NEONATAL GOITRE AND MENTAL DEFICIENCY

THE ROLE OF IODIDES TAKEN DURING PREGNANCY

BY

J. A. BLACK*

From the Royal Hospital for Sick Children, Glasgow

(RECEIVED FOR PUBLICATION NOVEMBER 21, 1962)

Case History

R.T., a male infant, was born at Thornhill Maternity Hospital, Paisley, on April 5, 1957, one month after the expected date. Delivery was by face presentation: the birth weight was 7 lb. 12 oz. (3.4 kg.). Shortly after birth a moderate-sized goitre was noticed, which was thought to have been responsible for the malpresentation. The baby appeared well and active and there was no evidence of tracheal compression, nor of hypothyroidism. On the second day jaundice developed, lasting for 11 days but was never severe. No treatment was given. Radiography of the knee at the age of 1 week showed absence of the lower femoral and upper tibial epiphyses, suggesting intrauterine hypothyroidism. At this time it was discovered that the mother was an asthmatic who had been regularly taking a proprietary preparation ('eucadine'), containing sodium iodide, for the past 11 years. Her daily intake of iodide was calculated to have been 22 gr. (1.3 g.). She had had no symptoms of thyroid disease, nor was there any enlargement of her thyroid; she was later examined by Professor E. J. Wayne at the Western Infirmary, Glasgow, who confirmed that there was no evidence of thyroid disease. There was no known history of thyroid disease in any relative. There were three other children, a girl aged 10 years and two boys aged 8 years and 7 years who were reported to be normal though they were not examined personally. In 1952 the mother had given birth to a stillborn infant, but the death certificate made no mention of any thyroid enlargement.

Progress. After discharge from hospital the baby progressed normally. At the age of 2 weeks the thyroid was smaller though still easily palpable. At this time there was some wrinkling of the forehead, suggestive of hypothyroidism, but two weeks later the wrinkling was no longer present, and the neck circumference had decreased by 0.5 in. (1.27 cm.). At 6 weeks the gland could just be felt but was not thought to be significantly enlarged. Further progress appeared to be satisfactory until the age of 1 year when it was clear that his motor

development was proceeding very slowly. He did not sit up until he was 1 year old, spoke only single words by 16 months, and at 2 years was not crawling or walking. At this time his pulse rate (as an out patient) was 160 and 120 per minute on two separate visits, and his palms felt hot and moist. A ferric chloride test on his urine was negative.

At 2 years and 7 months, in view of the obvious mental retardation and the possibility of mild hyperthyroidism (see Figure) he was admitted to the Royal Hospital for Sick Children, Glasgow, under the care of Dr. (now Professor) J. H. Hutchison for further investigation. There was at this time no clinical evidence of hypo- or hyperthyroidism, but his thyroid gland was slightly enlarged, the right lobe more than the left. His I.Q., tested by Dr. Schaffer on the Cattell Infant Scale,

FIGURE.—Relation of skeletal age to chronological age. Bone age assessments are from Vogt and Vickers (1938).

* Present address: Institute of Child Health, Great Ormond Street, London W.C.1.

was between 52 and 66, testing being handicapped by his failure to speak. Later investigation showed no evidence of hearing loss and at the age of 2 years and 11 months he was speaking short sentences. At 3 years 5 months he was walking unsupported; and his thyroid gland was still palpable.

Thyroid Function. In May 1957, at the age of 1 month, plasma cholesterol was 163 mg./100 ml.; alkaline phosphatase 16.1 King-Armstrong units. On December 2, 1959, at the age of 2 years and 8 months the thyroid uptake was measured by Professor E. M. McGirr at the Radio-Isotope Unit of Glasgow Royal Infirmary. Test dose, 25 microcuries I^{131} ; gland uptake 12% of dose at four hours, and 30% of dose at 24 hours (normal). On December 10, labelled moniodotyrosine was fully deiodinated to iodine, thus excluding a dehalogenase deficiency. On December 23, serum cholesterol was 200 mg./100 ml.

Discussion

Four points require consideration: First the evidence for pre- and postnatal hypothyroidism; secondly, the evidence for a later stage of hyperthyroidism; thirdly, the cause of the mental retardation, and finally the relation of the clinical picture to the ingestion of iodides by the mother during pregnancy.

