JUVENILE THYROTOXICOSIS TREATED WITH THIOURACIL

BY

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Prepubertal thyrotoxicosis is a condition of some rarity and comparatively few childhood cases have so far been recorded in the literature where the drug thiouracil has been used in treatment. A review of six cases so treated was published by Williams and Janney (1947). The present case provides a suitable example both of the clinical picture and the response to treatment.

Atkinson (1938) in a survey of world literature collected two hundred and eight cases of Graves's disease in children from the years 1851 to 1938. Of these, only 20 per cent. occurred in the age period six to nine years. The registers of the Royal Edinburgh Hospital for Sick Children record only two previous undoubted cases since 1925 of a total of over seventeen thousand children admitted to the medical and surgical wards.

Case Report

I.S. was admitted to the Royal Edinburgh Hospital for Sick Children on Feb. 3, 1948, aged 6\(\frac{1}{2}\) years. The illness dated from an attack of measles in the autumn of 1946, following which the child became emotional and jumpy with a tendency to drop things and to make restless, twitching movements with the hands. She was frequently off school with bouts of 'fever,' and her own doctor, to whom the case was presented as one of chorea, insisted on rest in bed for three months.

In May, 1947, the mother first noted that the child's eyes were becoming more prominent, but she did not mention this when reporting with the girl to the out-patient department of the Royal Hospital for Sick Children in June of that year. Hospital admission was not practicable, and the diagnosis remained unchanged. She was sent home to bed with a recommendation for tonsillectomy, as the tonsils were enlarged and obviously infected. Phenobarbitone and aspirin were prescribed. An attempt was made to send her back to school at the close of the summer vacation, but she was 'always tired' and had 'a hot skin.' She was found, once again, to be running a low-grade fever, and she was kept in bed for a few days at a time.

In November, 1947, a swelling at the root of the neck was noted, and the child was sent for by the local hospital for tonsillectomy, only to be returned home unfit for operation. The tonsils were acutely inflamed, the associated lymph glands were enlarged, and the right ear was discharging. During the month of January, 1948, the picture became even more typical with visible loss of flesh, insomnia, and excessive appetite.

The child's early development had been uneventful. As a baby she was breast-fed for fourteen days only. Her only previous illness had been whooping-cough at four years. The family stock was healthy, with the important exception of a maternal aunt of twenty-nine years who had a thyroidectomy for Graves's disease in October, 1947. The child spent much time in this aunt's company, and they had always been very fond of one another. The mother, although healthy, showed very slight diffuse thyroid enlargement. Conditions at home were comfortable, and there was no discord in the family, which was 'very happy at all times.' At school, the child was popular with teachers and scholars and, if anything was 'too interested in her lessons.' The child had not been subjected to corporal punishment, nor had she suffered from any other known physical or psychic shock. The two younger siblings were healthy.

On admission to hospital the child was tall (see fig. 1) for her age; she measured 51\(\frac{1}{2}\) inches, and weighed 51\(\frac{1}{2}\) lb. She was fair-haired, pale, slender, and keenly interested in her surroundings. She talked freely without shyness, laughed too readily, and was equally liable to burst into tears. She was in no way distressed. She remarked that she was always hungry and always hot, and that she sweated if made to wear a coat.

The bony skeleton showed no abnormality and the bone age radiologically was that of a white girl of 8\(\frac{1}{2}\) years. The skin was very warm, flushed, and moist, the handshake giving the characteristic sensation. Nutrition was poor, although the fatty layer was evenly distributed; the scapular and anterior iliac spines were prominent. Muscle tone and posture were rather poor.

A diffuse, readily visible fullness in the root of the neck presented the shape of the thyroid gland and moved on deglutition (fig. 3). The surface was finely granular, and a well-marked bruit was present on auscultation. The neck circumference one inch
FIG. 1.—Before commencing treatment with thiouracil. Girl on the right is a healthy child of the same age.

FIG. 3.—On admission, showing the goitre.

FIG. 2.—After ten weeks of treatment in hospital.

FIG. 4.—On admission, showing the goitre and exophthalmos.

PLATE V.
above the sternal notch was 10.6 inches. The eyes were symmetrically prominent (fig. 4) and there was evidence of lid lag. The hands were in ceaseless motion while she spoke, but were not choreiform. Unlike a case of chorea, she could, with concentration, print her name very neatly in block capitals with a pencil on paper. A fine tremor of the outstretched fingers was present. The glucose tolerance curve was normal, and the urine free from sugar and ketone bodies. Although the clitoris appeared a little hypertrophied, there was no other evidence of precocious puberty. A qualitative test for follicle-stimulating hormone in the urine proved negative.

