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MODIFICATIONS OF THYROID FUNCTION INDUCED BY CHRONIC ADMINISTRATION OF IODIDE IN THE PRESENCE OF «AUTONOMOUS» THYROID TISSUE

By

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ABSTRACT

Fourteen patients were studied before and during administration of a daily supplement of 0.5 mg of iodide over a period of 3 to 10 months. Only a slight increase in PBI was observed in three patients with a non-toxic goitre and in two myxoedematous patients under treatment.

The same supplements of iodine induced a marked rise in PBI in four euthyroid patients with a typical thyroid »hot« nodule. In the four cases, the PBI values reached the thyrotoxic range after only a few weeks. These elevated values were maintained throughout the period of iodine administration; data for the thyroxine content of the serum were strictly correlated with the PBI values. The T₃-resin test measurements also gave values characteristic of hyperthyroidism. Later on, three of these patients developed definite symptoms of hyperthyroidism, although not until several months after the appearance of the biological picture.

Finally a definite increase in PBI was also observed, albeit to a lesser

Supported by a grant of the Fonds de la Recherche Scientifique Médicale and by the contract Euratom-ULB-Pise (BIAC 026.63.4). Partly presented at the Sixth International Conference, Vienna, June 1970.

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extent, in five thyrotoxic patients previously treated with radioiodide or with methimazole. A progressive fall in the PBI was found in four patients after iodine supplements were discontinued.

These observations indicate that chronic iodine supplementation leads to marked over-production of thyroid hormones in two pathological conditions characterized by the presence of autonomous thyroid tissue. It is concluded that, in the absence of an adequate feed-back control mechanism, the amount of dietary iodine may be one of the main regulatory factors involved in thyroid activity in human subjects.

For many years, iodine has been added to the diet in several countries with the aim of overcoming a deficient iodine supply. Iodine deficiency has indeed been recognized as the major aetiological factor of endemic goitre. According to the British Bureau of Nutrition, minimal needs of iodine for adult men would be covered by a daily intake of 100 μg . The regular diet in Belgium (*Ermans & Camus 1966*) and in other European countries (*Harrison et al. 1955; Wayne et al. 1964*) is usually slightly lower. In other areas this level has been greatly exceeded since the introduction of iodized salt, iodine intakes of 300 and even 700 μg are reported by different investigators (*De Groot 1966; Gaitan et al. 1968; Pittman et al. 1969*).

Well-documented studies have demonstrated the harmlessness of large amounts of supplemental iodine in normal men. In this respect it has been confirmed that long-term administration of 0.1 and 1 mg of iodine per day does not modify the blood level of the thyroid hormones (*Pittman et al. 1969; Koutras et al. 1964; Fisher et al. 1965; Freund et al. 1966*).

For iodine intakes lower than 1 mg a day, adjustment of the iodine uptake in the thyroid gland is ensured by the thyro-hypophyseal feed-back mechanism: this control mechanism is known to depend on the peripheral level of the thyroid hormones (*Danowski 1962*). There is however some evidence of a small increase in the absolute iodine uptake of the thyroid gland after chronic administration of moderate doses of iodine (*Koutras et al. 1964; Fisher et al. 1965*).

In some thyroid disorders, the thyroid tissue can escape the thyro-hypophyseal feed-back mechanism. Thus autonomous activity has been shown to be one of the basic pathological features in Basedow's disease and in the »hot« thyroid gland (*Werner & Spooner 1955; Hales et al. 1961; Demeester-Mirkin & Ermans 1968*). In these conditions, iodine uptake in the thyroid gland remains unchanged or decreases only slightly when TSH stimulation is depressed by the administration of thyroid hormones.

The question thus arises as to how iodine supplements influence thyroid function in pathological situations in relation to the activity of autonomous thyroid tissue. The present investigations were undertaken to try and throw more light on this question. The long-term action of extra-iodine was in-

vestigated in patients with either treated thyrotoxicosis or non-toxic »hot« nodules. A similar investigation was carried out as a control experiment, i. e. in patients with simple goitre or with treated hypothyroidism.