Prenatal and Postnatal Hypothyroidism. An enlarged thyroid at birth is more likely to be associated with hypothyroidism than with hyperthyroidism. The absence of epiphyseal centres at the knee in a baby one month postmature by dates, and the rather prolonged neonatal jaundice (Åkerén, 1954; Christensen, 1956) are in favour of hypothyroidism. The wrinkled forehead, observed for a short time, was suggestive of hypothyroidism, and the normal plasma cholesterol and alkaline phosphatase levels do not, at the age of 1 month, exclude the diagnosis. It seems probable therefore that the goitre was associated with an intrauterine and transient postnatal hypothyroidism such as may occur after the use of thiouracil compounds during pregnancy.

Later Hyperthyroidism. The clinical evidence of this is inconclusive and investigation of thyroid function, possibly done too late, gave no support for increased activity. Nevertheless, the sustained tachycardia and the warm sweating palms stimulated investigation of the skeletal development (Fig.). It is difficult to explain the rapid acceleration of skeletal development during the first two years of life, followed by a slowing down, on any other basis than a temporary mild hyperthyroidism. In this connexion Frisk and Josefsson's (1947) case is

of interest; they studied a baby whose mother had received thiouracil during pregnancy. At birth the skeletal development was somewhat delayed and the baby was slow in feeding, but there was no other evidence of hypothyroidism. During the second month of life hyperthyroidism with exophthalmos developed and continued for two months, the eye signs persisting alone for a further month. The thyroid gland was not enlarged at any stage. This sequence of events is very similar to that in the case described here except that in Frisk and Josefsson's case there was no acceleration of skeletal development, which was normal at the age of 8 months.

The Cause of the Mental Retardation. It is generally agreed that in sporadic athyroidic cretinism the final level of intelligence may be either low or normal in children who have received early and adequate treatment (Andersen, 1961), and it is thought that the irreversible mental retardation may be related to intrauterine hypothyroidism (Pitt-Rivers and Tata, 1959a). It is now recognized that the use of thiouracil compounds during pregnancy may cause mental retardation in the infant (Elphinstone, 1953; Berg and Kirman, 1959). This is almost certainly due to the effect of foetal hypothyroidism upon the developing brain, a suggestion which has received support from experimental work with thiouracil (Eayrs, 1960). Thus, in the infant described above, the combination of mental retardation, probable intrauterine hypothyroidism and goitre at birth, appears analogous to the thiouracil effect, though in this case iodides must be considered as the possible cause.

Maternal Ingestion of Iodides and the Clinical Picture. The investigations of thyroid function were unfortunately only helpful by exclusion. The normal uptake of I^{131} certainly indicated, at 2 years and 8 months of age, no evidence of hypo- or hyperthyroidism, and the normal breakdown of the labelled moniodotyrosine excluded goitrous cretinism, due to dehalogenase deficiency (McGirr, Hutchison and Clement, 1959a). Other forms of goitrous cretinism could not be excluded with certainty, but on testing there was no evidence of deafness which is frequently associated with the other common form of goitrous cretinism, probably due to a peroxidase deficiency (McGirr, Hutchison and Clement, 1959b). Moreover, none of the known forms of goitrous cretinism unless untreated is associated with mental retardation.

The role of the high intake of iodides by the mother during pregnancy must therefore be considered. There are numerous reports, in both

adults and children without any known previous thyroid disorder, of goitres with and without hypothyroidism resulting from the prolonged ingestion of iodides, also iodopyrine (Morgans and Trotter, 1959; Anderson and Bird, 1961). The subject has been reviewed extensively (Bell, 1952; Turner and Howard, 1956; Rubinstein and Oliner, 1957; Paley, Sobel and Yalow, 1958; Paris, McConahey, Owen, Woolner and Bahn, 1960; Burrows, Niden and Barclay, 1960; Taguchi and Skillman, 1960; Burrell, 1961; Oppenheimer and McPherson, 1961). More rarely similar results are due to the retention of iodine compounds in the body, as after the injection of iodized oil (Léchelle and Troisier, 1950) and following bronchography (Raben, 1953). In some cases in which thyroid function became normal on withholding iodides myxoedema recurred each time iodide therapy was resumed (Nixon, 1957; Paris *et al.*, 1960; Taguchi and Skillman, 1960). In most instances both myxoedema and goitre regressed completely when the iodides were stopped but occasionally the gland remained slightly enlarged (Dimitriadou and Fraser, 1961).

