Papers and Originals

Childhood Thyrotoxicosis: A Long-term Perspective*

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Thyrotoxicosis is a puzzling disorder, especially from the standpoint of aetiology and epidemiology. Basically it represents a disturbance in thyroidal homeostasis so that there is unrestricted hormone secretion. Clinically this is manifested as hypermetabolism, goitre, and exophthalmos.

The overall paediatric contribution to the incidence of thyrotoxicosis is small, the age-group 0-15 years contributing only about 5% of the total cases. However, this has been one of the commonest thyroid disorders encountered at our Children's Endocrine and Metabolic Clinic, constituting about 45% of all goitres. The present report summarizes experience with 70 juvenile thyrotoxic patients seen over the 20-year period 1941-61. The prolonged follow-up in these patients has provided an opportunity to appraise many of them as adults and thus judge the end-products of our paediatric workmanship.

Of the 70 patients, 55 (79%) were female. The ratio of females to males, roughly 4:1, compares with the overall ratio of 6:1 reported in the childhood age-group (Hayles, 1962) and 7:1 in adults with Graves's disease.

Onset of Disease

Onset of hyperthyroidism in both boys and girls was most commonly in the early adolescent group aged 10 to 13 years (29 patients). The age of onset was from birth to 5 years in 9 children, 6 to 10 years in 19, and 11 to 16 years in 42. One patient with neonatal thyrotoxicosis, born of a thyrotoxic mother, constituted the only subject under 3 years of age in this series. In about one-third of the patients the onset of thyrotoxic symptoms so closely followed physical or psychic stress as to arouse suspicion that the stress was directly involved in precipitating the condition. Thus in six instances the child has been in an automobile accident within a few weeks of the onset of the disease. In seven children convalescence from an infectious disease merged imperceptibly into thyrotoxicosis. In seven others serious psychic trauma, including attempted rape, death of a parent, or separation of parents, immediately preceded the thyroid disorder.

The onset was usually insidious, and for this reason many children had advanced disease before coming to medical attention. In retrospect, mild symptoms were present for four to six months or even longer before being noted by parents, teacher, or physician. In eight patients the onset was more acute in nature. It was interesting to note that even well-marked symptoms were passed off as "nervousness," "school phobia," "chorea," etc., thyrotoxicosis being omitted from consideration because of its presumed rarity. Looking back

at these children, it seems that the diagnosis was almost written on their faces. A higher index of suspicion, obviously, is important to avoid delay and errors in diagnosis.

Symptoms and Signs

Some of the earliest symptoms to appear were nervousness, restlessness, and a deteriorating quality of school work. Extreme emotional disturbance manifest as spells of crying, temper tantrums, irritability, and lack of concentration was often present and contributed to the child's difficulties at home and school. Hyperkinesia, restlessness, thyroid enlargement, and eye signs often, although not invariably, followed in that order. Table I enumerates the more commonly encountered symptoms and signs.

Thyroid.—The thyroid was usually enlarged to about three to four times normal size by the time the patient came to the clinic. The goitre was soft, smooth, and diffuse, and except in two cases it was not tender. Increased vascularity was obvious by the presence of thrill and bruit, especially over the upper poles of the lobes. The degree of gland enlargement bore no close correlation with the severity of thyrotoxic symptoms.

Eyes.—A peculiar "stare" was one of the most characteristic features of these children. Exophthalmos, present in 77% of the patients, was usually bilateral, but quite often a discrepancy in the degree of proptosis of the two eyes was either clinically