MATERIAL AND METHODS

Fourteen patients suffering from different thyroid disorders were given a supplement of 500 μg of stable iodide for a period of 3 to 10 months. The iodine supply related to the food intake was postulated to be similar in all the patients during this period. All but two (patients No. 1 and No. 2) were female. Clinical and biological data obtained before supplementation began are shown in Table 1. The patients were divided into four groups.

Group I

Three euthyroid patients each with a small, diffuse or nodular goitre. Routine investigations showed that the thyroid function was within the normal range of the values obtained in this laboratory (Table 1).

Group II

Two patients with severe myxoedema treated with small doses of triiodothyronine or thyroid extract; substitution treatment was maintained without modification during the present investigations.

Group III

Four euthyroid patients with a thyroidal »hot« nodule. The scintigram of the thyroid gland performed 24 h after the administration of 50 μCi ^{131}I shows a single hyperactive nodule; the remainder of the gland was not visualized. A euthyroid condition was diagnosed on the basis of the clinical findings and of the values obtained for the plasma PB^{127}I and for the T_3 -resin test. As shown in Table 1, the four patients presented abnormally high values of plasma PB^{131}I at the 24th hour; as reported previously (Demeester-Mirkin & Ermans 1968), this finding is associated with the presence of an autonomous »hot« nodule, even in the absence of thyrotoxicosis.

Group IV

This group consisted of five patients previously treated for thyrotoxicosis associated with a diffuse or multinodular goitre, none of them showing exophthalmos or related abnormality of the eyes. Patient No. 1 had methimazole treatment for 18 months; this had been discontinued 9 months before the start of the present investigations. Patients 2, 6, 9 and 11 had been treated with ^{131}I , 2 to 6 years previously; three of them gave clinical and biological evidence of hypothyroidism when the present study was started (Table 1).

Iodide supplements were administered in the form of Lugol's solution which was given to the patients in three drops, measured by means of a calibrated pipette (1 drop = 55 μg of stable iodide), three times a day, during meals.

The blood and urine samples were collected immediately before administration of supplemental iodine and afterwards, at intervals of 1 to 4 months. Collections

Table 1.
Clinical and biological data before the administration of supplementary iodide.

Group	Diagnosis	Patient Number	Age (years)	¹³¹ I thyroid uptake % d/24 h	Plasma PB ¹³¹ I % d/l 24 h	Plasma PB ¹²⁷ I µg/100 ml	T ₃ -resin test (% control serum)	Clinical status.
I	»Simple« goitre	21	49	58	0.04	6.4	—	Euthyroid
		22	57	38	0.05	6.9	92	id.
		23		49	0.01	5.9	99	id.
II	Treated myxoedema	8	67	—	—	2.6	—	Slight hypothyroid
		31	54	—	—	2.2	73	id.
III	Non toxic »hot« nodule	3	38	65	0.52	7.6	96	Euthyroid
		4	28	49	0.11	6.2	97	id.
		5	63	51	0.92	7.4	92	id.
		14	42	69	0.17	7.2	130	id.
IV	Treated thyrotoxicosis	1	40	83	0.11	5.2	102	Euthyroid
		2	76	76	0.52	4.3	71	Slight hypothyroid
		6	62	15	0.23	2.5	57	Hypothyroid
		9	65	16	—	1.7	—	Hypothyroid
		11	61	46	1.08	6.2	94	Euthyroid
Normal range				35–55	< 0.10	4–8	85–115	

were generally performed at 3 to 4 p.m. The levels of plasma $PB^{127}I$ and of total iodine were determined in all the blood samples; the measurements of T_4 -iodine and of the T_3 -resin test were also carried out in some samples. Urine samples were used for the measurement of total iodine content.

Iodine concentrations were estimated according to the method of *Barker et al.* (1951), adapted for use with a Technicon Analyser as described in a previous study (*Camus et al.* 1968); plasma $PB^{127}I$ measurements were carried out after extraction of iodide by an ion exchange resin (Iobeads Technicon). It was observed that after the addition of increasing quantities of iodide to normal human serum, iodide extraction by the resin was complete (100%) up to an iodide concentration of 500 $\mu g/100$ ml. In order to prevent any contamination due to increased iodine intake, three successive extractions of plasma iodide with the Iobeads Resin were carried out, before the chemical assay of the $PB^{127}I$. Measurements were made in duplicate.

