

GOITROUS CRETINISM IN TWINS DUE TO BIOSYNTHETIC DEFECT IN FORMATION OF THYROID HORMONES

By G. S. Lee, M. L. Black, K. B. Chia, M. L. Wellby and B. S. Hetzel

(Department of Clinical Medicine, Faculty of Medicine, University of Singapore, Singapore, 3)

and

(University Department of Medicine, The Queen Elizabeth Hospital, Woodville, South Australia)

INTRODUCTION

A cretin has been defined (Stanbury and Querido, 1956) as a patient who has permanent retardation in development of the skeleton or central nervous system resulting from thyroid deficiency existing during early foetal or neonatal life. It is generally considered that hypothyroidism before the age of 12 months produces the clinical picture of cretinism. Cretinism occurs sporadically with and without goitre. Osler (1897) pointed out that a number of these cases of goitrous cretinism were familial. Recent studies, notably by Stanbury and McGirr (1960), have demonstrated various defects in biosynthesis of thyroid hormones in some of these cases. In this paper the occurrence of such a defect is reported in twins. Detailed studies revealed a defect in the deiodinase enzyme.

CLINICAL RECORD

These two patients (Fig. 1) were first brought to hospital by a neighbour to see whether something could be done about their goitres. The parents had no complaints about them but on direct questioning said that they had always been slow.

They were born on 25th January 1929. They were full term, normally delivered babies of birth-weight about 5 lbs. each. Raman was the first born of the twins.

They had never been feeding problems, even as babies. Raman had always been constipated, moving his bowels once every 2 to 3 days. The parents are rather vague about dates but their milestones were definitely delayed.

Sat	-	-	2-3	years
Walked	-	-	3-4	years
Talked	-	-	9-10	years
Ate on own	-	-	12-13	years
Attended to own toilet			15	years

They were both sent to school at the age of 6 years but after one year, the school principal asked the father to remove them as he said the boys were unable to learn anything and were holding up the rest of the class.

A goitre was noticed in Raman at the age of 15 years and in Latchman at the age of 18 years. Since then the goitres have gradually increased in size.

Family History

Parents are first cousins.

1st pregnancy—twins, Raman and Latchman

2nd pregnancy—female, 33 years. Alive and well. Married with 2 normal children.

3rd-7th pregnancies—all ended in stillbirths around 7-8 month of gestation. Foetuses said to have looked normal with no goitres.

8th pregnancy—male, 24 years. Alive and well. Married with 2 normal children.

9th pregnancy—male, 15 years. Suffers from rheumatoid arthritis.

Physical examinations

Both are short in stature, dull and very slow in movements and answering questions. Blood groups are B Rh positive (R) and A Rh positive (L). In both the skin was dry and cool, but not particularly coarse. In both delayed relaxation of tendon jerks was present.

Raman: Pulse 70/min. Blood pressure 90/60. Palpation of the neck defined large thyroid mass about 6 inches in diameter pointing towards the left with a smooth surface. Arterial pulsations were visible with palpable and audible systolic bruit over the mass. The trachea was pushed to the right. There was scanty pubic hair and no axillary or facial hair. The testes and penis were within normal size. The testes were rather soft. May 1963—height 3' 11½", weight 65 lbs.; September 1966—height 4' 0½", weight 71 lbs.