TABLE I.—Symptoms and Signs

Symptoms	Patients		Signs	Patients	
	No.	%		No.	%
Nervousness	56	80	Thyroid :		
Prominence of eyes ..	55	79	Enlarged thyroid (goitre) ..	70	100
Fatigability	50	71	Bruit over thyroid ..	50	71
Increased perspiration ..	49	70	Pressure signs from		
Increased appetite ..	50	71	goitre	11	16
Weight loss	47	67	Tenderness over thyroid	2	3
Enlargement of thyroid ..	45	64	Eyes :		
Restlessness	44	63	"Stare"	70	100
Deterioration of school			Exophthalmos	54	77
work	30	43	Cardiovascular system :		
Palpitation	29	41	Tachycardia	64	91
Irritability	28	40	Increased systolic B.P. ..	59	84
Emotional disturbances ..	28	40	Increased sweating ..	49	70
Intolerance to heat ..	28	40	Increased temperature ..	46	66
Breathlessness	21	30	Murmur in heart ..	25	36
Frequency of micturition			Flushing of skin ..	20	29
and/or enuresis ..	16	23	Liver enlargement		
Sleeplessness	12	17	(cardiac failure) ..	6	8.5
Headache	12	17	Central nervous system :		
Diarrhoea	11	16	Nervousness and irrit-		
Difficulty in swallowing			ability	70	100
or hoarseness	11	16	Hyperactive tendon		
Pain and aches in body ..	10	14	reflexes	56	80
Dizziness	8	11.5	Tremors	53	76
Easy bruisability	6	8.5	Muscle weakness ("leg-		
Menstrual disturbances ..	5	7	raising test") ..	47	67
Increased thirst	3	4	Increased movements		
Obesity	3	4	(hyperkinesia) ..	44	63
Pain in neck (thyroid) ..	3	4	Behavioural :		
Anorexia	2	3	Emotional disturbances		
			Frequency of micturi-		
			tion, enuresis ..	16	23

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apparent or revealed by exophthalmometry. The severity of exophthalmos did not seem to bear a direct relation to the severity of other symptoms, thyroid size, or protein-bound iodine (P.B.I.) levels. With control of hyperthyroidism, while the "stare" disappeared promptly in almost all children, exophthalmos took a much longer time to resolve. None of the children showed an increase in exophthalmos after treatment.

Cardiovascular System.—Increased pulse rate, high systolic blood-pressure with a wide pulse-pressure, mild to moderate enlargement of the heart, and a precordial systolic murmur were frequent (Table I). In six patients cardiac decompensation was evident by an enlarged tender liver.

Neuromuscular System.—The central nervous signs and symptoms were among the first to become manifest. Hyperkinesia was occasionally so extreme as to suggest chorea. Tremor of the outstretched hands and tongue was seen in 53 patients and tended to linger for some time even after euthyroidism had been achieved. Muscle weakness constituted a striking feature of thyrotoxicosis in children. Clinically it varied in severity from mere increased fatigability to an extent that even sitting up from a reclining position was difficult. In one child exquisite muscle tenderness, which subsided dramatically on control of thyrotoxicosis, was noted. To obtain a more objective index of muscle strength we employed the "leg-raising test" in which the patient, while sitting on the edge of the bed, was required to keep his legs raised in a horizontal position. Very few could do so for as much as two minutes. The muscle weakness and atrophy appeared to be related more to the duration of hyperthyroidism than its severity. The rapid and striking improvement noted in muscle power after treatment indicated that the myopathy was secondary to thyrotoxicosis.

Growth and Development

An appreciable number of children in whom the onset of the disease was before the age of 10 years were taller than average for their age (see Chart). This tendency was not as

noticeable in the older children, although many showed a period of rapid growth concomitant with the phase of thyroidal overactivity.

Determination of bone age in 20 patients showed no variation from normal in 16, significant increase over expectation for chronological age in three, and marked decrease in one.

Sexual maturation occurred unusually early in two girls who had menarche at age 9 years 6 months and 10 years 2 months

respectively. In two others menses started at the age of 11 years. The mean age at menarche was 12.8 ± 1.37 years, as compared with a mean of 13.66 ± 0.83 years found in a survey of patients without endocrine disease attending the paediatric clinic for various acute illnesses. The male patients showed neither delay nor hastening of their maturation.

Associated Disorders

Table II summarizes various other illnesses found in these patients in association with thyrotoxicosis. It is evident that "behaviour" disorders and diseases involving collagen tissue

TABLE II.—Associated Disorders

Case No.	
2	Congenital buphthalmos, cataracts, myopia
4	Speech impediment; schizophrenia developed post-operatively
5	Patent ductus arteriosus; extreme psychiatric disturbance
7	Anxiety neurosis, hypochondriac
9	Fibrous dysplasia, myopathy, unilateral exophthalmos, schizophrenia (post-operatively)
12	Prosis
14	Fibrous dysplasia with multiple fractures, nerve deafness
15	Neurilemmoma, obesity
17	Osteoporosis, pyelonephritis, anxiety neurosis
20	Anorexia nervosa (post-operatively)
22	Epilepsy, osteoporosis, papillary carcinoma thyroid adenocarcinoma breast, schizophrenia (post-operatively)
23	Splenomegaly
24	Precocious puberty
25	Precocious puberty, enuresis
28	Suicidal tendency, anxiety neurosis
32	Ovarian cyst
40	Hashimoto's disease?
43	Psychosis (post-operatively)
53	Rheumatic heart disease and chorea. Died of cardiac arrest
55	Rheumatic heart disease
61	Pernicious anaemia
63	Rheumatic heart disease, chorea
64	Diabetes mellitus. Died of diabetic acidosis
65	Hypertrichosis, obesity
66	Rheumatoid arthritis