The T_3 -resin test was performed according to the method of *Mitchell et al.* (1960) by means of Triosorb (Abbott); the results are expressed as a percentage of the values obtained in a control serum collected from normal male subjects. Thyroxine assays were carried out according to the method of *Murphy et al.* (1966) by means of Tetrasorb (Abbott); the results are expressed as T_4 - ^{127}I in $\mu g/100$ ml of plasma.

RESULTS

Behaviour of plasma $PB^{127}I$

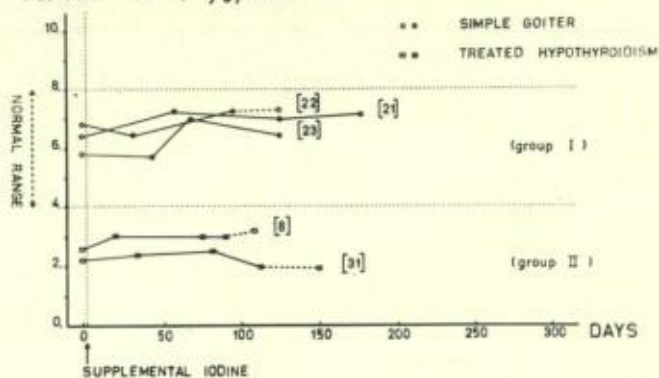
$PB^{127}I$ levels in the plasma are shown in Figs. 1, 2 and 3 as a function of the time elapsed after the extra-iodine administration had started. In patients with simple goitre (group I) and in patients treated for hypothyroidism (group II), these levels retain approximately constant values (Fig. 1): for both groups, the difference between the starting level and the maximum value observed during supplementation corresponds to an average increase of 0.6 ± 0.3^1 $\mu g/100$ ml.

In four euthyroid subjects with a »hot« nodule (Fig. 2) a quick rise of the $PB^{127}I$ into the thyrotoxic range is already observed for all the patients only a few weeks after the start of the iodine supplementation. Thereafter as shown in Fig. 2, the $PB^{127}I$ levels go up progressively or are maintained at high levels during the whole supplementation period, i.e. from 6 to 10 months. The mean $PB^{127}I$ values reach 10.3 ± 1.3 $\mu g/100$ ml between the 3rd and the 4th month, the maximum difference from the starting level corresponds to an average increase of 3.7 ± 1.7 $\mu g/100$ ml. For patient 3, a marked fall in $PB^{127}I$ can be observed after the 6th month; this is related to the onset of treatment with an antithyroid drug.

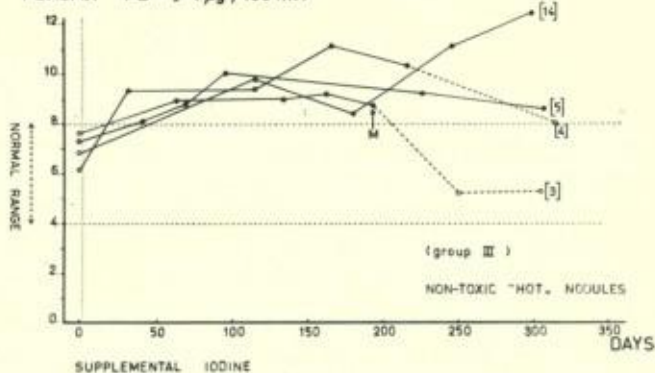
The results obtained from the patients previously treated for thyrotoxicosis (group IV) are less homogenous (Fig. 3). In patient 1, who had previously been treated with methimazole, the $PB^{127}I$ levels showed a progressive rise

¹) Standard deviation.

