THYROTOXICOSIS IN CHILDREN: A FOLLOW-UP STUDY

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Thyrotoxicosis in childhood is uncommon and there are few reports regarding either its treatment or prognosis. There is no agreement on whether medical or surgical therapy is better. Arnold, Talbot, and Cope (1958) summarized the choice as follows.

(a) *Surgical excision*: short in duration, but carrying a mortality risk and the possibilities of recurrence or hypothyroidism.

(b) *Medical therapy*: frequent and prolonged, with the need for supervision, the risk of toxic reactions, and the chance of eventual failure.

Surgical mortality may be small but is present in most of the recorded series (Hayles, Kennedy, Beahrs, and Woolner, 1959; Kunstadter and Stein, 1955; McClintock, Frawley, and Holden, 1956; Van Wyk, Grumbach, Shepard, and Wilkins, 1956) where a total of 7 children died after 275 operations. Arnold *et al.* (1958) and Root, Bongiovanni, Harvie, and Eberlein (1963) had no mortality in 28 patients. In all these series the recurrence rate was not less than 5%, while no less than 73 children operated on were subsequently found to be hypothyroid. On the other hand some patients were submitted to operation only because medical therapy had failed.

Medical therapy carries few risks. There are few reports of toxic drug reactions in children who seem to be at less risk than adults. Kunstadter and Stein (1955) had no reactions in 17 children treated with thiourea derivatives; Hung, Wilkins, and Blizzard (1962) reported maculo-papular rashes and fever in 2 of 9 children treated with perchlorate, urticarial rashes in 3 of 23 children who had propylthiouracil, and 'granulocytopenia accompanied by buccal ulceration and sore throat' in 1 of these children; Root *et al.* (1963) noted that 3 of their 17 children had mild leucopenia with fever and a skin rash.

With these 9 and one child in the present series who developed leucopenia while on a small dose of methylthiouracil, there were, therefore, 10 children

out of 99 treated who developed toxic reactions. This figure is similar to the incidence (2-10%) reported in adults.

In some reported series medical therapy has had to be abandoned because of the lack of co-operation by patient or parents. Though this did not occur in the present study, it may have to be considered an important factor influencing the choice of therapy.

As nearly all patients respond to some anti-thyroid drug, the duration of medical therapy may be the main factor dictating the choice between medical or surgical therapy. There is little recorded experience of this yet. Hung *et al.* (1962) suggest that probably over one-third of thyrotoxic children are cured by therapy lasting for two years or more.

In the decade 1953-63, 26 children attended The Hospital for Sick Children with thyrotoxicosis. With the records of 7 other children seen before 1953, they are here reviewed in an attempt to assess the therapy of this condition in childhood.

Of the 33 children, 29 were girls and 4 were boys. Symptoms appeared before the age of 5 years in 10 patients, between 5 and 10 years in 14 patients, and between 10 and 14 years in 9. It is likely that the last figure is artificially low because some children with onset at this age are referred to adult units. The duration of symptoms before the diagnosis was made is shown in Table 1.

There was no relation between the age of the child and the delay in diagnosis. The shortest history was 2 weeks, the longest 19 months.

The long delay in diagnosis in nearly one-third of

TABLE 1
INTERVAL BETWEEN ONSET OF
SYMPTOMS AND DIAGNOSIS

Time in Months	Number of Children
0-3	7
3-6	9
6-9	7
9-12	0
> 12	10

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the series reflects, as in adults, the difficulty of differentiating the insidious onset of thyrotoxicosis from longstanding behaviour, and emotional disturbances, and anxiety states. The occurrence of other thyroid disorders in the families did not always reduce this delay. Of 11 families, 17 members had thyroid abnormalities of some kind, i.e. either goitre or thyrotoxicosis; these included 6 parents, 3 grandparents, and 8 aunts or cousins.

