FURTHER STUDIES ON THE RECOVERY OF THYROID FUNCTION IN NON- ENDEMIC GOITROUS CRETINISM

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As previously reported, we have been able, through the short-term administration of unphysiologically large doses of thyroid substances, temporarily to return to normal disturbed thyroid function in two siblings who suffered from sporadic goitrous cretinism due to genetically determined enzymatic defects (Zondek *et al.*, 1958, 1959, 1960a, 1960b). As a result of this "stoss-therapy" both patients remained perfectly euthyroid for the next six to seven months without further treatment. Their hitherto very voluminous, partially diffuse and partially nodular goitres remained greatly reduced or virtually absent during these periods.

Investigations of thyroid function performed before treatment revealed a steep rise of thyroidal ^{131}I uptake to abnormally high values during the first two hours followed by a gradual drop to abnormally low values at 24 and 48 hours. This pattern, together with the low serum protein-bound iodine (P.B. ^{127}I) found in both siblings, is suggestive of an inability of the thyroid gland to hold and utilize the trapped iodide—that is, of a metabolic block involving the first stages of hormone synthesis. In contrast, the uptake curves showed in one sib a practically normal pattern three and four months

after stoss-therapy and, in the other, elevated values three weeks and two months after stoss-therapy.

The third affected sib came under our observation about a year and a half ago. Our purpose is to report the results of stoss-therapy in this patient, special stress being laid on serial investigations of thyroid function performed on a more extensive scale than in the other two sibs.

Case Report

The patient, a man aged 24, was one of a family of nine sibs, two more of whom were similarly affected. He had been given thyroid therapy only sporadically in the past and had had none during the last three years. On admission he was as severely myxoedematous as the other two affected sibs when first seen by us. He was of small stature (1.51 m.) and his appearance and behaviour were characteristic of myxoedema. The face was puffy, the skin dry and wrinkled, the voice hoarse, and the speech and general responsiveness were slow and sluggish. The pulse rate was 56–60 per minute, the heart shadow was somewhat enlarged to the left, and the Achilles tendon reflexes were sluggish. The basal metabolic rate was -34% , and serum cholesterol was 230 mg./100 ml. The patient had a large goitre in which three nodules the size of large walnuts were imbedded. The serum P.B. ^{127}I was less than $0.75 \mu\text{g.}/100 \text{ ml.}$, and thyroidal ^{131}I uptake followed exactly the same pattern as in investigations previously undertaken in his two sibs (first line of Table). Previous examinations at another hospital had revealed an identical uptake pattern, and, moreover, a practically complete discharge of the trapped iodide by potassium thiocyanate (Steinberg and Czerniak, 1955).

The patient was given stoss-therapy in the same manner as his two sibs (90 mg. of "triac" within nine days), and he also became free from goitre—with the exception of a small remnant the size of a hazel-nut in the middle lobe—and clinically in every respect euthyroid, the symptoms and signs described above having fully regressed in the course of treatment. The B.M.R. was -9% on the last day of therapy, and rose to ± 0 seven days later. The patient has remained euthyroid and virtually free from goitre up to the time of writing—that is, 18 months after stoss-therapy was discontinued (see Figs.).

As regards thyroid function, the following data seem pertinent. During stoss-therapy the two-hour uptake was, as expected, largely suppressed. The 24-hour uptake was, however, only slightly lower, and the 48-hour uptake was even somewhat higher than the corresponding values in the

Serial Investigations in Case of Familial Sporadic Cretinism with Goitre Before, During, and After 90 mg. of Triac

	Clinical State	B.M.R. %	Goitre	Serum P.B. ^{127}I $\mu\text{g.}/100 \text{ ml.}^*$	Thyroidal ^{131}I Uptake (% of Dose) †						
					2 hr.	4 hr.	24 hr.	48 hr.	72 hr.	96 hr.	148 hr.
Before treatment	Myxoedema	-34	+++	<0.75	60		30	15			
During "			++		9.1	12.5	21.1	22.8			
4 days after ..	Euthyroid	-12	++	3.2	28.8		63.8	66			
1 month after ..	"	+9.5	++	6.1	15	17.2	34.2	30.2			
3 months after ..	"	-6	++	3.3	11.8	18.5	25.0	28.5			
6 " "	"	-10	++	3.2	32	53.5	90	52	50	48.5	41
7½ " "	"	+4	++		36	51	52.5	46	35	32	
9 " "	"	± 0	++		61.6		55.5	46.6		37.5	33.6

	Urinary Excretion (% of Dose)		Total Plasma ^{131}I (% of Dose l.)						P.B. ^{131}I (% of Dose/l.)					Non-butanol-soluble ^{131}I (% of Dose l.)			
	24 hr.	48 hr.	24 hr.	48 hr.	72 hr.	96 hr.	148 hr.	24 hr.	48 hr.	72 hr.	96 hr.	148 hr.	24 hr.	48 hr.	96 hr.	148 hr.	
Before treatment		14.0	1.6														
During "	54.5	8.2	0.88	0.2				0.08	0.06								
4 days after ..	41.5	5.5	0.96					0.37									
1 month after ..		6.0	0.52					0.05									
3 months after ..	44.5	3.2	0.32					0.05									
6 " "	6.9	3.2	0.36	0.56				0.19	0.43				0.041	0.09			
7½ " "	19.5		0.76	0.88	1.16	1.4		0.37	0.56	1.0	0.86						
9 " "	17.5	9.4	1.7	1.2		1.8		1.05	0.83		1.44	1.6	0.12	0.15	0.31	0.28	