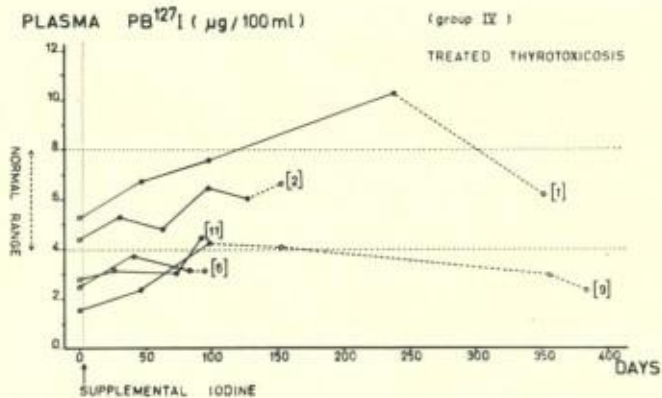
PLASMA $PB^{127}I$ ($\mu g/100 ml$)



PLASMA $PB^{127}I$ ($\mu g/100 ml$)



PLASMA $PB^{127}I$ ($\mu g/100 ml$)



for several months and also reached the range of thyrotoxicosis. Among the four patients pretreated with radioiodine, the maximum $PB^{127}I$ increase was respectively 1.9, 1.3, 2.4, and 1.2 $\mu g/100$ ml for patients 2, 6, 9 and 11. For all the patients of group IV, the mean difference between the starting level and the maximum $PB^{127}I$ value under iodine administration was 2.3 ± 1.4 $\mu g/100$ ml.

The $PB^{127}I$ levels were followed in patients 1, 3, 4, 9 and 11 after iodine supplements had been discontinued (Figs. 2 and 3). A progressive decrease in $PB^{127}I$ occurs and initial values are regained after a lapse of 2 to 6 months.

Modifications of total iodine in the blood and in the urine

Measurements of total iodine in the plasma have been plotted in Fig. 4 against the corresponding values of the $PB^{127}I$ obtained in the same samples. The difference between the assays gives an estimate of the concentration of plasma iodide. Before supplementation, this difference is in the range of 0.2 $\mu g/100$ ml which, is within the limits of error of the technique. For the samples collected during the administration of iodine, the iodide concentration rises to an average of 1.0 $\mu g/100$ ml, and in 28 samples out of 32 it is lower than 2.0 $\mu g/100$ ml.

The mean concentration of urinary iodine averages 3.4 ± 2.1 (range 1.5 to 6.2) $\mu g/100$ ml before iodine administration. During supplementation, all the samples give values higher than 20 $\mu g/100$ ml; after appropriate dilution of the urine samples, the iodine concentration is found to average 38.6 ± 34.0 (range: 20.0 to 88.5) $\mu g/100$ ml in ten samples.

Modifications of T_3 -resin test measurements and of the plasma thyroxine content

Results of the T_3 -resin test, carried out in eight patients before and during iodine supplementation, are shown in Fig. 5. In four of the patients, who did not show a marked increase in plasma $PB^{127}I$, the resin-uptake of T_3 remains remarkably constant (Fig. 5, left part).

On the other hand, in four patients, in whom extra-iodine had caused a significant rise in $PB^{127}I$, the T_3 -resin test also showed a marked increase, this reached the thyrotoxic range ($> 115 \%$) in three cases in which the $PB^{127}I$ levels were higher than 8 $\mu g/100$ ml (Fig. 5, right part).

The levels of thyroxine ^{127}I were estimated in 40 plasma samples arbitrarily chosen in the course of the present investigation; the results are compared to

Figs. 1, 2 and 3.

Modifications of plasma $PB^{127}I$ induced by continuous administration of 0.5 mg iodide per day, in patients with various thyroid disorders; Euthyroid goitre and treated hypothyroid subjects (Fig. 1), non-toxic »hot« nodules (Fig. 2) and formerly treated thyrotoxicosis with an actual hypo- or euthyroid state (Fig. 3).