TABLE 2
MAIN SYMPTOMS AT THE TIME OF DIAGNOSIS
IN 33 CHILDREN

Symptom	No. of Patients
Nervousness	26
Prominent eyes	26
Goitre	21
Excessive growth	16
Loss of weight	16
Excessive sweating	12
Diarrhoea	8
Restlessness	7
Choreiform movements	5
Insomnia	4
Excessive appetite	3
Other personality change	3

Symptoms and Signs

The *symptoms* are listed in Table 2. They are similar to those noted in adults though the choreiform movements are probably peculiar to children. Young patients do not evidently complain of feeling too hot. A thyrotoxic crisis occurred only once and was precipitated by an operation.

The symptom of personality change merits special attention. As a presenting feature it was uncommon. Closer inquiry, however, elicited that in 13 children abnormal behaviour had been noted for some years, often beginning long before any other symptom appeared. Only in retrospect did the parents recognize that such behaviour change had become more marked when other symptoms began. Since behaviour problems sufficiently marked to require medical advice occur in about 5 to 10% of children,* it is difficult to know how much of these features could be attributed to hyperthyroidism. There was no specific pattern. Misbehaviour, lack of concentration, bullying, 'not trying' and backwardness at school, perversity, wilfulness and temper tantrums at home, as well as enuresis, and other symptoms of being 'highly strung' were recorded. Recovery from them was sometimes dramatic when thyrotoxicosis was controlled but it was not always either rapid or complete. The first symptom of a relapse was usually behaviour disorder.

* Ministry of Education (1955). *Report of the Committee on Maladjusted Children.*

TABLE 3
HEIGHT AND WEIGHT BY PERCENTILE DISTRIBUTION

Percentile	Height		Weight	
	No.	%	No.	%
> 90	15	51	9	27
75-90	8	27	5	15
50-75	3	11	8	24
< 50	3	11	10	30
Not known	4	—	1	—

In most patients *signs* were sufficiently clear to confirm the diagnosis suggested by the history. Most were similar to those seen in adults. Thus 30 patients had an abnormal tachycardia and 21 an unusually high pulse pressure; warm moist palms were noted in 26 patients. Prominent eyes, whether due to lid retraction or exophthalmos were obvious in 23 and present in another 4 patients but absent in 6. Lid lag and other ocular signs could be demonstrated in 14 patients, usually in the older age-groups. Only 2 patients had no abnormal movements. Though tremor was commonly recorded it was seldom of the classical thyrotoxic fine type. Choreiform movements were seen in 7 patients. Anxiety, nervousness, restlessness, and fidgeting were evident in 25.

The accelerated growth associated with hyperthyroidism is shown in Table 3. It will be noted that excessive height was common but that nearly half the children were able to eat enough to keep their weight approximately commensurate with height.

All the patients had an enlarged thyroid gland, but in 4 this was very slight and only in 2 was it described as large. All the glands were smooth, most were symmetrical, and over most a *bruit* was heard.

Investigations

1 Estimation of the blood cholesterol was unhelpful. In 5 patients the level was over 200 mg./100 ml.; in 16 it was within the normal range of 100-200 mg./100 ml., and in 1 it was low.

2 The basal metabolic rate (BMR) was measured in 24 patients. In 8 it was unequivocally raised, i.e. over 140% of the normal levels related to surface area; in 8 it was less clearly raised, i.e. between 120 and 140% and in 8 it was hardly abnormal, i.e. 100 to 120%. In no child was it less than 100%. In one other child, lack of co-operation twice prevented any worth-while measurement. There was considerable discrepancy (over 30%) between duplicate measurements in three children.

3 The level of protein bound iodine (PBI) before treatment was obtained from only 12 patients. Of

TABLE 4
RELATION BETWEEN PROTEIN-BOUND IODINE
AND BASAL METABOLIC RATE

Basal Metabolic Rate (%)	Protein-bound Iodine ($\mu\text{g./100 ml.}$)		
	< 4	4-8	> 8
100-120			3
120-140		1	2
140		2	1

these, 9 had high levels (greater than $8 \mu\text{g./100 ml.}$), and 3 had normal levels ($4-8 \mu\text{g./100 ml.}$), the lowest level being $5.5 \mu\text{g./100 ml.}$ The correlation between BMR and PBI in the 9 patients in which both were estimated was not high (see Table 4).