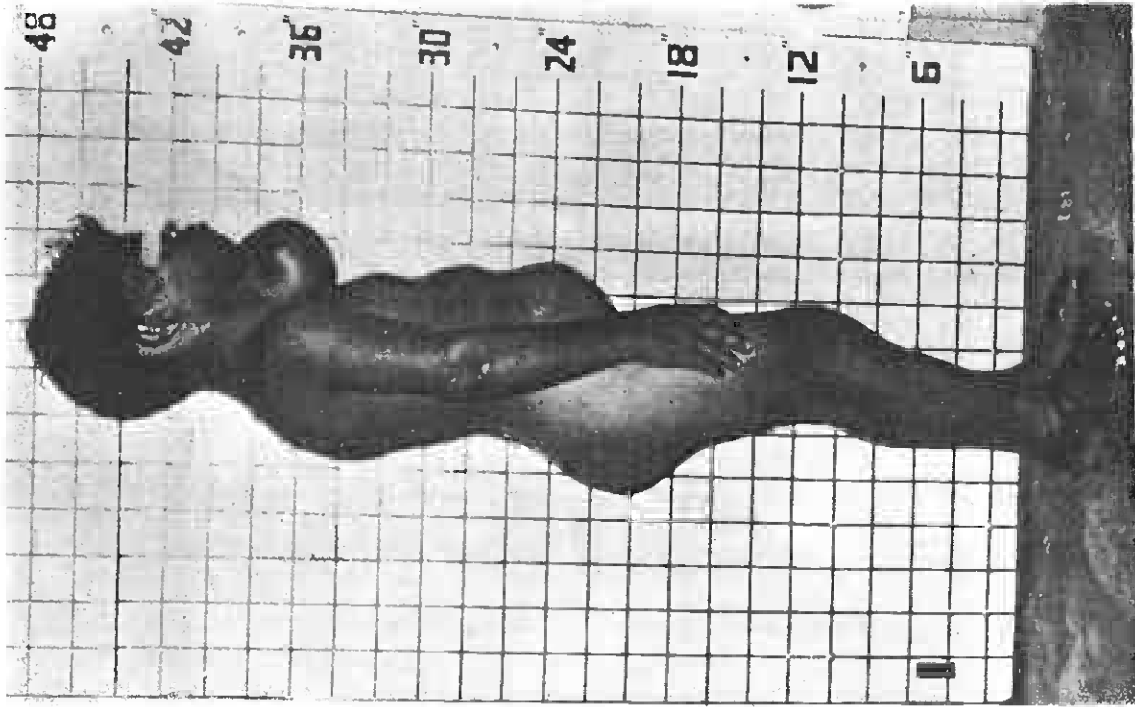


Fig. 1b. Raman side view.

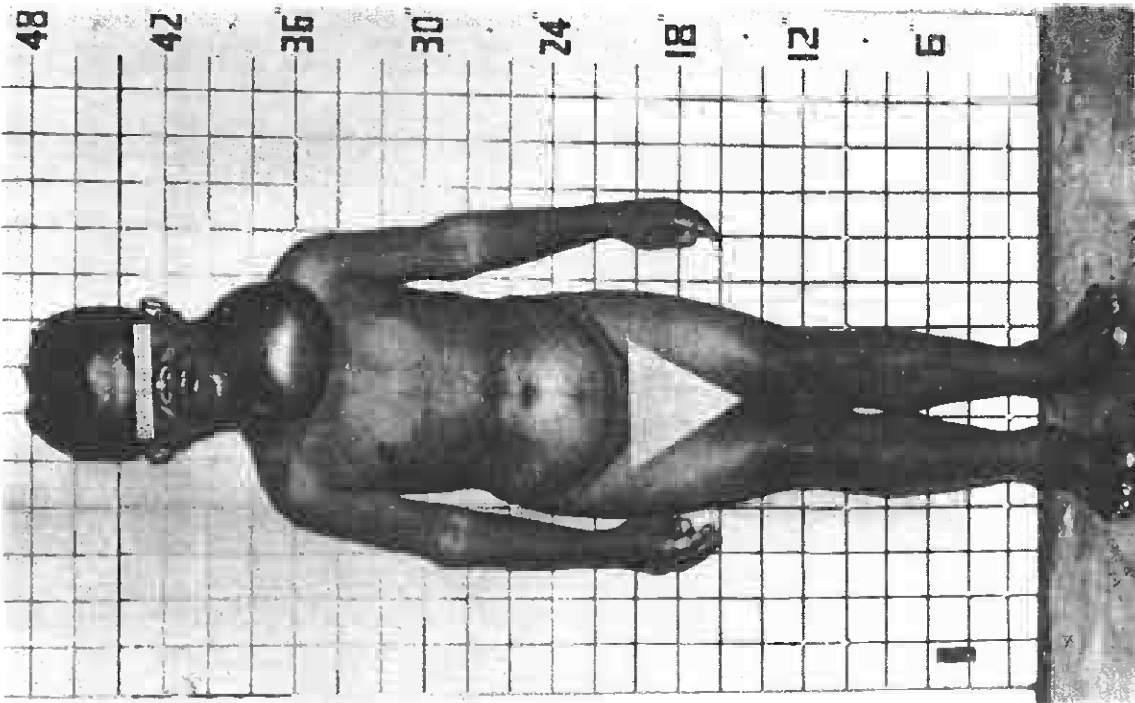


Fig. 1a. Raman front view.

