HYPOFUNCTION OF THE THYROID GLAND, DUE TO PROLONGED AND EXCESSIVE INTAKE OF POTASSIUM IODIDE

By

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ABSTRACT

Five patients are reported, who developed various degrees of thyroid hypofunction and/or goitre while taking iodide-containing mixtures for bronchial asthma. After stopping the iodide treatment, their thyroid condition returned to normal.

The clinical features of the condition are described. Particular attention has been paid to the factors responsible for the development of thyroid hypofunction. Most important among these was the prolonged, regular and high intake of iodides.

It is concluded that patients using iodide-containing medication should interrupt the intake for 2–4 weeks at a time, several times a year.

The mechanism by which iodine depresses the function of the thyroid gland is discussed.

Iodine, the indispensable element for thyroid hormone production, may under certain circumstances exert the paradoxical effect of inhibiting this process. It is well known that even minute doses of iodine seriously hamper the activity of the gland in Graves' disease (Plummer 1923; Childs et al. 1950).

There is also evidence that iodine also exerts an inhibitory effect on thyroid hormone production in normal glands. Large doses of iodine interfere with organic binding of the element both in the human (Stanley 1949) and in the rat thyroid. However, in spite of continued high blood levels of iodide, escape from the inhibition occurs after 1–2 days (Wolff et al. 1949). Continuous consumption of iodine has therefore generally been considered not harmful to the
healthy thyroid. This, however, is not entirely true. Prolonged ingestion of iodine in rather large doses may lead to the development of goitre and even myxoedema.

The purpose of the present paper is:
1. to draw attention to a condition that is not very well known, in spite of more than 50 recorded cases in the literature (none of which from Scandinavia). It is our belief that the condition is more common than previously thought. The reasons for this are:
   a. it is not diagnosed as such,
   b. it is possible that the development of iodine myxoedema, under certain circumstances to be described, is the rule rather than the exception.
2. to contribute to the clinical description of the syndrome, which has so far seen presented in short case reports, only 5 authors presenting more than 3 cases.
3. to comment on certain biochemical findings that have so far received scant attention, and in this connection comment on the mechanism and nature of the inhibitory effect.

METHODS

Serum cholesterol was determined by the method of Carr & Dreker (1956). Butanol extractable iodine in serum (BEI) was determined by the method of Kontaxis & Pickering (1958). Protein-bound iodine in serum (PBI) was determined by the method of Foss et al. (1960). With this method, iodinated tyrosines contribute to the PBI value when the proteins are precipitated with Zn(OH)₂. The following experiment was performed by Dr. O. P. Foss in order to see whether this is the case when the proteins are precipitated with trichloracetic acid (TCA):

Mono-iodotyrosine (MIT) and di-iodotyrosine (DIT) were dissolved in 0.01 N NaOH and diluted with distilled water until a final concentration of approximately 1 µg iodine/ml was reached. Mixtures of these solutions and serum from a serum pool were prepared as follows:

<table>
<thead>
<tr>
<th>Sample</th>
<th>Amount</th>
<th>µg organic iodine/ml</th>
<th>µg organic iodine/11 ml of sample</th>
<th>µg/100 ml organic iodine in sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>10 ml</td>
<td>0.064</td>
<td>1.63</td>
<td>14.8</td>
</tr>
<tr>
<td>+ MIT</td>
<td>1 ml</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>10 ml</td>
<td>0.064</td>
<td>1.62</td>
<td>14.7</td>
</tr>
<tr>
<td>+ DIT</td>
<td>1 ml</td>
<td>0.98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PBI was estimated after precipitation of the proteins by Zn(OH)₂ or TCA. All determinations were carried out in duplicate. The PBI value of the serum pool was established by 10 separate determinations, using precipitation with Zn(OH)₂.
<table>
<thead>
<tr>
<th>Sample</th>
<th>$\mu g/100~ml$ PBI after precipitation with $Zn(OH)_2$</th>
<th>$\mu g/100~ml$ organic iodine in the sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>12.0</td>
<td>6.3</td>
</tr>
<tr>
<td>Serum + MIT</td>
<td>13.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Serum + DIT</td>
<td>6.0</td>
<td>6.4</td>
</tr>
</tbody>
</table>

It was concluded that precipitation with $Zn(OH)_2$ includes MIT and DIT in the PBI value, while this is not the case when precipitation is done with TCA.

The serum from patients was treated with ion exchange resin before precipitation.

CASE REPORTS

No. 1, A. U., male aged 72 years. He had suffered from chronic asthmatic bronchitis for 20 years, and for the last 10 years had been continually taking an expectorant mixture containing potassium iodide (KI). The yearly intake of KI was calculated to be more than 500 g. He had no known thyroid disease, or serious contributory illness.

On examination in 1957 he was euthyroid.