Diagnosis

In spite of the newer techniques, such as the study of radio-iodine uptake by the thyroid, measurement of BMR by diapherometry, and estimation of PBI, the diagnosis of thyrotoxicosis remains a clinical exercise. In none of the children in this series was the diagnosis suggested by any such investigation and the chief value of these tests was in confirming the diagnosis *vis-à-vis* psychological disorder more rapidly and certainly. They also enabled a more rational approach to the control of the condition by drug therapy; but they have not so far eased the problem of how long treatment should continue.

Therapy

Therapy is summarized in Table 5.

The early patients in this series were either subjected to partial thyroidectomy or were treated with sedation and prolonged bed-rest. Of the 4 who were operated on, 3 were known to have remained well (and euthyroid) for $6\frac{1}{2}$, $10\frac{1}{2}$, and 20 years respectively, though one child developed an inactive thyroid adenoma. The fourth child was well $1\frac{1}{2}$ years later, after which she was lost to follow-up. This apparently favourable outlook must be tempered by the fate of 2 of the 5 children who were operated on after apparent failure of medical therapy: one died suddenly on the day after an

TABLE 5
SUMMARY OF THERAPY

Therapy	Initially	Subsequently
Methyl thiouracil	5	0
Carbimazole	12	3
Perchlorate	8	1
Surgery	4	5
Other therapy	4	—

uneventful thyroidectomy; the other relapsed within a year of operation and is threatened with a further thyroidectomy. Two other children in this group have been operated on too recently to be able to comment on the result.

Methyl Thiouracil. The experience with methyl thiouracil is summarized in Table 6. This group of 5 cases is too small and the results too variable to allow of any generalization. The only child who showed any toxic reaction (P.N.) was in this group.

Carbimazole. Table 7 summarizes the results with this drug in 15 patients.

All the patients except one treated with carbimazole became euthyroid within 3 months, and over half of them within one month. There seemed little difficulty in maintaining this state for several years but even after nearly 6 years of therapy, relapse could still occur while on therapeutic doses.

Five patients have remained euthyroid for more than a year after cessation of one course of therapy. The duration of the course, however, has varied from 3 to 39 months. Only one patient has relapsed after having stopped treatment for more than a year; 7 others have relapsed either within 9 months of cessation or while still on maintenance therapy. There is no relation between liability of relapse and duration of therapy or rapidity of control of symptoms.

Of these 15 patients, 4 became hypothyroid during therapy. Though they all had low serum PBI levels, only one showed clinical signs. Serial estimation of PBI level undoubtedly facilitated smoother control in the other 3 as well as those who relapsed.

TABLE 6
THERAPY WITH METHYL THIOURACIL

Patient	Age (yr.)	Initial Dose (mg./day)	Maintenance Dose (mg./day)	Duration of Therapy (mth.)	Result	Subsequent Therapy
C.A.	10	300	50	9	Euthyroid	
P.N.	10	50	—	20 days	Leucopenia	Carbimazole
H.T.	$5\frac{1}{2}$	200	50	9	Erratic control	Surgery
L.W.	4	300	25-50	142	2 mild relapses	
E.H.	4	50	—	1	No control	Surgery†

† died.