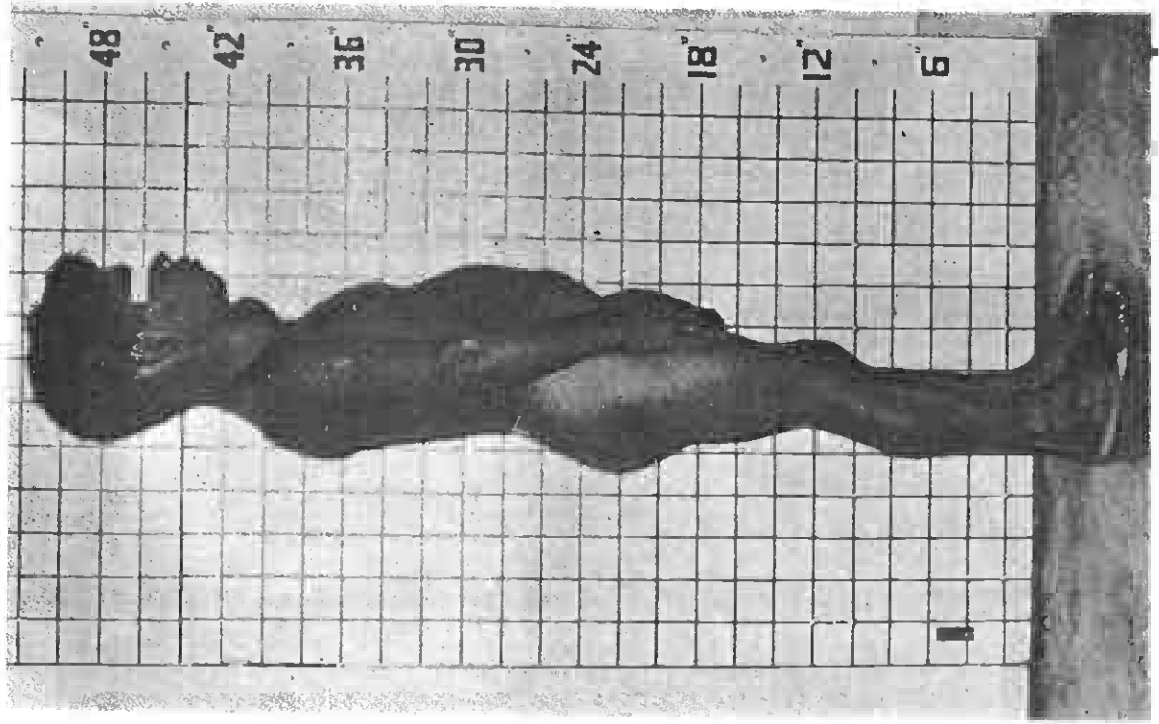


Fig. 1d. Latchman side view.

