BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 21 1956

THYROID DISORDERS IN CHILDHOOD*

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Despite the activities of a great number of investigators which have resulted in considerable advances in our knowledge of the physiology and pathology of the thyroid gland, the vast territory of the unknown still dwarfs the area of certainty. We do not, for example, understand the nature of the hypothalamic control of the thyroid-stimulating hormone, and, while some of the chemical and physical qualities of thyrotropin (T.S.H.) are known, it has not yet been characterized, and we have to depend on biological methods for its assay in the blood. Indeed, some observers believe there are two hormones in thyrotropin—both a “growth” and a “metabolic” factor for the thyroid (Greer, 1955). Although the thyroid hormone regulates the output of T.S.H.—by the usual inverse relationship between the anterior pituitary hormones and their target glands—we do not know whether this regulation occurs at the hypothalamic or the pituitary level.

Until the discovery of triiodothyronine by Dr. Jack Gross and Mrs. Pitt-Rivers (1952) we were satisfied that thyroxine (tetraiodothyronine), synthesized in the classic researches of Sir Charles Harington as long ago as 1927, was the effective thyroid hormone. Both thyroxine and triiodothyronine have now been identified in the gland and in the plasma, and triiodothyronine has been shown to be more active than thyroxine in its metabolic effects. The steps in the synthesis of thyroxine are approximately understood, but the enzymes concerned in this synthesis and the mechanisms whereby iodine depresses the output of thyroxine and thyrotropin stimulates it are not known. Thyroxine is protein-bound in the plasma, but both the nature of the hormone which is active at the periphery and its site of action are unknown.

It has been recently shown by Compston and Pitt-Rivers (1956) that tribromothyronine is as effective as thyroxine or triiodothyronine in the cure of hypothyroidism, so that if our fishy forebears could have had the wit to foresee that the waters would one day uncover the earth and that some of their descendants would take to the hills they might have used another handy halogen, chlorine or bromine, in the synthesis of the thyroid hormone.

As we now proceed to the consideration of new knowledge in the clinical aspects of thyroid disorders of childhood it is salutary to remind ourselves that the

“backroom boys and girls”—those unheeding arbiters of our destinies—have, as yet, no encouragement to cease from their remarkable exertions.

Cretinism and Hypothyroidism: Pathogenesis

Sporadic cretinism was described by Hilton Fagge in 1871, and we have since learnt nothing of its aetiology which would have convicted of error an eminent contemporary of Fagge's, who believed the cause of cretinism to be that “the parents of the child, one or both, were drunk at the time of conception.” The baby born with cretinism which is recognizable at or within a few weeks of birth has no palpable thyroid gland. Confirmatory evidence of intrauterine athyroidism is found in the absence of the epiphyses (knee and cuboid) which should develop in the foetus. Obviously not enough maternal thyroxine has travelled across the placenta to prevent foetal cretinism in these children. Dorff (1934) concluded from such facts that the foetus was normally dependent on its own production of thyroxine, and there is no transmission of thyroid hormone through the placenta from either the mother or the foetus. McGirr and Hutchison (1955) have reviewed recent evidence in support of Dorff's theory, including the demonstration of thyroxine in the foetus at the age of 14 weeks.

Cretins born in countries where goitre is endemic may themselves be born with a goitre; babies whose mothers when pregnant have been given antithyroid therapy may be born with goitres; babies whose mothers have been given iodide during pregnancy may be born with goitres. It is a fundamental hypothesis to-day in thyroid pathology that, whatever may be the agent which is interfering with the synthesis of thyroxine, the enlargement of the gland results from stimulation by thyrotropin. These congenital goitres indicate that the foetal thyroid is dependent on its own T.S.H. regulation, which can be deranged before birth by agents whose varied effects have been the subject of much investigation in adults.