Investigation of the mechanism of iodide goitre and myxoedema has shown that iodine uptake is inhibited in the myxoedematous phase and that any inorganic iodine accumulated in the gland is completely discharged by thiocyanate (Oppenheimer and McPherson, 1961). These results were confirmed by biopsy by Dimitriadou and Fraser (1961) who showed that the gland contained a very small proportion of organically combined iodine. In a number of cases (Morgans and Trotter, 1953; Rubinstein and Oliner, 1957; Paley *et al.*, 1958; Paris *et al.*, 1960; Burrows *et al.*, 1960) there has been a very transient increase in iodide uptake on stopping iodides, suggesting a 'rebound' hyperthyroid state, but only in Vanderlaan's case (1956) and in one of Morgans and Trotter's (1959) 'iodopyrine' cases did hyperthyroidism persist and become clinically evident. Pitt-Rivers and Tata (1959b) have suggested that the glands which respond in an unusual manner to iodides are functionally abnormal beforehand, and this may explain the occasional failure to return to normal size after stopping the iodides.

That neonatal goitre may be due to the ingestion of large amounts of iodides by the mother during pregnancy has been known for some time (Parmelee, Allen, Stein and Buxbaum, 1940; Talbot, Sobel, McArthur and Crawford, 1952; Wilkins, 1957; Packard, Williams and Wheelock, 1960), but in every instance in those surviving, the gland has apparently returned to normal, and mental retardation has not been mentioned. In one of Morgans

and Trotter's (1959) cases the mother who had a goitre gave birth to an infant with a large goitre which had completely regressed by the age of 6 months; at the age of 5 years he was quite normal. A similar case was described by Anderson and Bird (1961) when the mother who had an iodopyrine goitre gave birth to non-identical twins both of whom had a goitre. Nevertheless, only a small proportion of newborn babies whose mothers have been taking iodides during pregnancy develop goitres and in these there is probably the same type of abnormal response to iodides as is seen in adults and older children. It is not known whether the goitre can be reproduced in such children by giving iodides later on. It is also possible that, as in adults, the gland does not always return to normal size.

There seems to be good evidence therefore for suggesting that the clinical picture of neonatal goitre and mental retardation, with probable intra-uterine hypothyroidism followed by transient hyperthyroidism, could all result from the excessive ingestion of iodides by the mother during pregnancy. It is likely that this response to excessive iodides only occurs in a gland whose metabolism is in some way inherently abnormal.

Summary

A description is given of an infant born with a goitre, whose mother had taken large quantities of sodium iodide before and during pregnancy. Unusual features in the child's subsequent development were a transient acceleration of skeletal development and permanent mental retardation.

I am grateful to Professor J. H. Hutchison for his help in the investigation of this case and for his advice throughout.

REFERENCES

- Åkerrén, Y. (1954). Prolonged jaundice in the newborn associated with congenital myxoedema. A syndrome of practical importance. *Acta paediat. (Uppsala)*, 43, 411.
- Andersen, H. J. (1961). Studies of hypothyroidism in children. 50, Suppl. 125.
- Anderson, G. S. and Bird, T. (1961). Congenital iodide goitre in twins. *Lancet*, 2, 742.
- Bell, G. O. (1952). Prolonged administration of iodine in the pathogenesis of simple goitre and myxoedema. *Trans. Amer. Goiter Ass.*, p. 28.
- Berg, J. M. and Kirman, B. H. (1959). Some aetiological problems in mental deficiency. *Brit. med. J.*, 2, 848.
- Burrell, C. D. (1961). Transient myxoedema. *J. clin. Endocr.*, 21, 213.
- Burrows, B., Niden, A. H. and Barclay, W. R. (1960). Goitre and myxoedema due to iodide administration. *Ann. intern. Med.*, 52, 858.
- Christensen, J. F. (1956). Prolonged icterus neonatorum and congenital myxoedema. *Acta paediat. (Uppsala)*, 45, 367.
- Dimitriadou, A. and Fraser, R. (1961). Iodide goitre. *Proc. roy. Soc. Med.*, 54, 345.
- Eayrs, J. T. (1960). Influence of the thyroid on the central nervous system. *Brit. med. Bull.*, 16, 122.
- Elphinstone, N. (1953). Thiouracil in pregnancy; its effect on the foetus. *Lancet*, 1, 1281.
- Frisk, A. R. and Josefsson, E. (1947). Thiouracil derivatives and pregnancy. *Acta med. scand.*, Suppl. 196, 85.