form the bulk of them. Thus Albright's syndrome of fibrous dysplasia was present in two male patients, osteoporosis in two other children, and rheumatoid arthritis in one. Three of the children developed schizophrenia requiring institutionalization for varying periods of time. Behaviour disorders in other patients included anxiety neurosis, suicidal tendency, anorexia nervosa, and hypochondriasis. Emotional instability appears to be a basic personality feature of some of these patients even when thyrotoxicity is absent (Dunlap and Moersch, 1935; Lidz and Whitehorn, 1949). In keeping with the experience of others (Ruesch *et al.*, 1947) more than half of our patients developed the psychoneurotic expressions after their hyperthyroidism had come under control (Table II).

Diagnosis

Laboratory aids were not required for diagnosis in most instances; they were more important in following the course of the disease.

1. **Basal Metabolic Rate.**—The B.M.R. has been almost completely abandoned in our clinic in favour of less cumbersome and more discriminating and reliable tests. In the 44 children in whom this test was performed the mean B.M.R. was +32% (range +2% to +79%). In 15 of the 44 patients the B.M.R. was less than +20% and thus within normal range.

2. **Protein-bound and Butanol-extractable Iodine.**—Serum P.B.I. proved to be one of the best diagnostic criteria. The range of normal for our laboratory is 3.5 to 7.5 $\mu\text{g.}/100\text{ ml.}$ In the thyrotoxic patients the P.B.I. ranged from 8.9 to 27.5 $\mu\text{g.}/100\text{ ml.}$, with a mean of 13.7 $\mu\text{g.}/100\text{ ml.}$ The reliability of this test was good inasmuch as the level was elevated in every child with thyrotoxicosis. On the other hand, it is to be remembered that the combination of high P.B.I. and goitre may be encountered also in children with lymphocytic thyroiditis (Saxena and Crawford, 1962) and other non-toxic goitres due to enzymatic defects (Greenspan *et al.*, 1963). However, the B.E.I.

was low or normal in these patients. Another source of confusion was iodide administration as illustrated by one 7-year-old boy in whom the P.B.I. and B.E.I. were 45 and 41 $\mu\text{g./100 ml.}$ respectively. Clinical examination did not support the diagnosis of hyperthyroidism and a history of iodide ingestion was lacking. On careful questioning it was learned that a cholecystography had been performed on his mother nine months preceding his birth. The dye used for the procedure was Teridax (DL-3-hydroxy-2,4,6-triiodo- α -ethylhydrocinnamic acid, or iophenoxic acid). This can persist in the patient's blood for years (Astwood, 1957) and, in addition, can pass the placenta and raise the child's serum iodine (Shapiro and Man, 1960; Shapiro, 1961). In the present case the mother's P.B.I. was 164 $\mu\text{g./100 ml.}$ (B.E.I. 157 $\mu\text{g./100 ml.}$) and that of the patient's younger sister 51 $\mu\text{g./100 ml.}$ (B.E.I. 44 $\mu\text{g./100 ml.}$).

Serial P.B.I. estimations were of value in following the progress of thyrotoxic patients during treatment. An important exception to this rule obtained during the first few weeks of propylthiouracil administration when P.B.I. remained at a higher level than expected from the clinical condition of the patient. Three to five weeks were required for P.B.I. to return to normal levels, and often the patient was clinically hypothyroid when P.B.I. was still in the high normal range. The explanation of this phenomenon probably lies in the extrathyroidal action of propylthiouracil, which blocks the deiodination of thyroid hormone in body tissues (Escobar del Rey and Morreale de Escobar, 1961). As a result of this, thyroid hormone may circulate in the blood but fail to be metabolically active at the end-organs. We have observed a similar phenomenon in rats given thyroxine and propylthiouracil simultaneously. Their P.B.I.s remained high when they were grossly hypothyroid as judged by other criteria. Under these circumstances the erythrocyte- T_3 - ^{131}I test was more reliable than P.B.I. or B.E.I. in judging the true thyroid status (Saxena *et al.*, 1964).