The study of goitrous cretinism and goitrous hypothyroidism in children has greatly advanced our knowledge of the defects in thyroxine synthesis. Several families of such children have now been described and three types of defect have been elucidated (Stanbury and Hedge, 1950; McGirr and Hutchison, 1953; Hubble, 1953a; Stanbury, Ohela, and Pitt-Rivers, 1955; Stanbury, Kassenaar, *et al.*, 1955; Burrell and Gairdner, 1955). The first is an inability to incorporate iodide

*An address delivered to the Liverpool Paediatric Club on February 19.

into an organic iodine compound; the second, a failure to retain mono- and di-iodotyrosine in the gland; and the third, a defect in the normal coupling of two molecules of diiodotyrosine to make thyroxine. In their large family of tinkers, in whom the defect belongs apparently to the second group, McGirr and Hutchison (1956) state that the pedigree indicates that there is a simple recessive inheritance of a single gene. It is possible that other defects in synthesis will be revealed as new methods of investigation are elaborated.

Cretinism and Hypothyroidism Without Goitre

Goitrous cretinism and hypothyroidism are rare, and unfortunately there has not been an equal advance in our knowledge of the aetiology of the very much commoner non-goitrous cretinism and hypothyroidism of childhood. Thyroid failure occurring at any age is still a mystery. If agenesis is one mechanism in cretinism how often does it depend on a failure of T.S.H. stimulation? Athyroidism is sometimes recognizable in the first few weeks of life, but more often it declares itself insidiously during the first year of life, whether or not the bone-age suggests that thyroxine production was deficient in the foetus. McGirr and Hutchison (1955) have in two hypothyroid children, two girls aged $7\frac{1}{2}$ and $4\frac{1}{2}$, identified, by scanning the neck after a tracer dose of ^{131}I , small amounts of thyroid tissue just above the hyoid bone at the base of the tongue. They conclude, therefore, that maldevelopment of the thyroid is characterized both by failure to descend and by impaired function. This is an important observation, and when we all have directional counters at our disposal we shall be able to discover how frequently the undescended thyroid provides the pathogenesis of child hypothyroidism. I have so far looked for it twice and failed to find it.

That it cannot be the only cause of cretinism must be assumed from the many post-mortem records in the literature, and it has been demonstrated again by my colleague, Dr. G. R. Osborn, in a patient of mine who died recently in hospital of cretinism at the age of 3 months. He cut sections from some tissue in the correct situation of the thyroid gland and identified this pinhead of unmistakable thyroid tissue 2 mm. in diameter, yet larger than the parathyroid gland alongside it. This is sufficient proof that even the gland which has made its normal journey may fail to develop. The histological appearances show degenerate thyroid tissue, without colloid formation and containing small cysts which hold serous fluid (Fig. 1). The appearance is similar to the thyroid of one of the family of goitrous cretins (reproduction in Hubble, 1953a). Dr. Calvin Ezrin,

FIG. 1.—Degenerate thyroid tissue showing cystic spaces filled with serous fluid (a). A small area of parathyroid tissue (b) is shown at the left of the section. ($\times 39$. Dr. G. R. Osborn.)

of the Banting Institute, Toronto, kindly reported on the pituitary of this baby. He writes: "The cretin's pituitary shows an extreme change from normal which is comparable with the view that the gland was making excessive quantities of thyrotropic hormone. There is an increase in the number of very finely granulated cells, which would be

called chromophobes with the standard stains. This is at the expense of the three heavily granulated chromophilic cells which are the two types of basophils and the acidophils. . . . In Addison's disease and hypothyroidism the uninhibited pituitary gland shows an increase on the number of lightly granulated cells with copious cytoplasm and large vesicular nuclei. The immediate source of the light-purple cells appears to be the heavily granulated purple cells which vary reciprocally with one another in mildly overactive glands, such as in cases of myxoedema incompletely treated with desiccated thyroid. If the gland is very active the red granulated 'basophils' and the acidophils are also decreased. This is seen in this case of cretinism and in many cases of Addison's disease." (Fig. 2.) These finely granulated purple cells also produce corticotrophin, and, since adrenocortical

FIG. 2.—Section of the anterior pituitary ($\times 500$) from a cretin aged 4 months. Note the great excess of lightly granulated purple cells, indicative of extreme activity. (Dr. Calvin Ezrin.)

function is frequently defective in hypothyroidism, these cells may be forming a reduced amount of corticotrophin while providing an increased output of T.S.H.