TABLE 7
THERAPY WITH CARBIMAZOLE

Patient	Age	Initial Dose (mg./day)	Maintenance Dose (mg./day)	Duration of Therapy (mth.)	Time Since Stopping Therapy (mth.)	Result
J.A.	7½	15-20	10-15	28	15	Relapsed
J.C.(1)*	7½	20	15	42	9	Relapsed
(2)	11½	10-15	10	5	—	Euthyroid
S.C.	4½	20	7.5	21	Continues therapy	Euthyroid
C.D.	9½	20	5-15	70	Continues therapy	Relapsed (P)
J.F.	4½	15	5	6	80	Euthyroid
A.H.(1)	8½	15	10	12	6	Relapsed
(2)	9½	10	5	32	3	Relapsed
(3)	12½	2.5	2.5	20	12	Euthyroid
J.M.	10	20	5-15	39	16	Euthyroid
D.N.	12	20	10-15	27	24	Euthyroid
P.N.†	10	10	2.5	3	84	Euthyroid
T.O.	11½	30	10-15	45	Continues therapy	Relapsed on maintenance dose
K.R.	9½	20	10-45	99	Continues therapy	Relapsed × 3 (S)
P.T.	11½	30	10-45	47	—	Relapsed (S)
V.W.(1)	10½	30	10	40	5	Relapsed
(2)	14	40	7.5	11	Continues therapy	Euthyroid
S.B.	4	15	10	12	Continues therapy	Euthyroid
V.M.*	11½	—	—	40	—	Poor control (S)

* Previously treated with perchlorate.

† Previously treated with methyl thiouracil.

(P) Subsequently treated with perchlorate.

(S) Subsequently treated by operation.

Perchlorate. This drug was introduced relatively recently and only 9 patients received sodium (or potassium) perchlorate (see Table 8). Though only one patient has so far been followed up for more than a year after treatment, this group suggests that perchlorate has little advantage over carbimazole. Of the 9 patients, one failed to respond to a moderate dose and subsequently responded quickly to carbimazole. All the others became euthyroid in less than 3 months (on average rather less than 2 months) irrespective of the dose given. So far 3 have relapsed, one while on perchlorate, the other 2 five months after stopping treatment.

Hypothyroidism as judged by serial PBI estimations has been commoner, occurring in 5 of the 9 patients.

Discussion

Therapy with anti-thyroid drugs was given to 25 patients. All except 3 were brought under control within 3 months and of the exceptions, 2 (E.H., Table 6 and J.C., Table 8) were inadequately treated; 7 have completed one or more courses lasting in all between 3 and 39 months and subsequently remained euthyroid for more than a year; 7 relapsed after completing up to 42 months therapy; with one exception all relapsed within a year of cessation of therapy and all except 2 had been treated for more than 2 years; 6 have relapsed while still on maintenance therapy, 2 more than once, and these relapses have been as early as 5 months or as late as 11 years after beginning treatment; 8 patients (including some

TABLE 8
THERAPY WITH PERCHLORATE

Patient	Age (yr.)	Initial Dose (mg./day)	Maintenance Dose (mg./day)	Duration of Therapy (mth.)	Time Since Stopping Therapy (mth.)	Result
J.C.	7	400-600	—	3 wk.	—	No effect (C)
P.C.	10½	800	—	27	1	Euthyroid
C.D.*	15	1,500	500	18	Continues therapy	Euthyroid
J.E.	11½	400	200	17	5	Relapsed
V.M.(1)	11½	400	300-600	16	—	Relapsed
(2)	13	500	500	20	—	Unsatisfactory (C) (S)
C.M.†	14½	1,000	200	5	12	Euthyroid
L.R.(1)	10½	1,500	250	38	5	Relapsed
(2)	—	1,000	—	—	—	—
K.V.	10	300	400	6	6	Euthyroid
S.W.	5½	700	300	14	Continues therapy	Euthyroid

N.B. In 5 patients the PBI fell to hypothyroid levels.

* Previously treated with carbimazole.

† A mongol child in whom assessment was difficult.

(C) Subsequently treated with carbimazole.

(S) Subsequently treated by operation.