3. *Thyroidal Radioiodine Uptake*.—The 24-hour ^{131}I -uptake by the thyroid ranged from 41 to 86% (normal 20–50%). The thyroid-suppression test (Werner and Spooner, 1955) was of great diagnostic help in an occasional doubtful case.

4. *Erythrocyte or Resin- T_3 - ^{131}I Uptake*.—The uptake of ^{131}I -labelled triiodothyronine by erythrocytes (Hamolsky *et al.*, 1957) proved to be a reliable indicator of thyroid function. In our hands the range of normal uptake was 11 to 17%. In thyrotoxic children the uptake varied from 19 to 50%. The greatest usefulness of the test was to follow the patient's progress when iodide or propylthiouracil was being administered.

5. *Assay for Long-acting Thyroid Stimulator (L.A.T.S.)*.—Sera of 11 of our patients were assayed by Dr. Aldo Pinchera for L.A.T.S.—the abnormal thyroid-stimulating substance described by Adams (1958, 1961), Adams *et al.* (1962), McKenzie (1958a, 1958b, 1960), and McCullagh *et al.* (1960). Only 3 out of 17 estimations were positive (Table III). These results are significantly lower from those in adults suffering from Graves's disease with exophthalmos. Of the 44 adults tested 29 (6%) showed presence of L.A.T.S. (Pinchera, personal communication, 1964).

TABLE III.—Results of Assay for L.A.T.S.

Thyroid Status	Exophthalmos	No. of Patients	L.A.T.S.	
			Positive	Negative
Active thyrotoxicosis	Present	3	1	2
Active thyrotoxicosis	Absent	2	—	2
Euthyroid on treatment	Present, stable	3	—	3
Euthyroid on treatment	Absent or decreasing	8	1	7
Recurrence—hyperthyroid	Increasing	1	1	—

Treatment

Of the 70 cases in the present series, 52 underwent subtotal thyroidectomy. The remaining patients had been treated with

iodides in the past and with antithyroid drugs more recently. The number of patients in the medically treated group is small and the follow-up too brief to permit drawing broad conclusions.

In the large surgically treated group attention to the pre-operative management has yielded dividends in terms of a smooth post-operative course. We have not experienced thyroid storm in a single patient. The main features of the pre-operative management were provision of adequate rest, diet, and sedation. Propylthiouracil was administered in a dose of 150 mg./m.²/day in three divided doses for six to eight weeks to achieve euthyroidism. Potassium iodide, 5 drops daily, was added to this regimen about 10 days before surgery. Subtotal thyroidectomy was then performed in one stage (except in four earlier patients who had a two-stage operation), leaving behind approximately 1 g. of thyroid tissue (Arnold *et al.*, 1958).

Histology

On pathological examination the glands showed diffuse hyperplasia in various stages of involution. In one gland a focus of papillary carcinoma was discovered adventitiously. This patient has been followed post-operatively for 11 years without recurrence of thyroid carcinoma though she developed an adenocarcinoma of the breast. Moderate to marked lymphocytic infiltration of the thyroid was present in 15 children. Although none had clinical evidence of nodular goitre, five showed nodularity on histological examination; in two of these cystic degeneration of the nodular areas was also seen.

Immediate Post-operative Period

In the post-operative period the children were put on U.S.P. thyroid in a dose of 100 to 120 mg./m.²/day for a year. At the end of this time treatment was discontinued for approximately eight weeks and thyroid status was then evaluated clinically and by P.B.I. Other laboratory tests were required only in occasional patients. If the children were euthyroid no further treatment was given, though follow-up in the clinic was maintained. Of the 52 operated children, 30 (58%) became hypothyroid on discontinuation of replacement therapy one year after surgery. Substitution therapy was continued in them with re-valuation of thyroid function at approximately yearly intervals. At final follow-up 12 of the 30 had returned to euthyroid status, thus leaving only 18 (35%) permanently hypothyroid.

The immediate post-operative period was characterized by tetany in 9 (17%) children. The condition was most frequently noted on the second day. Low serum-calcium values ranging from 6 to 8.2 mg./100 ml. were found in all these patients. Treatment consisted of intravenous calcium gluconate and oral calcium lactate and vitamin D. By the end of a week the patients were clinically fit to be discharged. Five patients (10%) developed permanent hypoparathyroidism requiring continuous treatment with calcium and vitamin D.