We may hope that in the next decade we shall learn how often there is a selective deficiency of T.S.H. to account for failure of the thyroid gland to develop. This has been described occasionally in adults, and inferred once in a child aged $5\frac{1}{2}$ years by Silverman and Wilkins (1953), who were able to stir a slumbering gland to activity (assessed by improved ^{131}I uptake) by injections of 30 mg. of T.S.H. T.S.H. injections may not give a correct answer to our aetiological question, for the glands of secondary athyroidism (T.S.H. deficiency) may become either incapable of response or may require a too expensive awakening. Bio-assay of T.S.H. by any method may similarly give misleading results, for DiGeorge *et al.* (1955) have demonstrated that T.S.H. activity may sometimes be reduced in hypothyroidism, although it is usually increased, only to reappear when euthyroidism is established by thyroid therapy. The same observation has been reported in this country by Gilliland (1955). There is more than one reason, therefore, for a low level of circulating T.S.H. in hypothyroidism.

The observations of Andersen *et al.* (1955b) are consequently of great interest. They believe that myxoedema of the skin is good evidence of T.S.H. overactivity (Andersen *et al.*, 1955a), and they have correlated the T.S.H. activity of the plasma by bio-assay (tadpole method) with skin biopsies in hypothyroid children. The correlation between the two tests was good, and in nine cases of proved hypothyroidism six showed positive tests by both methods and three tests were negative by both methods. Therefore in three children out of nine tested by both methods the hypothyroidism was due to a failure of T.S.H. In these three cases the hypothyroidism developed late and slowly, and it is in such children that a selective deficiency of T.S.H. may be expected. In nearly half the patients with hypothyroidism the skin biopsy was negative, so this method by itself is not

likely to be diagnostic between primary and secondary hypothyroidism, except where the skin biopsy is positive. We have not yet found it easy to apply Asboe-Hansen's criteria to our skin biopsies.

Recognition of Hypothyroidism

Although the clinical picture of hypothyroidism in children has been well described in a hundred textbooks and articles, it is a common experience that diagnosis is frequently delayed, and both by history and by examination it can be demonstrated that a deficiency of thyroxine has been present for months before the diagnosis is achieved and treatment instituted. Although parental negligence and medical ineptitude may sometimes be factors contributory to this delay in diagnosis, there are exonerating reasons to be found in the natural history of hypothyroidism. While the fully developed appearances of hypothyroidism—dwarfism, apathy, cold dry skin, constipation, slow motor development, large tongue, umbilical hernia, and so on—are unmistakable, the concept of a progressive inadequacy of thyroxine formation explains the slow development of the recognizable picture in many children. This progressive inadequacy is usually attributed to the increasing demands of the growing child for thyroxine. The cretin under the age of 2 usually requires about half the dose of thyroid that it will require later. If a hypoplastic gland is capable of producing a sufficient amount of thyroid hormone in the first few months of life, and is under effective T.S.H. stimulation, it is surprising that it cannot double and even treble its output as required. We can assume that there may sometimes be a progressive deficiency in hormone output, whether or not associated with T.S.H. deficiency or excess.

There is a second reason for our diagnostic difficulties to which I believe quite inadequate attention has been given, and that is the varying emphasis which thyroid lack—and thyroid excess—have on the different systems of the body in different individuals. This is a commonplace in the diagnosis of adult thyrotoxicosis—in one patient unilateral exophthalmos and in another cardiac failure may be the only symptom and sign of excessive thyroxine output. In hypothyroid children there may be myxoedema, anaemia, mental retardation, hypercholesterolaemia, reduced serum alkaline phosphatase, and electrocardiographic and electroencephalographic changes—but there may not. Failure of growth and skeletal retardation are the essential requisites for the diagnosis of hypothyroidism in children. Such signs may be of varied aetiology, as all paediatricians know, but a deficiency of thyroid hormone cannot be diagnosed in their absence.