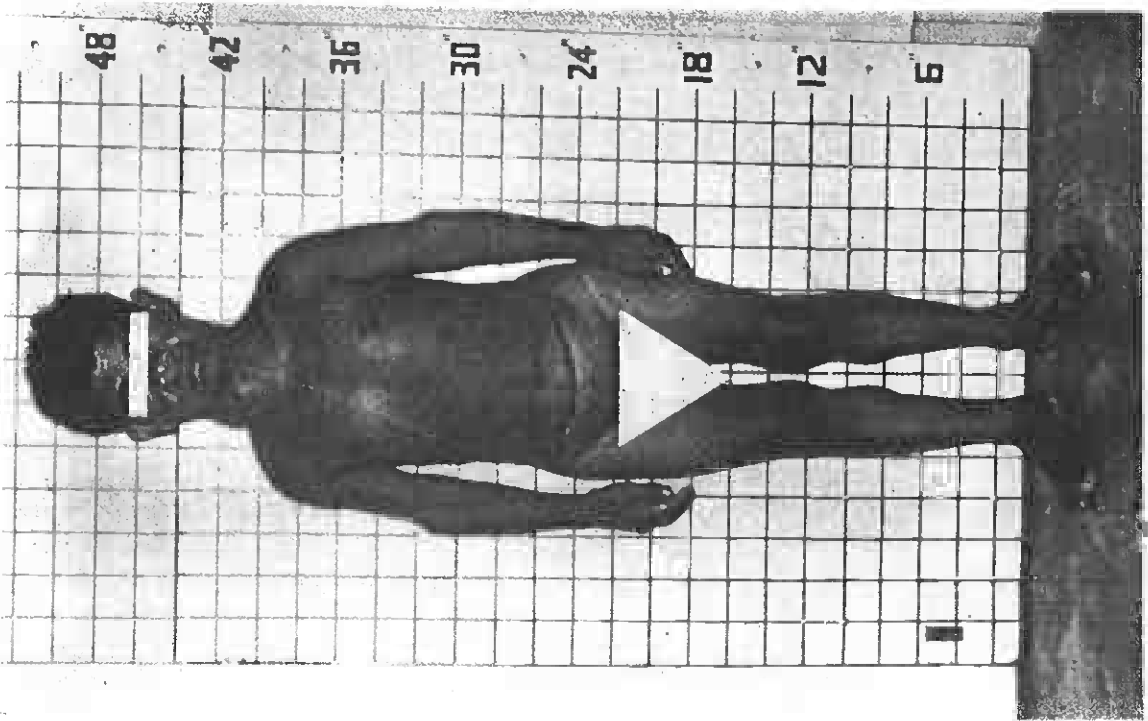


Fig. 1c. Latchman front view.

Latchman: Pulse 80/min. Blood pressure 90/60. There was a left corneal opacity (no past history of trauma). There was nodular enlargement of the thyroid, but no pulsations or bruits were demonstrable. The right kidney was enlarged and palpable, but not tender. There was good growth of pubic hair with some axillary and facial hair. He has not had to shave. The penis and testes were well within normal size. May 1963—height 4' 2", weight 65 lbs.; September 1966—height 4' 2½", weight 69 lbs.

LABORATORY STUDIES

The results of routine laboratory investigations revealed haemoglobin levels of 11.2 G.% (R) and 11.8 G.% (L). Total serum proteins were 6.1 G.% (R) and 6.7 G.% (L) with serum albumin levels 2.9 G.% and 3.6 G.% respectively. Globulin levels were 1.7 G.% and 1.4 G.%. 24-hour urine amino acids were 81 mg. and 36 mg.

Thyroid function studies

Clinically, hypothyroidism was more marked in Raman than in Latchman. Electrocardiography revealed poor T waves in both patients but the voltage of the complexes was normal. Plasma PBI levels were 2.8 and 2.9% in Raman and 2.0 and 1.8% in Latchman (normal range 3.5-7.5%). The serum cholesterol was 303 and 325 mg.% in Raman and 245 mg.% and 274 mg.% in Latchman. X-rays of the hips revealed the characteristic fragmented femoral epiphyseal dysgenesis of cretinism in both brothers (Fig. 2). Bone age was calculated to be approximately 20 years in each. A water excretion test gave a normal result (90% of the standard load excreted within 4 hours) in Raman; Latchman excreted only 54% but he was known to have a stone in the right ureter. Assay for thyrotropic hormone in the plasma using a modification of the method of McKenzie (1961) revealed levels of 0.4 milliunits per ml. in both patients. These levels are excessive (approximately ten times normal) and indicative of primary hypothyroidism with pituitary response to the lowered circulating hormone level.

Studies of thyroid gland

At operation (Mr. J. E. Choo) on Raman on 30th June 1964, it was found that the thyroid mass consisted of a large cyst which occupied the whole of the left lobe. There was a right lobe present which looked normal.



Fig. 2a.



Fig. 2b.

Fig. 2. X-rays showing fragmented femoral epiphyses characteristic of cretinism in (a) Raman and (b) Latchman.

A left hemithyroidectomy was done. Microscopically, the left lobe consisted of a round smooth cyst of 6 inches diameter (Fig. 3). It weighed 783 gms. On cutting open the cyst, it was found to contain stale blood. The wall of the cyst was 1½ inches thick. The cut surface of the wall showed whitish firm tissue with light brown fleshy areas in it. There were also tiny cystic areas.

Sections were reported as follows: "Microscopically, sections show adenomatous patterns heavily subdivided by large fibrous septa. There are foetal areas follicular patterns and Askanazy changes. In other words, various types of adenomatous pictures are seen. However, there is no colloid throughout. A basophilic mucoid secretion was present instead. The major portion of the tumour was composed of sheets and trabeculae of epithelial cells. (Fig. 4). The picture is characteristic of goitrous cretin due to enzyme defect".



Fig. 3. The left lobe of the thyroid after hemithyroidectomy on Raman. A large cyst is shown. The weight was 783g.

