects severe enough to cause nearly complete hypothyroidism are exceedingly uncommon. However, it now seems certain that the same (or at least a closely related) defect can cause Pendred's syndrome. The site A defect in this syndrome is not usually severe enough to cause hypothyroidism. The occurrence of a convenient 'marker' in the form of congenital deafness makes it possible to form some estimate of the population frequency of this condition; this is of the order of 15 to 30 per million. We cannot as yet assess the prevalence of other types of inherited thyroid defect, and it may well be that there are others still to be discovered. It is, however, unlikely that the sum total of inborn errors of metabolism will ever account for a substantial proportion of simple goitres. The main reason for this inference is that such goitres rarely recur after partial thyroidectomy; hence it is unlikely that the thyroid is under the constant T.S.H. stimulation, which is the inevitable sequel of a block in thyroxine synthesis. It is of some practical importance to be able to recognize goitres due to inborn errors, because they are so readily controlled with thyroxine. The main interest of these conditions is, however, that they provide an opportunity for studying the long and complex sequence of events which leads from mutant gene to specialized enzyme.

REFERENCES

1. DEGROOT, L. J., and STANBURY, J. B. (1959), *Amer. J. Med.*, **27**, 586.
2. EDWARDS, D. A. W., ROWLANDS, E. N., and TROTTER, W. R. (1954), *Lancet*, **ii**, 1051.
3. FRASER, G. R., MORGANS, M. E., and TROTTER, W. R. (1960), *Quart. J. Med.* (to be published).
4. GARROD, A. E. (1908), *Lancet*, **ii**, 1, 73, 142, 214.
5. HARRIS, H. (1959), 'Human Biochemical Genetics,' Cambridge University Press.
6. HUTCHISON, J. H., and MCGIRR, E. M. (1956), *Lancet*, **i**, 1035.
7. MCGIRR, E. M., HUTCHISON, J. H., and CLEMENT, W. E. (1959), *Ibid.*, **ii**, 823.
8. MCGIRR, E. M., HUTCHISON, J. H., and CLEMENT, W. E. (1959), *Scot. Med. J.*, **4**, 107.
9. MORGANS, M. E., and TROTTER, W. R. (1958), *Lancet*, **i**, 607.
10. PENDRED, V. (1896), *Ibid.*, **ii**, 532.
11. PITT-RIVERS, R. (1948), *Biochem. J.*, **43**, 223.
12. QUERIDO, A., STANBURY, J. B., KASSENAAAR, A. A. H., and MEIJER, J. W. A. (1956), *J. clin. Endocr.*, **16**, 1096.
13. STANBURY, J. B., and HEDGE, A. N. (1950), *Ibid.*, **10**, 1471.
14. STANBURY, J. B., MEIJER, J. W. A., and KASSENAAAR, A. A. H. (1956), *Ibid.*, **16**, 848.
15. STANBURY, J. B., OHELA, K., and PITT-RIVERS, R. (1955), *Ibid.*, **15**, 54.
16. STANBURY, J. B., and MCGIRR, E. M. (1957), *Amer. J. Med.*, **22**, 712.
17. TROTTER, W. R. (1957), *Postgrad. med. J.*, **33**, 338.
18. WERNER, S. C., BLOCK, R. J., MANDL, R. H., and KASSENAAAR, A. A. H. (1957), *J. clin. Endocr.*, **17**, 817.