TABLE 9
DAILY DOSAGE OF DRUGS USED IN DIFFERENT PUBLISHED SERIES

Drug		Present Series	Hung <i>et al.</i>	Root <i>et al.</i>
Methyl or propyl thiouracil	{ Initial (m.g.)	50-300	300	150-300*
	{ Maintenance (m.g.)	25-50	100-150	50-150*
Carbimazole	{ Initial (mg.)	15-40	40	15-30*
	{ Maintenance (mg.)	5-20	10-20	5-15*
Sodium or potassium perchlorate	{ Initial (g.)	0.3-1.5	3.0	
	{ Maintenance (g.)	0.2-0.6	0.5-0.75	

* Initial doses expressed as 6.7 mg./kg. and 0.6-0.8 mg./kg. respectively and maintenance as one-third to one-half of these doses.

who have previously relapsed) are at present euthyroid while on therapy having been treated for periods of up to 12 years.

It is difficult to compare the results of therapy in the series with those of other workers; numbers are small and other factors are too variable (e.g. duration of therapy and of follow-up after therapy has ceased). Nevertheless they differ probably only slightly from those reported by Hung *et al.* (1962) and Root *et al.* (1963). In the former 15 of 28, and in the latter 7 of 14, patients have so far remained euthyroid for more than a year after one or two completed courses of medical therapy. In the former series, only 5 of 33 patients were treated by operation; in the latter 7 of 17. In the present series, 7 of 17 adequately treated medically have remained euthyroid for over 1 year following cessation of therapy and 6 of 23* have come to operation. It is possible that smaller dosage of drugs may be responsible for the difference (Table 9).

The average initial doses of carbimazole and perchlorate used were about half those stated by Hung *et al.* and Root *et al.* The incidence of drug reactions, 1 in 33, was less than in either of these series. With the 2 patients in this series who were given clearly inadequate dosage this comparison suggests that dosage must be higher than the minimum needed to control symptoms. The risk of more frequent toxic reactions may be outweighed by the higher proportion of patients who do not require operation. Very few patients, provided co-operation is adequate and toxicity does not occur, require operation before puberty. In view of the high incidence of post-operative hypothyroidism this is an important advantage.

The optimum duration of therapy is even more difficult to assess. Three of the present series were apparently cured by one course of less than 6 months' duration. Three others have not responded permanently in 6, 8, and 12 years, respectively. Such prolonged therapy is undesirable, for there is always

the risk of 'breaking through' control especially if after long periods administration of the drug becomes less regular.

The scheme suggested by Root *et al.* seems the best compromise. Drugs are used for two years and then stopped. One relapse is treated similarly but any subsequent relapse is an indication for operation as are toxic drug reactions and lack of co-operation. It also seems reasonable to treat pre-pubertal patients medically even if this means more than 2 years of therapy.

Summary

In an attempt to assess the value of medical therapy of thyrotoxicosis in children, the progress of 33 children was studied. Most were girls and the onset of symptoms occurred at all ages after 4 years. The more valuable diagnostic features were nervousness, proptosis, goitre, tachycardia, sweating, and abnormal movements. Excessive growth was common. Abnormal behaviour tended to delay the diagnosis. Special investigations were of relatively slight value in the initial diagnosis but facilitated the later supervision.

One of 9 children treated by operation died; one more has relapsed. All except 1 of 23 who were given adequate medical therapy were controlled without difficulty. About one-third have remained euthyroid for over a year after the cessation of therapy. Similar proportions have relapsed either on maintenance therapy or within a year or so of its cessation. The slightly lower dosage of drugs used (compared with other series) may have accounted for this less satisfactory result and for the lower incidence of drug toxicity.

On the basis of this and other series it is suggested that a two-year course of medical therapy should be given in the first place. A relapse should be followed by a second course also lasting two years. Any further relapse should be treated by operation.

Thanks are due to the Physicians of The Hospital for Sick Children for permission to include patients under their care in this series.

* E.H. and J.C. are omitted from this total.

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Addendum

Since this paper was submitted, a review of 70 patients cared for over 20 years has been published by Saxena, Crawford, and Talbot (1964). 52 were treated surgically. Permanent hypothyroidism occurred in 18 (38%), and hypoparathyroidism with tetany in 10%. Three developed a recurrence of thyrotoxicosis. The remaining 18 patients had been treated with iodides and latterly antithyroid drugs. The follow-up of most of these was too brief to draw conclusions.

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