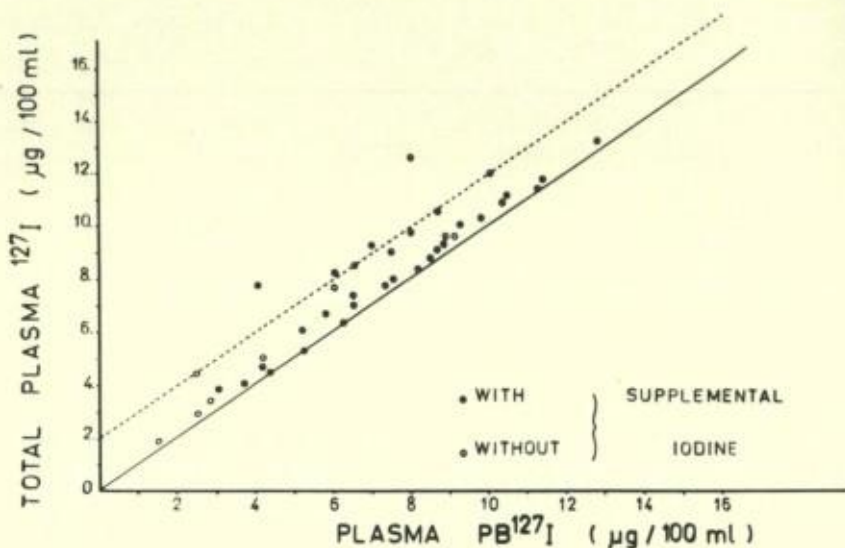


Fig. 4.

Comparison of the measurements of total iodine and $PB^{127}I$ in plasma, before or during the daily administration of 0.5 mg iodide. Strict equality of both values is represented by a continuous line. A systematic difference of $2.0 \mu\text{g}/100 \text{ ml}$ related to such a concentration of inorganic iodide in plasma is shown by the dotted line.

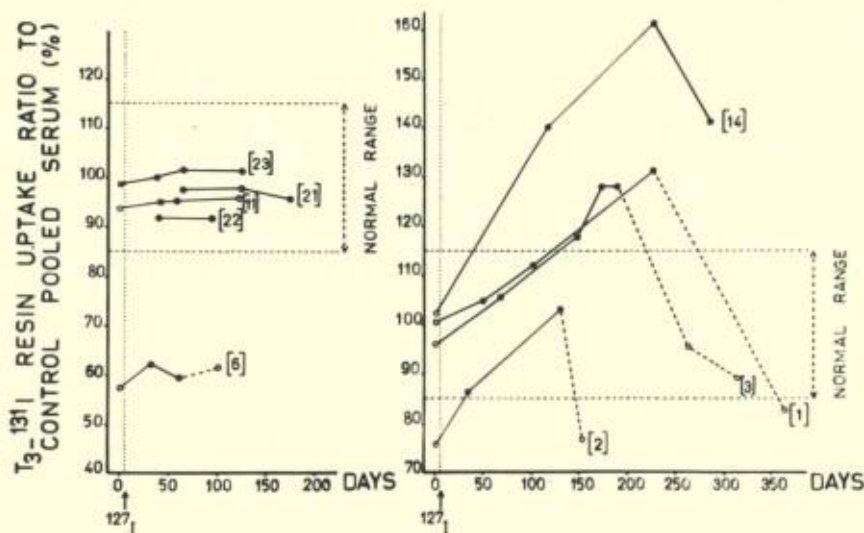


Fig. 5.

Values of the T_3 -resin test during iodide supplementation. Left: in four patients who did not show any definite increase in plasma $PB^{127}I$. Right: in four patients who, on the contrary, presented a marked increase in plasma $PB^{127}I$.

the corresponding values of the $PB^{127}I$ observed in the same samples (Fig. 6). A highly significant increase in the thyroxine levels appears, associated with the elevation of the $PB^{127}I$ values; nevertheless, as shown in Fig. 6 the thyroxine increase is found to be proportionally reduced in contrast to the $PB^{127}I$ rise.