The skeletal system in children is, of all systems, the one most sensitive to thyroxine lack. Many years ago I saw a hypothyroid girl aged 14 whose growth had stopped two years previously, but who had maintained without difficulty her position in her class at school.

Difficult diagnostic decisions sometimes arise. Children of short stature may show no evidence of hypothyroidism in any system except the skeletal; and, there, retarded growth, delayed epiphyseal development, and epiphyseal dysgenesis may be demonstrated. Are the bones in these children relatively insensitive to the action of thyroxine? A boy aged 3½ years was referred because of slow growth. His height-age was 2 years, but his skeletal development was that of a 6-months child. There was no other evidence of hypothyroidism, and his radio-iodine uptake was within normal limits. With thyroid therapy for one year his height advanced by 3 in. (7.5 cm.) and his bone-age by 2 years. Moreover, dysgenesis was shown in the epiphysis of the radius, in the navicular, the internal cuneiform, and the epiphyses of the third and fourth metatarsals. The details of similar cases have been communicated to me by Drs. John Hay and Alex Russell. It must be required, as an essential diagnostic criterion, that the bone-age in such children should be more retarded than the height-age, and, if this is so, thyroid should be certainly used in treatment.

Our diagnostic criteria have not greatly advanced in the last five years. It is a pity that the chemical determination of protein-bound iodine is so rarely available in this country, for it is of more value in the diagnosis of hypothyroidism in childhood than in any other disorder. If radioactive iodine is used in diagnosis, the peak uptake of ¹³¹I is usually below 15% of the administered dose in hypothyroid children, except in those with goitres, when the uptake is rapid and high.

Evans (1952) has drawn attention to the dystrophy of the twelfth dorsal and first and second lumbar vertebrae which occurs where the spinal stress is greatest when the baby begins to sit up. This is often found and is worth looking for. In a cretin aged 10 months whose hypothyroidism had

developed slowly this dystrophy is well seen (Fig. 3). This baby also had a uraemia (blood urea 85, 78, 65 mg. per 100 ml.) for which no cause other than hypothyroidism was found and which dropped gradually to normal levels with thyroid therapy. Although diminished urea clearance has been described in adult myxoedema (usually without a high blood urea) I do not know that azotaemia has been

FIG. 3.—Vertebral column showing dystrophy of lumbar spine in a cretin aged 10 months.

referred to in cretinism. This baby also had defective adrenocortical function. The urinary output of 17-ketosteroids was normal for his age group, but the output of 17-ketogenic steroids (Norymberski) was only 0.2–0.5 mg./24 hours and increased to 1.5–1.7 mg./24 hours with treatment. Since the output of the adrenal cortex can be elevated by exogenous corticotrophin stimulation, while the hypothyroidism remains uncorrected, I believe that the adrenocortical deficiency is produced by a reduced corticotrophin output, secondary either to "hypothyroidism" of the pituitary (compare the defective output of T.S.H. in hypothyroidism already discussed) or to an exaggerated T.S.H. output with consequent corticotrophin depression (Hubble, 1955).

The assessment of progress under treatment is of the first importance. Each propagandist for a diagnostic criterion—such as the electroencephalographic deviation—will tell you that you can best assess progress by his particular investigation. Of course, it is essential to know that the anaemia is corrected (and this requires iron therapy in addition to thyroid), and nice to know that the electroencephalogram, the electrocardiogram, the blood cholesterol and the alkaline phosphatase, the blood urea and adrenocortical function are normal; but in practice all that is necessary is to watch the height and the epiphyseal development. Particularly is it important to watch the bone-age, for it is easy to advance this beyond the child's chronological age with a dose of thyroid which does not appear to be excessive for other systems (Hubble, 1953b). I take this to be further evidence of the varying sensitivity of the different systems.