- Léchele, P. and Troisier, F. (1950). Observation d'un cas de myxoedème acquis de l'adulte consécutif à des injections intramusculaires d'huile iodée. *Bull. Soc. Méd. Hôp. Paris*, 66, 960.
- McGirr, E. M., Hutchison, J. H. and Clement, W. E. (1959a). Sporadic goitrous cretinism; Dehalogenase deficiency in the thyroid gland of a goitrous cretin and in heterozygous carriers. *Lancet*, 2, 823.
- (1959b). Sporadic goitre due to dys-hormonogenesis: impaired utilisation of trapped iodide. *Scot. med. J.*, 4, 107.
- Morgans, M. E. and Trotter, W. R. (1953). Two cases of myxoedema attributed to iodide administration. *Lancet*, 2, 1335.
- (1959). Iodopyrine as a cause of goitre. *ibid.*, 2, 374.
- Nixon, P. G. F. (1957). Recurrent myxoedema and goitre attributed to potassium iodide. *Brit. med. J.*, 1, 748.
- Oppenheimer, J. H. and McPherson, H. T. (1961). The syndrome of iodide-induced goitre and myxedema. *Amer. J. Med.*, 30, 281.
- Packard, G. B., Williams, E. T. and Wheelock, S. E. (1960). Congenital obstructing goitre. *Surgery*, 48, 422.
- Paley, K. R., Sobel, E. S. and Yalow, R. S. (1958). Some aspects of thyroidal iodine metabolism in a case of iodine-induced hypothyroidism. *J. clin. Endocr.*, 18, 79.
- Paris, J., McConahey, W. M., Owen, C. A., Woolner, L. B. and Bahn, R. C. (1960). Iodide goitre. *ibid.*, 20, 57.
- Parmelee, A. H., Allen, E., Stein, I. F. and Buxbaum, H. (1940). Three cases of congenital goiter. *Amer. J. Obstet. Gynec.*, 40, 145.
- Pitt-Rivers, R. and Tata, J. R. (1959a). *The Thyroid Hormones*, p. 81. Pergamon Press, London.
- (1959b). *ibid.*, p. 161.
- Raben, M. S. (1953). Endocrine conference. *J. clin. Endocr.*, 13, 469.
- Rubinstein, H. M. and Oliner, L. (1957). Myxedema induced by prolonged iodide administration. *New Engl. J. Med.*, 256, 47.
- Taguchi, J. T. and Skillman, T. G. (1960). Iodine-induced myxedema; Report of a case and review of the literature. *Amer. J. med. Sci.*, 239, 417.
- Talbot, N. B., Sobel, E. H., McArthur, J. W. and Crawford, J. D. (1952). *Functional Endocrinology*, p. 44. Harvard University Press, Cambridge, Massachusetts.
- Turner, H. H. and Howard, R. B. (1956). Goitre from prolonged ingestion of iodide. *J. clin. Endocr.*, 16, 141.
- Vanderlaan, W. P. (1956). Myxedema and goitre attributed to iodine ingestion in a patient subsequently developing hyperthyroidism. *Metabolism*, 5, 640.
- Vogt, E. C. and Vickers, V. S. (1938). Osseous growth and development. *Radiology*, 31, 441.
- Wilkins, L. (1957). *Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, 2nd ed., p. 149. Charles C. Thomas, Springfield, Illinois.