Clinical changes induced by the extra-iodine

Among the five patients whom the rise in plasma $PB^{127}I$ induced by the extra-iodine reached the range of thyrotoxicosis, three developed clear cut symptoms of hyperthyroidism 6 to 9 months after the iodine administration had started (pat. 3, 4 and 14). Before this time, repeated clinical examinations failed to detect any symptoms of thyrotoxicosis, in spite of the considerable rise in $PB^{127}I$ and in the T_3 -resin test values for several months. Table 2 summarizes the principal clinical and biological findings observed in these patients. None of the patients presented any ocular abnormalities. Two other subjects (No. 1 and No. 5) who also had a very high $PB^{127}I$, did not show any clinical symptoms of hyperthyroidism at any time during the present investigations. None of the other patients had any obvious clinical changes following iodine administration, with the exception of patient 9 who showed a perceptible reduction in the symptoms of hypothyroidism.

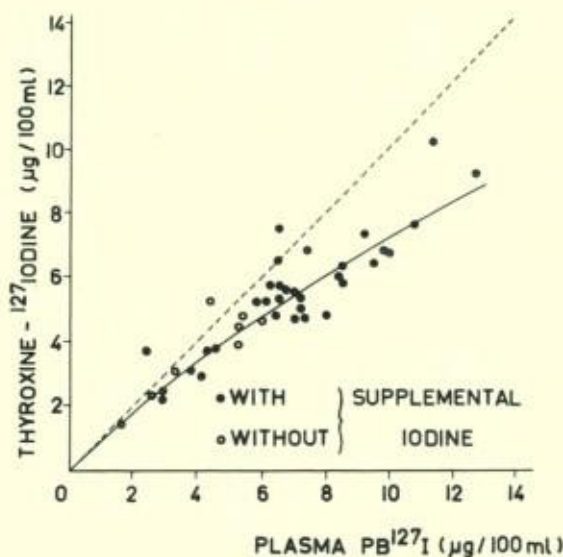


Fig. 7.

Comparison between the measurements of thyroxine - ^{127}I and $PB^{127}I$ carried out on the same plasma samples. The samples were collected either before or during the iodine supplementation. Solid line corresponds to the observed relationship between both estimations, the dotted line to a strict equality of both values.

Table 2.

Appearance of clinical signs of thyrotoxicosis in three patients with thyroid »hot« nodule submitted to continuous iodine supplementation (0.5 mg IK/day).¹⁾

Patient	Lapse of time ²⁾	Plasma PB ₁₂₇ I (μ g/100 ml)	T ₃ -resin test (% of normal)	Clinical changes ³⁾	Further evolution ⁴⁾
No. 3	6 months	8.9	130	Tremor, profuse sweating, weakness, marked activity; no tachycardia. Loss of weight (3 pounds)	Treatment with methimazole started. One month later: complete correction of the clinical symptoms; gain of weight 3.6 kg; PB ₁₂₇ I and T ₃ -resin test normal
No. 4	7 months	10.4	111	Tremor, weakness, increased nervousness. Loss of weight (6 pounds). Tachycardia (27×4)	No antithyroid drugs. Three months later: complete correction of the clinical symptoms. Pulse rate: 20×4 . Gain of weight 1.8 kg; PB ₁₂₇ I and T ₃ -resin test normal
No. 14	9 months	12.9	141	No complaint about increased nervousness. Tachycardia (25×4). Loss of weight (10 pounds).	No antithyroid drugs. Follow-up not possible

¹⁾ »Euthyroid« state was carefully assessed before iodine supplementation (Table 1).

²⁾ Lapse of time from the beginning of IK administration, when clinical changes were first noticed.

³⁾ The fourth patient (No. 5) of group III did not exhibit any thyrotoxic symptoms after 9 months.

⁴⁾ IK administration was immediately discontinued when clinical changes appeared.

DISCUSSION AND CONCLUSIONS

From a methodological point of view, the moderate increase in the plasma iodide concentration observed during iodine administration (i. e. about $2 \mu\text{g}/100 \text{ ml}$) precludes the possibility that iodine contamination of the samples could have interfered with chemical assays of the PB^{127}I . Indeed even for the higher values, the iodide concentrations remained ten times lower than the amounts of iodine discarded by a single resin extraction. The validity of the PB^{127}I assays is further emphasized by the slight difference observed before and during iodine treatment in two hypothyroid patients maintained on substitution therapy.