Treatment of Hypothyroidism

Talbot (1952, 1955a) assesses the requirements of thyroid at 90 mg. (1½ gr.) per square metre of body surface. This calculation will allow the average child of 1 year about ½ gr. (30 mg.) of thyroid daily. This is usually insufficient, and I prefer the pragmatic approach of Lawson Wilkins (1950), who finds that the required dose does not correlate exactly

with either age or size; I agree with him that most cretins under the age of 2 or 3 years require 1 or 2 gr. (60–120 mg.) daily. Talbot likes to give thyroid every eight hours and Wilkins is content with a single daily dose. This might be taken to explain the considerable difference in their estimates, though I doubt it. I have never given a hypothyroid child more than 3 gr. (200 mg.) daily, but three paediatrician friends—Drs. Wickes, Jolly, and Gairdner—allow me to say that they have each treated one child who required higher doses than this to attain euthyroidism—5, 13, and 8 gr. (320, 850, and 520 mg.) respectively (the last in a child of a hypothyroid family, Burrell and Gairdner, 1955)—and in each case this dose eventually became excessive and required reduction to the usual level.

These are important observations, not, I think, previously reported, and indicate that there was in these children a resistance to thyroxine which can be overcome by raising the dose. I find it an easily acceptable observation when one considers how often an identical situation is met with in diabetes. It is a rare situation, however, for some attention has been given to the strange contrast between the hypothyroid and the euthyroid in this regard—the former so sensitive to thyroid therapy and the latter often capable of taking very large doses without ill effect. If this resistance to thyroid is encountered it would be of great interest to use triiodothyronine in equivalent dosage; in a hypothyroid child patient of Professor Stanley Graham's with an ectopic thyroid the dose of thyroid was increased to 20 gr. (1.3 g.) daily without inducing euthyroidism, but triiodothyronine in daily dosage of 100 µg. (approximately equivalent to one-quarter of the dose of thyroid used) quickly eliminated all signs of hypothyroidism (McGirr and Hutchison, 1955, and personal communication).

Triac (triiodothyro-acetic acid) has been shown by Lerman and Pitt-Rivers (1955) to reduce the weight, to cause water loss, and to correct hypercholesterolaemia in hypothyroidism without elevating basal metabolism, and it will be interesting to see, when it becomes generally available, whether this substance will accelerate bone growth and epiphyseal development in hypothyroid children. It does restore the depressed growth rate of thyroidectomized young rats to that of control animals (Pitt-Rivers, personal communication).

Treatment of Thyrotoxicosis

Thyrotoxicosis in children is fortunately a rare disease and few paediatricians have had sufficient experience of it to speak dogmatically of its treatment. We must therefore rely for guidance on the recorded results of therapy in the largest centres. Wilkins (Van Wyk *et al.*, 1955), at the Johns Hopkins Hospital, has preferred to use antithyroid drugs; Talbot (1955b), at the Massachusetts General Hospital, has called in the surgeons. Out of 16 children given antithyroid drugs in Baltimore, eight have maintained long remissions after treatment has been stopped and four are still being maintained in a euthyroid state by therapy. Four patients, for various reasons, were treated ultimately by subtotal thyroidectomy; one of these died and the other three developed hypothyroidism.

Kunstadter and Stein (1955) have treated 17 children with thyrotoxicosis by antithyroid drugs—eight have been in prolonged remission, four are still under treatment, while five have for various reasons required subtotal thyroidectomy. Talbot has treated his patients by subtotal thyroidectomy, leaving approximately 1 g. of thyroid tissue, and "less than half" the cases required continued treatment by thyroid after the operation. McClintock *et al.* (1956) have recently reported the results of surgical treatment in 45 children under the age of 15 with thyrotoxicosis, with complications in one-third of them. I may perhaps summarize this evidence, not I hope injudiciously, by suggesting that antithyroid drugs should always be given a trial in the treatment of childhood thyrotoxicosis, and that a proportion of cases successfully treated by surgery will require permanent substitution

therapy. My personal experience is limited to four patients in the last ten years—two of them doctors' children—who have been treated by methylthiouracil and methimazole. Two are still under treatment and two are cured. Medical treatment if successful should be continued for two to three years, when the drugs may be stopped and remission or relapse awaited.