One death occurred with cardiac arrest post-operatively in 1947. The girl had rheumatic heart disease with A-V block. She was treated with antithyroid drugs but failed to respond and her cardiac functions rapidly deteriorated. Emergency thyroidectomy was performed as a last resort, but she died on the second day. Necropsy disclosed cardiac hypertrophy, atelectasis of the right lower lobe of the lung, and congestion of the gastric mucosa.

Two children developed unsightly scars with keloid formation; both finally recovered without specific therapy. In two other patients collection of fluid in the wound necessitated drainage. Recurrent laryngeal-nerve paralysis and thyroid crisis were not encountered, nor did malignant exophthalmos occur in any child.

The initial response was uniformly good so far as remission of hyperthyroidism was concerned. In a recent attempt to reduce the high incidence of post-operative hypothyroidism, approximately 4 to 5 g. of thyroid tissue was left behind instead of the usual 1–1.5 g. The results have been poor, all three patients thus treated having suffered relapses of thyrotoxicosis within two years of surgery. These were the only instances of post-operative recurrence in our series. The implication is clear that relapses of thyrotoxicosis can be entirely prevented by removing sufficient thyroid tissue, but only at the risk of a high incidence of post-operative hypothyroidism.

A Long-term Look

The prolonged follow-up in most of our patients (Table IV) has provided an opportunity to evaluate the prognosis of surgically treated patients with unusual perspective. The

TABLE IV.—Length of Follow-up of 52 Surgically Treated Patients

Year... No. of cases	>1 5	1–2 4	2–5 13	5–10 16	10–15 10	Over 15 4
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experience is in general accord with those of others that surgical treatment offers a quick and effective method of obtaining remission in hyperthyroid children. Certain observations, however, merit more detailed comments.

Thyroid Status.—Permanent hypothyroidism has occurred in 18 (35%) of the 52 operated children (Table V). Twenty-five (48%) have maintained euthyroid status. In six more the

TABLE V.—Thyroid Status at Final Follow-up

Thyroid Status	No. of Patients
Euthyroid	25 (48%)
Hypothyroid	18 (35%)
Recurrence of thyrotoxicosis	3 (6%)
Follow-up inadequate	6 (11%)

period of follow-up was inadequate to permit evaluation. Many children remained hypothyroid for one to five years before attaining euthyroidism. However, no child who was euthyroid a year after thyroidectomy developed hypothyroidism at a later date. Experience with radioiodine treatment is significantly different in this regard, since the incidence of hypothyroidism following ^{131}I continues to rise steadily at a rate of about 3% each year (Beling and Einhorn, 1961). There was a significant correlation of post-operative hypothyroidism with lymphocytic infiltration of the thyroid. Of 12 patients with marked infiltration 8 became permanently hypothyroid as against only 4 out of 15 without lymphocytic infiltration. These observations are in line with those of other workers (Whitesell and Black, 1949; Greene, 1950). Circulating antibody titres have also been observed to have a correlation with post-operative hypothyroidism sufficiently significant to be of some prognostic value (Irvine *et al.*, 1962; Hjort *et al.*, 1963).

Other Endocrine Functions.—Information about marital status was available in 27 of the 39 patients who were over 20 years of age at the time of writing. Of these 17 were married, and most girls had undergone uncomplicated pregnancies and childbirth. There was an increased requirement for thyroid substitution in one of the hypothyroid patients during each of two pregnancies. As mentioned earlier, five patients developed permanent hypoparathyroidism following surgery and require continuous treatment with vitamin D (25,000 to 50,000 units daily).

Growth.—Notwithstanding the tendency towards superior height at the onset of childhood thyrotoxicosis, the height of affected individuals after maturity was not significantly different from average adult height. A rapid gain in weight persisting for several months was noticed in almost all patients after institution of therapy. Presumably the children had become

accustomed to overeating, in keeping with their high metabolism, and this resulted in obesity when the metabolism was brought down. The weight gradually reverted to normal for age over a period of months.

Psychosocial Adjustment.—The mild emotional disturbances present during the period of active hyperthyroidism improved when the thyroid problem was controlled. The post-operative school performance, social adjustment, marital history, and economic independence of the patients have been in keeping with their social and familial backgrounds. This was equally true of the group returned to euthyroidism by surgery and those who became hypothyroid and required permanent substitution therapy. On the other hand, the more serious behavioural disorders tended to persist; in five instances they developed after thyrotoxicosis had been brought under control (Table II). The association of thyrotoxicosis and behavioural disorders in these children is interesting. It would, however, be necessary to study the incidence of such disorders in a matched group of control children to realize its full significance.