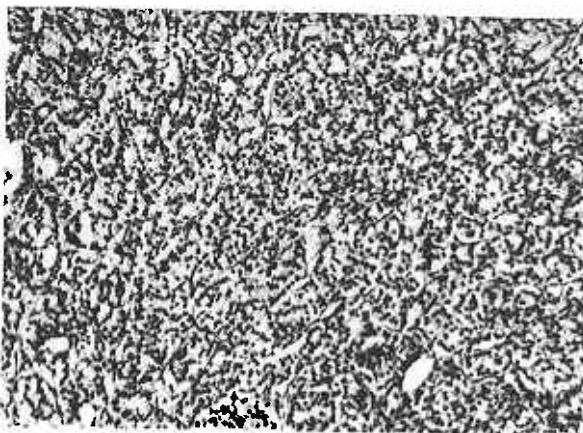


Fig. 4a.

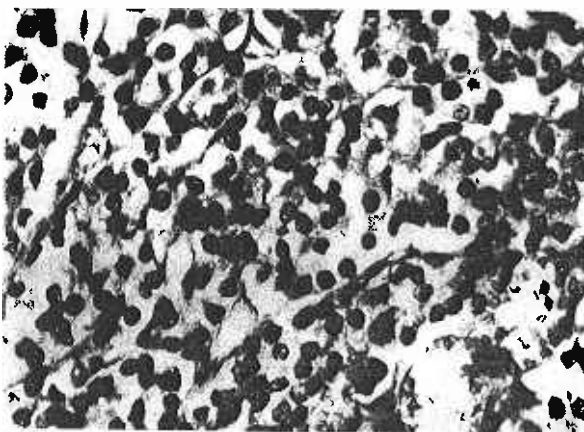


Fig. 4b.

Fig. 4. Microscopic section of left lobe of thyroid from Raman showing great hyperplasia with absence of colloid. (a) low power view (b) high power view.

A dose of 1 millicurie of radioiodine was administered to each patient five days before subtotal thyroidectomy was performed. Pieces of thyroid subjected to radiochemical analysis following digestion with pancreatin using chromatographic procedures described fully elsewhere (Wellby, 1962) revealed an almost complete absence of labelling of organic iodine compounds with radioiodine in both cases. Neither was any labelled material detected in the plasma at the same time (5 days after radioiodine) in both cases.

Chemical analysis of the gland revealed very low levels of iodotyrosines but there was a considerable excess of monoiodotyrosine (MIT) (5 times) over diiodotyrosine (DIT) (normally these amino acids are present in equal quantities or there might be an excess of DIT). No thyronines were detected chemically. Determination of total iodine content revealed a very low value, namely, less than 10 ug per gram net weight in each subject.

In view of the lack of bound radioiodine in the gland attempts were made to demonstrate an organification defect. Four hours following an oral dose of radioiodine 0.5 g. of potassium perchlorate was given. No discharge occurred. This was repeated on another two occasions using potassium thiocyanate with a similar result.

It was then decided that the block in synthesis of thyroid hormone was more likely to be due to a dehalogenase defect. Plasma samples were taken 6½-7 hours and urine samples 7-7½ hours after administration of a dose of 0.50 mc to each twin. Chromatographic separation following extraction (Wellby, 1963) revealed mainly iodotyrosines in both blood and urine in both subjects. The findings were more striking in Raman (Fig. 5) who showed virtually no thyronines but Latchman showed a small amount of thyronines in the plasma.

Serial measurements of radioiodine in the thyroid revealed the following values (% dose:)

Time in hours	Raman	Latchman
1	27	22.4
2	42	43.5
3	45.6	46.6
4	63.5	52
5	58.5	53
6	52.5	53.5
24	41.5	52
48	49	49
PBI 131 (48 hours)	0.785%	0.98%