Hazards to Thyroid Stability in Childhood

An enlarging thyroid gland should be regarded as evidence of thyroid instability which, so far as we know, depends on an output of thyroxine which is inadequate for the body's requirements; this results in an increased output of T.S.H. from the anterior pituitary with consequent hyperplasia of the gland and subsequent involution of the gland when the output of thyroxine becomes sufficient to depress T.S.H.—Marine's classic cycle. This process is frequently deranged or there would be no colloid goitre (hyperinvolution), no nodular goitre (? degeneration of the gland associated with slow thyroxine formation with excessive T.S.H. action), and no thyrotoxicosis (? excessive output of thyroxine with derangement of T.S.H. control).

The commonest enlargement of the thyroid gland in childhood occurs at puberty or before, and is regarded as a response to the increased requirements for thyroxine. This seems a reasonable explanation, but it has never been proved; that it is commoner in areas where the iodine content of the water and the soil is low (therefore an inadequate supply of iodine for thyroxine synthesis) supports the hypothesis but does not prove it. Another hypothesis, equally possible and not alternative, is that the thyroid is overstimulated by an increased T.S.H. output occurring as a result of pituitary activity at puberty and the formation of thyroxine in an iodine-deficient gland is not sufficient to regulate T.S.H.

There has been much debate in recent years concerning iodine deficiency as a cause of goitre; I cannot here summarize it, but we may conclude that, while iodine deficiency is the chief cause of endemic goitre, few simple sporadic goitres are due to this cause alone. How often have we all remarked, in repeating the prescription of iodine for a simple goitre, that while iodine deficiency may have caused the goitre, an ample supply does not make it disappear. Nevertheless, it is a great disappointment that the Ministry of Health agreement with the salt manufacturers for the addition of iodide to salt, which was promised for July, 1952, has not been implemented. We require 100–200 µg. of iodide daily, and many in our country—sea-girt though it is—do not get it. In the treatment of simple goitre you should give 1 gr. (60 mg.) of iodide daily to make certain that iodine deficiency is corrected and not less than 2 to 3 gr. (120–200 mg.) of thyroid daily. The reason for thyroid therapy is not to provide thyroxine, which is already being adequately produced if the patient is not hypothyroid, but to suppress T.S.H. activity and thus to rest the gland. More than 3 gr. (200 mg.) may be required, and, since this therapy is frequently successful in reducing the size of the gland, we may assume that the T.S.H.–thyroxine regulation is deranged in the patient—either owing to a primary T.S.H. excess or because the gland is producing enough thyroxine for euthyroidism but not sufficient to depress the output of T.S.H.

Iodine deficiency, increased physiological requirements, and T.S.H. excess may account for some goitres, but often there seems to be no accessible explanation. The genetic defects of the biosynthesis of thyroxine in goitrous cretins make it possible that similar biochemical defects will be discovered in euthyroid patients with sporadic nodular goitre.

It has been discovered in our generation that a number of substances, from cabbage to cobalt, can exercise goitrogenic activity. In special ways these goitrogenic substances may hazard thyroid stability in children. The employment of isotopes of iodine, whether in investigation or in treatment, demands special consideration in childhood. One of

the chief objectives of the paediatrician is to ensure that children carry no preventable disorder into adult life. Any enlargement of the thyroid in children indicates a present derangement and a possible threat for the future—especially in girls.

The threats to the thyroid stability of children by goitrogenic drugs begin in the uterus. While babies in areas of endemic goitre are born goitrous as a result of iodine deficiency, it is paradoxical that neonatal goitre has been occasionally produced by the administration of iodide to the pregnant mother. The probable mechanism is that the high plasma levels of inorganic iodide block the conversion into organic iodine. It is easier to understand that the anti-thyroid drugs administered to the thyrotoxic mother may produce a goitre in the foetus, for the thiourea derivatives (thiocarbonamides) circulating in the child block the conversion of inorganic iodide to organically bound iodine, possibly by inhibiting a peroxidase-like enzyme (Astwood and Solomon, 1955). These babies are usually born euthyroid, but may show retardation of skeletal maturation or frank cretinism (Elphinstone, 1953; Morris, 1953; Moloshok, 1955). Another paradox emerges here, for congenital thyrotoxicosis with high levels of protein-bound iodine in the plasma has been described in these goitrous children (Bongiovanni *et al.*, 1956). Is this due to the excessive production of thyroxine by a system suddenly released from thiocarbonamide inhibition?