Discussion

The epidemiology of juvenile thyrotoxicosis is intriguing and deserves some comments. An interesting aspect is the relatively high incidence of thyrotoxicosis in children in the United States of America. Admittedly, there are no reliable figures on which to judge incidence. It is striking, none the less, that in recent years no large series of cases have been collected in Britain or other European countries to compare with those reported by Dinsmore (1926), Bram (1944), McClintock *et al.* (1956), Hayles *et al.* (1959), Hung *et al.* (1962), and others from various centres in the U.S.A. The incidence, if anything, is rising (McClintock *et al.*, 1956). No explanation for this higher incidence in the U.S.A. is available. Neither the ethnical origins of the population nor its dietary habits seem to provide the answer. Higher frequency of recognition does not appear to be an important variable. Most observers favour the loose explanation that "stresses and strains" of life are greater in the United States than in other countries. As pointed out earlier, in about a third of our patients the onset of disease did appear to be closely coincident with some sort of stress.

A high familial predisposition to thyroid disease was evident among our patients, as many as 36 (51%) children having other family members suffering from thyrotoxicosis (22), non-toxic goitre (9), or hypothyroidism. Two fraternal twin sisters developing thyrotoxicosis within a four-year interval are included in this series. Present evidence would suggest that thyrotoxicosis is an autosomal recessive trait (Bartels, 1941; Martin and Fisher, 1945) with a penetrance of about 70% in the homozygote. The occurrence of thyrotoxicosis in one of the parents of nine of our patients, and the relative rarity of sibling involvement would, however, suggest that a dominant transmission is possible in some cases. Laboratory support for the genetic theory is offered by the studies of Ingbar *et al.* (1956), who found supernormal thyroidal uptake of ^{131}I in approximately 50% of relatives of patients with Graves's disease.

Virtually nothing is known of the cause of thyrotoxicosis. The discovery of abnormal thyroid-stimulating substances (Adams, 1958; Adams *et al.*, 1962) has offered a new lead toward unravelling the aetiology of the disorder. Since the "abnormal thyroid stimulators" L.A.T.S. and S.A.T.S. are unregulated by any known feedback mechanism, it is not difficult to visualize how their uninhibited production could result in thyrotoxicosis. This, however, does not provide the final answer to the basic cause of Graves's disease. The nervous system, especially the hypothalamus-sympathetic axis, may be important in the pathogenesis of hyperthyroidism (Bauer, 1961; Maisterrena *et al.*, 1962; Futterweit *et al.*, 1962). Disorder of cellular enzymatic reactions (Hoch, 1962) is another interesting possibility. Perhaps in the final analysis "thyrotoxicosis" will

be found to be just a symptom-complex produced by several different entities. In this regard the association of lymphocytic thyroiditis and hyperthyroidism in children may be important. Several of our cases of juvenile lymphocytic thyroiditis (Saxena and Crawford, 1962) presented with clinical and laboratory evidence of hyperthyroidism. Histological examination revealed hyperplasia of the thyroid in many patients in the early stage of thyroiditis. At the other end of the scale many juvenile thyrotoxicosis showed marked lymphocytic infiltration and high titres of agglutinating thyroid antibodies.

The management of juvenile thyrotoxicosis remains controversial. The purpose of treatment, in the absence of specific knowledge of the cause, remains to obtain sustained remission of thyrotoxic overactivity with as effective, quick, and simple means as possible. Among the factors to be considered in judging the merits of any of the three available modes of treatment should be: the degree of success, the fate of the goitre, the incidence of complications and relapses, the length of treatment, the co-operation of family and patient, and the cost of treatment. As Cassidy (1962) has pointed out: "Comparisons of the effectiveness of medical and surgical treatment are difficult, and the best one can do is to examine the published results from each treatment and draw conclusions based upon the facts available."

Medical treatment with stable iodine has been used since the time of Plummer (1923), but was soon found to be ineffective in producing long-term remission. Its use is now more or less limited to pre-operative preparation of the patient to make the thyroid firm and less vascular. The rapidity of its action is also a boon in situations like thyroid crisis and neonatal thyrotoxicosis, where a delay in treatment can result in the death of the patient (Sclare, 1960).