* Normal range: $3.5\text{--}5.5 \mu\text{g.}/100 \text{ ml.}$ † With the exception of the last examination, when $300 \mu\text{c.}$ was given, $50 \mu\text{c.}$ ^{131}I was administered by the oral route.

untreated state. The conversion ratio was low (second line of Table), yet it is evident that the gland was already to some extent able to bind elementary iodine to protein. Five to seven days after the withdrawal of therapy, ^{131}I uptake was surprisingly high, while the conversion ratio was

Patient, aged 24, with familial sporadic cretinism with goitre. Left: Before treatment. Right: Same patient seventeen months after "stoss' therapy."

normal (third line of Table). One month and three months after stoss' therapy thyroid function was in the low normal range, or, as regards iodine binding, even below normal (fourth and fifth lines of Table).

This almost induced us to believe that the patient's thyroid gland, unlike those of his younger brother and sister, would lose its functional capacity at a comparatively early date. However, to our surprise, tracer studies performed at six, seven and a half, and nine months after stoss' therapy (sixth to eighth lines of Table) revealed an abnormally active pattern which was maintained during observation periods ranging up to seven days as regards both iodine uptake and the formation and release of a P.B.I. compound into the circulation. The urinary excretion of ^{131}I did not always conform to the uptake and conversion values, being at times even at variance with either or both of them (see, for example, the last line of Table). Total plasma ^{131}I activity was uniformly high during the whole period of observation and there was a distinct tendency towards its continuous rise during the two extended observation periods at seven and a half and nine months after stoss' therapy. The serum P.B. ^{127}I was at the lower range throughout the whole period of observation with the exception of one value above the upper normal limit. The butanol-insoluble fraction of the circulating iodine compound, which was determined only during the later stages of the remission, ranged, with the exception of one value, between 11 and 17%, as compared with normal values of 5 to 8% for our laboratory. The presence of thyroxine in the butanol-soluble fraction nine months after the triac stoss was demonstrated by paper chromatography performed with the ascending technique, using butanol-dioxane-ammonia (Gross, 1954); the chromatograms revealed definite evidence of thyroxine 24 and 48 hours after the ingestion of ^{131}I ; however, for technical reasons the exact amounts could not be determined. The nature of other iodine compound(s) in the chromatograms could also not be determined.

Discussion

The foregoing data demonstrate again that unphysiological quantities of thyroid substances—that is, quantities considerably greater than the amount produced daily by the thyroid and required by the organism—can induce functional recovery of the genetically diseased thyroid gland of goitrous cretins, and a prolonged clinical remission lasting in the case presented here so far for 18 months. In the two other

affected siblings the same therapeutic procedure (stoss' therapy) had also resulted in long-standing remissions, which, however, on no occasion exceeded seven months. In these two the functional state of the thyroid gland had been investigated only during the first half of the therapy-free remissions, while in the present case tracer studies were performed during both the early and the later stages of the remission.

Irrespective of the clinical state, we can distinguish in this patient three phases of thyroid activity induced by stoss' therapy: (1) immediately after its discontinuation, a rise; (2) one month and three months later, a drop to the low normal range; and (3) at six, seven and a half, and nine months after stoss' therapy, an even greater rise simulating in some respects genuine hyperfunction. At any rate ample evidence is provided by our investigations that—especially during the later stages of the remission—the thyroid was rendered not only capable of holding large amounts of iodine but also of forming therefrom P.B.I. and of releasing it into the circulation. The fact that the patient remained euthyroid and practically agoitrous indicates that at least part of the material was biologically active. This assumption was borne out by the chromatographic separation of the circulating iodine compound which revealed the presence of thyroxine in amounts which, in view of both the clinical state and the increase of the serum P.B.I. content, may be safely assumed to exceed those secreted in the pre-treatment period. This finding must be regarded as the crucial observation of the whole laboratory investigation.

The inconsistencies in this study—for example, the lack of correlation between ^{131}I uptake and excretion, or between the serum P.B. ^{127}I and P.B. ^{131}I —are as yet unexplained. Besides an increased re-utilization of iodine in the thyroid, an abnormal turnover of thyroid hormone in the peripheral tissues may be postulated. This will be the subject of further investigations.

The observation that in this patient (as also in the other two affected sibs) large doses of active thyroid substances failed to produce the practically complete suppression of thyroid activity which we are accustomed to find in nearly all conditions other than present and past hyperthyroidism may also be added to the list of notable findings in this group of patients.