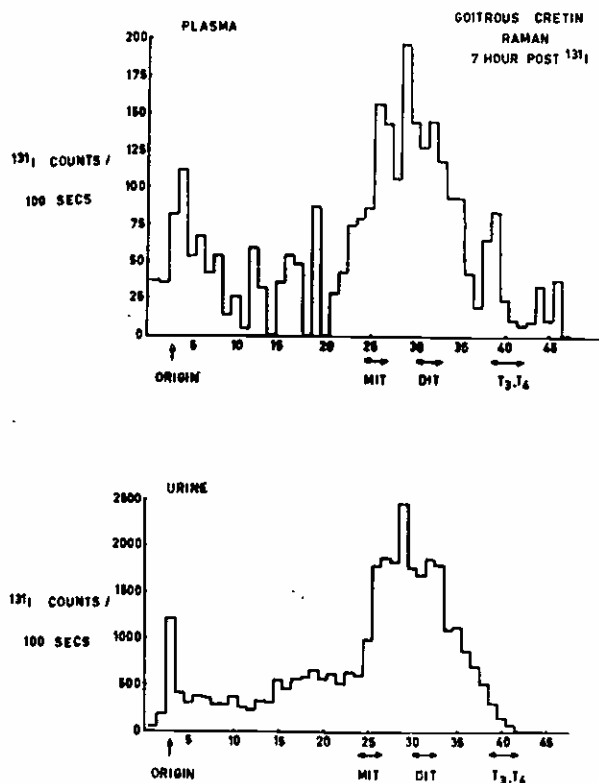


Fig. 5. Results of chromatographic studies on plasma and urine samples taken approximately seven hours following 0.50 mc radioiodine in Raman. There is a gross excess of monoiodotyrosine (MIT) and diiodotyrosine (DIT) in both plasma and urine with virtually no thyroxine (T₄) or triiodothyronine (T₃) indicating a dehalogenase defect.

DISCUSSION

The association of goitre and cretinism is most commonly seen in endemic goitre areas. However, the sporadic occurrence of this association while uncommon was well documented by the 19th Century clinicians (McGirr, 1960). In the last 20 years, intensive investigations with radioiodine have revealed various errors in the biosynthesis of thyroid hormones in many of these cases.

The first well-documented series was the family of goitrous cretins reported by Stanbury and Hedge (1950). Three of four siblings were affected. In each case, retarded development had been noted from infancy followed by gradually increasing goitre. On examination, there was gross hypothyroidism and a large goitre which showed a well-marked bruit as in the present cases. Similar cases have also been reported by Schultz et al (1957), Gardiner et al (1959) and Buchanan and Crooks (1959).

As expected, determination of plasma PBI as an indication of the circulating thyroid hormones revealed a lowered level in Raman and Latchman. The pituitary thyrotropic hormone

determined by bio-assay was elevated as expected with a low circulating thyroid hormone level. However, administration of tracer doses of radioiodine revealed a normal or high uptake in contrast with the low uptake usually seen with hypothyroidism. In this setting, this finding is suggestive evidence of a defect in the biosynthetic mechanism distal to the uptake of radioiodine.

Various defects in the biosynthesis of thyroid hormones associated with cases of familial goitrous cretinism have been demonstrated. These include an organification defect (which would be confirmed by a positive perchlorate or thiocyanate discharge test), failure of coupling iodotyrosines to produce iodothyronines, the production of an abnormal iodinated thyroid protein polypeptide and the lack of the normal dehalogenase which normally deiodinates the iodotyrosines to iodide.

In the present case there seems little doubt that the dehalogenase enzyme is defective as normally iodotyrosines do not appear in the circulating blood. Small amounts have been described following administration of thyrotropic hormone (Wellby and Hetzel, 1962) and are well documented in thyrotoxicosis (Bird and Farran, 1963) (Wellby, Hetzel and Good, 1963). The excretion of these iodotyrosines unchanged in the urine further indicates that the peripheral tissues are unable to deiodinate the iodotyrosines as well.

There is a big loss of iodine to the body which is reflected in the very low iodine content of the thyroid gland. Goitre results from this severe iodine deficiency which interferes with hormone production with a consequent fall in plasma PBI and increased TSH secretion (Hetzel, 1964). An excess of MIT over DIT in the gland as found in Raman has also been shown in a previous case by McGirr et al (1959), and is characteristic of iodine deficiency (Hetzel, 1964).

Nineteenth century physicians noted the occurrence of consanguinity in the parents of familial goitrous cretins. The present cases were the product of a first cousin marriage but they are non-identical twins from their blood group studies. It is of interest that females are only slightly more affected than males by sporadic goitrous cretinism or sporadic goitre with biosynthetic defect (2:1). By contrast, the very common sporadic goitre shows a marked predominance of females (8:1). This difference suggests that genetic factors cannot be the complete explanation of sporadic goitre—it points to

the importance of other factors such as puberty and pregnancy in females in whom goitre is so much more common.

ACKNOWLEDGEMENTS

We are indebted to Professor Bryan Hudson of the Department of Medicine, Monash University, Melbourne, for initiating the investigations of these patients.

We are indebted to Mrs. P. Millar, Mrs. L. Ratcliffe of the University Department of Medicine and Miss M. Carmen of the Department of Clinical Biochemistry, The Queen Elizabeth Hospital, Woodville, South Australia for assistance with the laboratory determinations.

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