Stereoscopic radiographs of the skull showed no pathological increase in the size and shape of the sella turcica. A persistent tachycardia at rest was present, and the pulse pressure was high on palpation. Clinically and radiologically the heart was not obviously enlarged; there was a very soft systolic murmur in the mitral area, the second sound being accentuated in the pulmonary, but not in the aortic area. The blood pressure at rest was 126 systolic and 62 diastolic. The skin flushing has already been described.

In the respiratory system the only abnormality found was the infected state of the tonsils, which were very large but had no associated adenitis. Straight radiographs of chest were negative, and also the Mantoux test (1 in 1,000). The ears were healthy. The tendon reflexes were brisk, those of the knee being sustained.

The blood picture on admission was: Haemoglobin 83 per cent.; red blood cells 5.55 million per c.mm. of blood; colour index 0.76; white blood cells 13,800 per c.mm.; reticulocytes less than 1 per cent.; neutrophils 48.6 per cent.; eosinophils 2.2 per cent.; large lymphocytes 12.4 per cent.; small and intermediate lymphocytes 31.2 per cent.; monocytes 5.6 per cent. The red cells were fairly well filled, and there were many platelets present.

Progress. In order to facilitate the description of the response to treatment, this has been recorded graphically and only a few explanatory notes will be added to each diagram. Following the eleventh week of treatment, the recording of clinical data was much less frequent owing to the usual changes in the resident staff.

A control period of two weeks in bed with adequate phenobarbitone sedation resulted in no clinical improvement and, in view of the child’s toxic state, it was decided to delay no further and thiouracil 100 mg. thrice daily was commenced.

General appearance. The appearance of the child eleven weeks after beginning treatment is shown in fig. 2. It not only shows the improved
nutrition but it has also captured the emotional state of the child. In the first photograph she is tense, alert, and nervous, whilst in the second she is lax and plump; the change is almost reminiscent of 'The Taming of the Shrew.'

**Basal metabolic rate** (fig. 5). In a highly emotional child, the use of any apparatus involving breathing into a mask was excluded as a means of giving an accurate reading. Assessment by calculation from the insensible perspiration presented other possibilities of error, and it was finally decided to make use of the formula devised by Read (1922). Accurate measurement of the basal metabolic rate is not claimed, but it is felt that the results* obtained while the child was asleep at twelve midnight are comparable in the same subject.

Having attained the level of +62, the basal metabolic rate made a most dramatic response to thiouracil therapy, flattening out on attaining single figures. When the maintenance dose was cut further from 50 mg. twice a day to 50 mg. daily, however, the basal metabolic rate again rose steeply to +27.5 in the twelfth week of treatment and was only controlled by increasing the dose once again. Tonsillectomy at the beginning of the eighteenth week resulted in further improvement, but the figure increased to +10.5 when the child was allowed to run about the day before her discharge.

**Weight** (fig. 5). This was the most striking index of progress and the rapid rise was dramatic on the commencement of thiouracil. A careful record of fluid balance was kept and at no time was there retention.

As with the basal metabolic rate, the weight flattened out on reduction to 50 mg. twice a day and fell quite steeply on further reduction to 50 mg. daily.

From the fourteenth to the seventeenth week, however, she became very excitable and restless and

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* Read's formula states that the basal metabolic rate = 0.683 (pulse rate + 0.9 × pulse pressure) − 71.5 when the subject is under basal conditions.
the weight was erratic. It had been originally intended to delay tonsillectomy until her general condition improved, but in view of her continued illness and their infected state, the tonsils were now removed under the protection of systemic penicillin.

**Cardiovascular Changes.** Fig. 6 represents changes in the cardiovascular system and needs little explanation. Once again the findings seem to depend directly upon the dose of thiouracil given. The falling systolic and rising diastolic pressures with resultant fall in pulse pressure are instructive while the sudden increase in the sleeping pulse rate on lowering of the thiouracil dosage to 50 mg. daily is most significant.

The sudden rise in all readings on the eve of the child's discharge was a response to a day of unrestricted activity after eighteen months of rest and the fact that the basal metabolic rate, which depended directly upon them, remained at 10.5 is surely a tribute to therapy.

**Biochemical Data**

Blood cholesterol (fig. 7). The blood cholesterol has frequently provided scope for argument in the assessment of thyroid activity.

Its importance was stressed by Hurxthal (1933), while Gildea et al. (1939) thought that it more frequently rose above normal in myxoedema than it fell below in hyperthyroidism. Schmidt (1935) believed it could not be correlated with the basal metabolic or other objective measures of thyroid activity, and more recently Dunlop (1948) had abandoned its use in thyrotoxicosis under treatment. Certainly in this single case of juvenile thyrotoxicosis it has proved the least sensitive and the most useless of the measures employed.

Creatinuria (fig. 7). Kepler and Boothby (1931) among others studied the urinary excretion of creatine in hyperthyroidism, while Palmer et al. (1929) discussed the influence of iodine upon the creatinuria of thyrotoxicosis.