The goitre has been described as large enough to produce obstetrical difficulties. More commonly the goitre has been reported to cause respiratory obstruction and dysphagia in the newborn child. The goitre will disappear in two to three weeks, but emergency treatment may be necessary. Thyroid therapy is rational, say $\frac{1}{4}$ gr. (15–30 mg.) daily, in the absence of thyrotoxicosis, and partial thyroidectomy may be required in thyrotoxicosis if improvement is not rapid.

Of the many drugs that have been shown to be goitrogenic only two are likely to be used in childhood in the treatment of disease outside the thyroid—cobalt and para-aminosalicylic acid (P.A.S.). Gairdner *et al.* (1954) have reported a goitre in a premature baby treated for anaemia with cobalt, and Komrower (1951) has recorded the development of a goitre in a child treated with P.A.S. Children in whom these drugs are used must be closely observed for the development of a goitre and hypothyroidism. If the continuance of these drugs is regarded as wise and necessary, then thyroid should be coincidentally administered until the goitre disappears and hypothyroidism is relieved (Macgregor and Somner, 1954).

Radioactive iodine constitutes a possible hazard for children. It has been assumed that the tiny tracer doses used in diagnosis—say 1 to 10 microcuries of ^{131}I —cannot be harmful. It has been suggested (*British Medical Journal*, 1956) that, since 30 microcuries of ^{131}I delivers 200 r to a gland weighing 10 g., this isotope should not be used diagnostically in children but that ^{132}I , with its shorter half-life, should be used instead. Although the dose of ^{131}I commonly used is much smaller than 30 microcuries, the possibility of local concentrations in the gland cannot be ignored, and the British Paediatric Association could perform a useful service by obtaining the opinion of a committee of experts. It has heretofore been generally accepted throughout the world that if a dose is used which produces 50 r or less in the thyroid gland no harm to the child, present or remote, can result. It is agreed that radioactive iodine should not be used in the treatment of thyrotoxicosis in children and young persons.

Werner's observation (Werner *et al.*, 1952)—which is unlikely to be confirmed—that thyrotoxicosis in children has been cured by repeated tracer doses of radioactive iodine is a little disturbing, for the therapeutic dose is usually several hundred times the diagnostic dose. However, the total dosage in these children averaged about 250 microcuries of ^{131}I —more than one-tenth of the expected thera-

peutic dose, so that the only conclusion to be made concerning this observation is that children are unusually susceptible to radioactive iodine—by no means a valueless conclusion for paediatricians. A similar conclusion may be drawn from the fact that cancer of the thyroid has developed in some children who received a radioactive dose of only 250 to 700 r for thymus enlargement (Simpson *et al.*, 1955). Miller and Weetch (1955) have usefully drawn attention to the fact that ^{131}I is concentrated in human milk to such a degree that 25 microcuries given to a nursing mother could adversely affect the thyroid gland of the baby fed on breast milk.

Conclusion

This short survey of the hazards to the foetus and child by goitrogenic drugs and by ^{131}I emphasizes that the increasing power both of the remedies and of the techniques employed in medicine to-day requires of the paediatrician even greater care than is employed by the physician in the diagnosis and treatment of disease in adults.

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A second revision of the Ministry of Health's *Memorandum on Vaccination against Smallpox* (H.M.S.O., London; price 6d. net) has just been issued. This useful pamphlet is designed to give practical information about vaccination, and many experts were consulted during its preparation. Among the matters discussed are the optimum age for vaccination in infancy, the site of insertion, and the method of insertion. The multiple pressure technique is clearly described: it is stated to be probably the best method for use in routine primary vaccinations. A section of the memorandum is devoted to revaccination. The primary vaccination of schoolchildren, adolescents, and adults is not recommended except in those exposed to infection by smallpox or who have to be vaccinated prior to foreign travel or service in the armed Forces.