The thiouracil group of drugs, introduced by Astwood (1943), generated high hopes. Many reports of their use in small groups of children have been published. Kunstadter and Stein (1955) reported 17 cases in which 8 (47%) underwent remission lasting more than two years. Four patients were under treatment at the time of writing and five had required surgery. Five patients (42%) experienced one or more relapses. Allen *et al.* (1954) treated 15 patients—five with thiouracil compounds alone and 10 with thiouracil drugs and iodine. According to the authors seven (46%) had a "satisfactory" outcome, but unfortunately the follow-up after completion of therapy was less than a year in 9 of the 15 patients. Relapses occurred in 4 (26%) and surgery had to be undertaken in 3 (20%). Sensitivity to the drugs was noted in two patients. Nilsson (1961), from Gothenburg, reported the use of thiouracil drugs in 17 patients, of whom 9 (53%) were assessed as cured. Five had required surgery and one was still on treatment. Only 4 of the 17 (24%) suffered relapses. Propylthiouracil and methimazole were used by Bauer (1961) in 15 children. "Complete" or "almost complete" remission was obtained in only 6 (40%). The period of post-therapy follow-up was not mentioned. Of 18 patients treated by Bongiovanni's group (Root *et al.*, 1963) seven had remissions during medical treatment, two were still under treatment, and in eight surgery was necessary for various reasons, including toxic drug reaction (three) and relapse after adequate medical treatment (two). The most extensive study of antithyroid treatment in children comes from Wilkins's group in Baltimore (Van Wyk *et al.*, 1956; Hung *et al.*, 1962; Hung, 1963). Of the 33 children followed 19 (8%) were in remission, 4 for less than a year. Five patients had to be submitted to surgery for various reasons and 9 were continuing treatment. Relapses were observed in 7 (21%) patients. Untoward reactions occurred in 4 (17%) patients on propylthiouracil (urticarial rashes in three and granulocytopenia in one) and 2 (22%) on potassium perchlorate treatment.

A review of the results (Table VI) shows that approximately 50% of juvenile thyrotoxic patients can be expected to do well on medical therapy. The average duration of treatment for best

results is about three years. Relapses and toxic reactions are frequent. About 25% of the medically treated patients required surgery for one reason or other. It is obvious that despite its shortcomings, especially the development of post-operative tetany and hypothyroidism, surgery still has an important place in the definitive treatment of childhood thyrotoxicosis. Removal of sufficient thyroid tissue can consistently and predictably control thyrotoxicosis and virtually abolish recurrences. When one considers the high percentage of patients who fail to respond or who relapse on medical therapy, the risk of hypothyroidism may seem preferable.

TABLE VI.—Results of Medical Treatment

Author	No. of Patients	Remission	Under Treatment	Relapses	Surgery	Toxic Reactions
Allen <i>et al.</i> (1954)	15	7 (46%)		4	3	2
Kunstadter and Stein (1955) ..	17	8 (47%)	4	5	5	0
Nilsson (1961) ..	17	9 (53%)	3	4	5	1
Bauer (1961) ..	15	6 (40%)		1	4	3
Hung <i>et al.</i> (1962)	33	19 (57%)	9	7	5	6
Root <i>et al.</i> (1963)	18	7 (39%)	2	2	8	3
Total ..	115	56 (49%)	18 (16%)	23 (20%)	30 (26%)	15 (13%)

This is not to say that surgery is the ideal treatment. The high incidence of hypothyroidism (35%) and hypoparathyroidism (10%) attending surgery and the prolonged follow-up required for these patients impel search for a better mode of therapy. One way to meet this challenge could be to explore cautiously the possibility of treatment with radioiodine, which has proved so eminently successful in adults.

Very few reports of radioiodine treatment of thyrotoxicosis in children are available (Crile, 1958; Sheline *et al.*, 1959, 1962; Starr *et al.*, 1961). We recently reviewed the results of a group of 26 patients under 20 years of age treated with radioiodine at the Massachusetts General Hospital under the supervision of Dr. Earle M. Chapman (Saxena and Chapman, 1962). They do not form part of the 70 patients in the present report. The dose of ^{131}I used in therapy was approximately 100 microcurie/g. estimated thyroid tissue. The period of follow-up and results of therapy are shown in Table VII. Approximately 80% of the patients had good control of the thyrotoxicosis.