We are not in a position to state with certainty in what way the at least partial correction of the genetically transmitted enzymatic defect of thyroid hormone synthesis was brought about. Nevertheless, we think as already suggested in previous communications (Zondek *et al.*, 1958, 1959, 1960b) that the end-product of thyroid secretion, if administered in doses exceeding the physiological range, may restore to normal a disturbed interaction between thyroid enzymes and the hormone-producing cell particles, thus setting in motion an intracellular mechanism regulating thyroid secretion.

Summary

The case is presented of a 24-year-old familial sporadic cretin with goitre in whom thyroid deficiency was due to a genetically transmitted inability of the gland to hold and utilize the trapped iodide. The short-term administration of unphysiologically large doses of thyroid substances produced in this patient a clinical remission with almost complete regression of the goitre which has so far lasted for one and a half years.

(Similar remissions, though of shorter duration, had previously been achieved with both triac and desiccated thyroid in two similarly affected sibs.)

Thyroid function was investigated during "stoss-therapy" and during both the early and the late stages of the remission. During stoss-therapy thyroid activity was suppressed only at two hours after the administration of the tracer, but not at 24 and 48 hours. Immediately after the discontinuation of stoss-therapy there was a hyperactive uptake pattern; one and three months later, a low-normal; and six, seven and a half, and nine months later a hyperactive pattern as to ^{131}I uptake, total activity, and conversion which was manifest during observation periods ranging up to seven days. The butanol-soluble fraction of the circulating ^{121}I compounds was somewhat lower than normal. Its chromatographic separation nine months after stoss-therapy revealed the presence of thyroxine and of another, as yet undefined, iodine compound(s). The serum P.B. ^{127}I was, with one exception, at the lower limit of the normal range throughout the whole course of observation.

The implications of these observations are discussed. It is suggested that the end-product of thyroid secretion, if administered in amounts exceeding the physiological range, induces a recovery of thyroid function by correcting a genetically disordered interaction between intracellular thyroid enzymes and hormone-producing cell particles (thyroidal autoregulation).

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"A noticeable change in the last ten years [in the general medical, haematological, endocrinological, and mental observation departments] is the increasing number of coloured people both in wards and out-patients; their diseases generally differ little from European illnesses except that they are occasionally infested with hookworm and so develop its resultant anaemia (a condition which can be easy to miss when their pallor is masked by their pigment). As a community they have a smaller number of old people than we do. The old people stay in the West Indies, while the young come to earn better money in England. Family feeling seems strong, and many regular payments are posted back home by those working here. As patients, they are shy and often suspicious, and their speech is so different from ordinary English that the exchange of ideas is slower and less accurate than with English patients. For these reasons West Indians sometimes appear to be moody, morose or ungrateful as patients when they are really embarrassed and fearful. Because their standard of education is lower, instructions like measuring insulin or adhering to particular articles of food are harder to explain. Although their homes are mostly of a lower standard than the average European, their health does not seem to be affected by this except that they have to be taken to hospital for minor illnesses which otherwise might have been managed at home." (Dr. Richard Asher in *Central Middlesex Hospital Annual Report*, 1959.)

THYROID FUNCTION IN THE EUTHYROID PARENTS OF THREE NON-ENDEMIC GOITROUS CRETINS

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We have under observation three siblings with goitrous cretinism who were born and reared in Israel, a comparatively goitre-free region. They are the fourth, fifth, and eighth of nine children, the other six being clinically healthy. Both parents come from Iraq, from allegedly healthy, unrelated families.

The purpose of this paper is to report the results of tracer studies in the parents. Observations on the affected offspring have been reported elsewhere (Zondek *et al.*, 1958, 1959, 1960a, 1960b, 1961).

The father, aged 62, is healthy and has no complaints. He is clinically euthyroid, and the thyroid gland was normal on palpation. The B.M.R. was +3%, and the serum cholesterol 210 mg./100 ml.

FIG. 1.—Clinically euthyroid mother, aged 50, of three non-endemic goitrous cretins.

His serum protein-bound iodine (P.B. ^{127}I) was 3.4 $\mu\text{g.}/100\text{ ml.}$ (normal range, 3.5–5.5 $\mu\text{g.}/100\text{ ml.}$), and tracer studies revealed perfectly normal values with regard to both uptake and conversion of ^{131}I ; thyroidal uptake was 12.2% at two hours, 20% at four hours, 39% at 24 hours, and 37% at 48 hours. The conversion ratio was 35% at 24 hours and 46% at 48 hours.

The mother, aged 50, at first sight has endocrine stigmata: she is of small stature (1.44 m.), is fat (50 kg.), and mentally dull, and she has a cretinoid appearance, with narrow palpebral fissures and a depressed root of the nose (Fig. 1). The thyroid gland is normal to palpation except for a very small nodule in the middle lobe.

From the clinical viewpoint the mother's thyroid function was found normal in all respects: B.M.R., -2%; serum cholesterol, 226 mg./100 ml.; heart function and configuration normal; E.C.G., normal. The serum P.B. ^{127}I was 4 $\mu\text{g.}/100\text{ ml.}$ Twice-repeated tracer studies (see Table and Fig. 2) revealed