Finally, minor modifications of PB^{127}I levels during iodine supplementation in three subjects with a simple goitre confirm previous studies reported in normal subjects (Koutras *et al.* 1964; Fisher *et al.* 1965; Freund *et al.* 1966; Pittman *et al.* 1969): these findings are in agreement with an adequate response to the feed-back control mechanism.

The present investigations show that a supplementary supply of dietary iodine of 0.5 mg per day markedly increases the PB^{127}I levels in patients with thyroid disorders related to an autonomous activity of the gland; changes higher than $1.5 \mu\text{g}/100 \text{ ml}$ were observed in 7 patients out of 9; in five of them, the PB^{127}I values rose to the thyrotoxic range. This increase appears much faster and more markedly in untreated patients with a »hot« nodule. This response is less in patients previously treated with radioiodine; to some extent, this difference could be explained by the metabolic disturbances induced by the irradiation of the thyrotoxic gland by ^{131}I .

A series of arguments support the view that the increased PB^{127}I induced by supplementary iodine reflects a net increase in the production of thyroid hormones by the gland. First of all, this situation is associated with an increased thyroxine content in the plasma; secondly, as shown by the changes in the T_3 -resin test, modifications of the thyroxine-binding protein occur which are characteristic of thyrotoxicosis. Finally over-production of thyroid hormones was confirmed in three patients by the development of typical symptoms of thyrotoxicosis. In two of these patients, it was possible to reverse the situation by discontinuing iodine supplementation; in the third one, however, treatment with antithyroid drugs had to be started. It is interesting to note the lapse of several months which separates the onset of a complete biological picture of thyrotoxicosis and the development of the clinical syndrome.

The findings observed in these patients are in keeping with the absence of an adequate control of iodine accumulation and organification in the gland. With moderate doses, any available iodine appears to be incorporated and transformed into thyroid hormones, whatever the size of the iodine intake and the peripheral level of the thyroid hormones. In the presence of autonomous

thyroid tissue, the size of the dietary iodine supply thus appears as one of the main regulatory mechanisms of thyroid activity. Further evidence for this view is given by the observation of a progressive decrease in the $PB^{127}I$ levels when supplementary iodine is discontinued.

In special experimental conditions, an increased production of thyroid hormones in response to the administration of iodine has also been reported in rats; *Nagataki & Ingbar* (1966) observed a progressive increase in the amounts of T_4 and T_3 present in the thyroid gland after single injections of graded amounts of iodine, in doses as high as 100 μg . These acute modifications reflect the action of the iodine only, without any interference from the thyro-hypophyseal control mechanism which takes some time to come into operation. In this respect, this experimental procedure imitates the situation observed in human subjects with autonomous thyroid tissue. In both conditions, the thyroid gland appears unable to prevent increased synthesis of active hormones in response to the administration of moderate doses of iodine.

For larger doses, the incorporation of excessive amounts of iodine into the thyroid gland is known to be prevented by a selfregulatory mechanism often called the »Wolf-Chaikoff effect« (*Wolff & Chaikoff* 1948). In man, this control mechanism only comes into play when the plasma iodide reaches a concentration higher than 6 to 12 $\mu g/100$ ml (*Stanley* 1949). In our patients, the mean plasma iodide only reaches 1.0 $\mu g/100$ ml so it seems improbable that the self-regulatory mechanism would intervene when quantities of iodine such as are described in the present study, are administered (*Stanley* 1949; *Stewart & Murray* 1967).

In conclusion, the present data seem to explain the pathogenic mechanism of iodide-induced thyrotoxicosis and the increased prevalence of hyperthyroidism observed after iodine prophylaxis. They also imply the need to re-evaluate carefully the optimum iodine intake when iodine deficiency has to be corrected on a large scale. Indeed, even when taking into account that the general incidence of autonomous thyroid glands is very low, it is questionable whether the risk of inducing thyrotoxicosis in these subjects is really by the advantages of maintaining iodine intakes three to seven times larger than the amount corresponding to minimum needs.

ACKNOWLEDGMENT

The authors wish to thank Mrs. F. Dubois for her excellent technical assistance.

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Received on November 10th, 1971.