TABLE VII.—Total Number of Patients 26 (All Girls)

	No.
Age at treatment (years) ..	
{ < 5 ..	0
{ 5-10 ..	3
{ 10-15 ..	11
{ 15-20 ..	12
Period of follow-up (years after treatment) ..	
{ 0-3 ..	15
{ 3-5 ..	3
{ 5-10 ..	5
{ > 10 ..	3
Result of therapy ..	
{ Good control of thyrotoxicosis ..	20 (77%)
{ Poor ..	2
{ Recurrence ..	4 (15%)
Complications ..	
{ Hypothyroidism ..	2
{ Nodules ..	1
{ Transient ..	2
{ Permanent ..	4 (15%)

One of the patients who had recurrence of thyrotoxicosis 18 years after her treatment was found to have developed a multinodular goitre. The thyroid was removed and adenomatous changes were noted histologically. No evidence of malignancy was found. Physical and sexual maturation of the patients has been normal and five have given birth to normal children after treatment.

There are many advantages of radioiodine therapy—for example, its simplicity and efficacy, the short time required for treatment, and the low cost. The development of thyroid nodules in several children (Sheline, 1962) has contributed to the present hesitation in employing this method. It should be mentioned, however, that in the experience of other workers the incidence of nodules has not been as high as that noted by Sheline. Starr *et al.* (1961) found only one case among 60

children and adolescents treated with ^{131}I for thyrotoxicosis. The occurrence of thyroid nodules in a few patients should not by itself cause rejection of this method of treatment. Similar nodules may occasionally recur after subtotal thyroidectomy (Sheline *et al.*, 1962). About 10% of our patients showed nodular changes in thyroid on histological examination at initial surgery. Of the general population approximately 10% are estimated to develop non-toxic nodular goitres eventually and only about 1% of these individuals develop carcinoma of the thyroid (Sokal, 1959). Most likely the nodular changes occur in response to increased T.S.H. stimulation secondary to hypothyroidism. On the basis of experimental work (Purves *et al.*, 1951; Bielschowsky, 1955; Maloof, 1955), thyroid substitution in ^{131}I -treated patients might be expected to abolish the development of nodules.

A more intangible danger of radioiodine treatment is genetic injury. Despite the lack of unequivocal evidence for such damage (Means *et al.*, 1963) it cannot be disregarded. The risk of genetic changes in succeeding generations has received quantitative attention. It has been estimated that apparent birth defects in the patients' children might increase from the present 4% to 4.008%¹ or up to 4.025%². However, while considering these hazards of ^{131}I one should not lose sight of the seriousness of the disease or the high incidence of side-effects from the other methods of treatment at present available. While not advocating indiscriminate use of radioiodine, we feel that it is worthy of further exploration in selected patients under careful medical surveillance.

In judging the merits of any mode of therapy, its psychological impact on the patient should also be considered. This is especially important when the patient happens to be in the highly impressionable and formative period of adolescence. It has previously been pointed out that medical management imposes a significant handicap on the child and its parents (Arnold *et al.*, 1958). Surgery also has its own risks. From the point of view of the child, radioiodine treatment should prove the least psychologically traumatic. It has the advantage of being a single-dose treatment which does not require admission to hospital or close medical supervision. It avoids the unquestionable stress of prolonged round-the-clock medication on a child's life and eliminates the necessity of his co-operation for the success of the treatment.

Summary and Conclusions

An unusual perspective on childhood thyrotoxicosis has been provided by reviewing 70 patients cared for over the past 20 years, 52 of whom were treated surgically.

The disease appears to have a higher incidence in the U.S.A. than elsewhere. A genetic influence was suggested by the frequency of disorders in close relatives of the patients. The onset of thyrotoxicosis was often related to physical or psychological stress.

The clinical manifestations were easily recognizable and diagnosis required few laboratory aids. In view of the lack of proper understanding of the aetiology, cure has not been achieved. Good control was, however, obtained with surgical treatment. Though certain underlying genetic and psychosomatic characteristics tended to persist after treatment, the physical, emotional, and mental development of these children was not affected. Hypothyroidism and tetany were serious complications of surgical treatment, and the frequency of their occurrence indicated the need for better therapeutic measures.

Medical treatment of juvenile thyrotoxicosis emerges as even less satisfactory. The incidence of failure, recurrence, and toxicity is so high that ultimately recourse to surgery is necessary in one-fourth of the patients. The inadequacy of the methods at present available necessitates urgent search for better therapeutic measures. Radioiodine treatment has proved to be eminently suitable for adults. The question whether this might prove useful in children also is still unanswered. Our experience with this method, though not extensive, appears hopeful enough to justify its further exploration under careful qualified medical supervision, with special emphasis on long-term follow-up.

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² Second Report of the United Nations Scientific Committee on the effects of atomic radiations, United Nations, New York, 17th Sess. Suppl. No. 16 (A/5216), 1962.