It was begun in this case solely out of interest and has shown itself to be simple and possibly sensitive. The total urine passed in twenty-four hours was noted and a sample from the collection was subjected to a comparatively simple but accurate analysis for (a) creatinine, and (b) creatinine + creatine. The creatine excretion, after a dramatic fall, rose again on the smaller dosage of thiouracil, but fell to near zero on 150 mg. thiouracil daily with tonsillectomy. The final reading was omitted as the child was up and about and part of the twenty-four hour collection was lost, thus invalidating the results as the excretion of creatine is irregular through the twenty-four hours.
Calorimetry. The results of this investigation have not been included as it was not possible to maintain a constant environment.

An efficient calorimeter was produced and the child's hand immersed in a measured volume of water for a given time at room temperature. The temperature rise was noted and the energy liberated in gramme calories per minute was calculated. Insulation was achieved by plastic polythene sleeving. Readings were taken at the same hour after the lunch-time meal, and the ward temperature was kept as constant as possible. The graph showed an interesting, if fortuitous, parallel to the daily output of creatine. Owing to the temperature change from winter to summer during the course of treatment, it was reluctantly decided to abandon the investigation.

Blood picture (fig. 8). The general blood picture showed, as was expected, a fall in total neutrophil polymorphonuclear cells on the increased, and a return to normal on the decreased, dosage of thiouracil.

Williams and Janney (1947) noted an increase in the total eosinophil count, which reached a maximum at the sixth week of thiouracil treatment and then became reduced. In the present case a similar increase was noted, reaching a maximum in the fourth week of treatment.

The peaks of the total leucocyte count rose with almost regular periodicity and whilst there is no direct evidence that this relates to oestrogenic activity, it is a possibility which might be considered. Ingiulla (1947) has discussed the leucocyte response to the administration of oestrogens in the newly born.

OTHER FACTORS. Throughout her illness, the child was a behaviour problem in the ward, but it was felt that this was largely due to the fact that her health was improving and she found rest in bed more and more tedious as the months passed. Although she was very 'wild' on discharge, it was the state of a healthy, spirited girl, perhaps somewhat spoiled by over-attention, and was not the labile emotional instability of the early weeks.

Sleep did not behave as at first expected. On admission it was virtually impossible to arouse the child at night by any means short of physical violence, but on discharge, although sleep was sound, she could be made to stir, sedation being identical at both periods. Tolerance to phenobarbitone may have played a part. Concentration...
on simple arithmetic or puzzles improved with treatment, but was never good.

Again contrary to expectation, the circumference of the neck remained almost constant throughout, with a variation never exceeding 0·5 inches. There was possibly some improvement in the exophthalmus, and lid lag was not present on discharge from hospital.

Progress after discharge from hospital. The child has been seen at two- to four-weekly intervals since her return home, the last attendance being on Sept. 22, 1948. Thiouracil therapy has been kept constant during this time, but owing to drowsiness the dose of phenobarbitone was reduced from 1 gr. three times daily to 1 gr. at night on Aug. 16, 1948. Her general improvement has been maintained, and is reflected in her nutrition, posture, and general behaviour. Since Aug. 30, 1948, she has been attending school regularly without disability. Her weight on Sept. 22, 1948, was 62·5 lb., a considerable gain since discharge. The skin was cool and dry and there was less pronounced exophthalmos, but the neck circumference had increased to 11⅛ inches. The systolic blood pressure was 98 mm. and the diastolic 68 mm., with a pulse pressure of 30 mm. The heart rate was 76 and regular, although the child was awake and had just completed a long journey to Edinburgh, in contrast to readings in hospital which were taken during sleep. Using Read's formula as before, a value of 1·2 was obtained. Throughout the period of observation as an out-patient, total leucocyte and differential counts were made, the only significant change being an eosinophilia of 11 per cent. on Aug. 30, 1948. This subsequently fell to 7 per cent on Sept. 22, 1948.

Discussion

It is not possible to draw conclusions from a single case, but should this observation be substantiated by other similar cases it would seem that in thiouracil and its derivations we might have an answer to Beilby and McClintock's (1937) statement that 'it is far more dangerous to attempt to cure hyperthyroidism in the young by medical means than it is in the adult.'

It must, however, be recognized that, despite the early dramatic results with thiouracil, the child improved after tonsillectomy. The part played by infection in the onset of thyrotoxicosis in young adults is well recognized, and Mackenzie (1931) and others have reported immediate recovery from exophthalmic goitre following the removal of very infected tonsils alone with no medical treatment.

Summary

A case of juvenile thyrotoxicosis is presented and the results of treatment with thiouracil recorded graphically over twenty-two weeks, with additional notes on progress since discharge from hospital. The possibility of its use as an alternative to surgery in the prepubertal period is suggested if similar success is met with elsewhere.

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