In March 1962 he was clinically euthyroid, but the thyroid gland was slightly en-

![Thyroid histology](image-url)

**Fig. 1.**

Thyroid histology in patient A. U. Showing "more or less dilated alveoli lined by a cuboidal epithelium, which in many areas proliferates into the lumen. The colloid is pale with marked vacuolisation. Thyroid tissue with thyrotoxic changes." (Leiv Kreyberg, sign.) Magnification $\times 192$. 107
Serum cholesterol was 237 mg/100 ml. Basal metabolic rate (BMR) 104 %, and serum PBI 14.8 µg/100 ml.

In June 1962 his thyroid gland had increased in size. In October 1962 he was admitted to the hospital because of increasing dyspnoea. He complained of cold intolerance, spending his day in bed fully dressed, and had stools once a week. On examination he appeared severely myxoedematous with typical changes in skin, voice and tendon reflexes. The thyroid was greatly enlarged, and was estimated to weigh about 80 g. It was soft, with a regular surface and no nodules. The BMR was 77 % and 63 % on two separate occasions. In addition there was slight cardiac decompensation and evidence of a long-standing bronchial disease.

Thyroid biopsy showed parenchymatous hyperplasia (Fig. 1). Results of determinations of serum cholesterol, PBI, BEI and thyroid uptake of ¹³¹I before and after stopping the KI medication are shown in the graphs (Figs. 2, 3, 4, 5). The PBI determination was carried out after ion exchange, and precipitation was done both with Zn(OH)₂ and TCA with almost identical results. Total iodine in the serum was over 100 µg/100 ml and fell to 15 µg/100 ml after 3 weeks. The iodine determinations were carried out by Dr. Liv Theodorsen.

Course after stopping KI. Within one month the patient's ptosis disappeared and the reflexes became normal, but his voice was still hoarse and he still had a goitre. After

![Graph](Fig. 2)

Serum cholesterol of patients with iodine hypothyroidism after stopping iodine.
two months he was clinically euthyroid, had lost 5.5 kg in weight, and the thyroid was normal in size and consistency. The BMR increased to 90 and 96%. After seven months he had lost 7.5 kg in weight, the thyroid was normal and the patient euthyroid. Withdrawal of iodide caused no deterioration of his asthma. Serum cholesterol was 221 mg/100 ml and BEI 5.1 µg/100 ml. With the gradual disappearance of the myxoedema, his bronchial asthma and cardiac condition improved considerably. He stated that he felt »better than ever«.

No. 2. B. J., male aged 43 years. He had had asthma since childhood, and for the last 15–20 years chronic asthmatic bronchitis with continual distress. For 15 years he had been taking iodine-containing expectorants every day, with a yearly consumption of KI in excess of 300 g, and possibly 500 g. He had had no thyroid disorder, nor any contributory disease.

In 1957 nothing was said about his thyroid condition.

In September 1962 he complained of loss of energy, loss of libido, loss of hair, swollen legs and constipation. He appeared hypothyroid with hoarseness and typical changes in the skin and hair. The thyroid was enlarged and estimated to weigh about 40 g, with irregular surface, but no distinct nodules. The ECG showed flat T-waves. In addition there was evidence of bronchitis and emphysema. The BMR was 94 and 86%. Thyroid biopsy showed parenchymatous hyperplasia (Fig. 6).

Results of laboratory studies before and after stopping KI are shown in Figs. 2–5.

Course after stopping KI. Within 6 weeks he had lost 7.5 kg in weight and the BMR
Fig. 4.
Serum butanol-extractable iodine of patients with iodine hypothyroidism after stopping iodine.

Fig. 5.
Thyroid uptake of $^{131}$I in patients with iodine hypothyroidism. Figures in brackets indicate number of days after stopping iodine.
Thyroid histology in pat. B. J. Showing «more or less dilated alveoli lined by a low cuboidal epithelium, which in a few areas is higher and proliferating into the gland lumen. The colloid is rather evenly stained with slight peripheral vacuolization. Thyroid tissue with slight thyreotoxic changes.» (Leiv Kreyberg, sign.)

Magnification × 192.

increased to 106 and 119 %. The goitre disappeared. He felt keener, was able to walk without stumbling, and the stools became normal. The skin became softer, and a new crop of soft hairs appeared on the lower arms. The T-waves became higher. As his thyroid condition improved, his asthma improved proportionally. Five months later he was euthyroid, had lost altogether 12 kg in weight and had a normal thyroid gland. The BEI was 5.3 µg/100 ml and the serum cholesterol 240 mg/100 ml. At this time the patient requested reinstution of iodide because of increasing asthmatic distress. The dose was 1 g daily. After 3.5 months on iodides he again experienced cold intolerance and constipation. He appeared mildly hypothyroid and had gained 3.5 kg. The thyroid was normal. BEI was 2.3 µg/100 ml (below normal) and serum cholesterol 284 mg/100 ml. It was apparent that he was sliding back into overt hypothyroidism.

No. 3, A.B., male aged 56 years. Asthmatic bronchitis for 30 years. For the last 10 years continual use of iodide-containing mixture, with a calculated yearly consumption of more than 500 g KI. In addition he suffered from cardiac failure of moderate degree, ascribed to previous myocardial infarction and to his bronchial disease.

On examination in 1957, -58 and -59 nothing was said about his thyroid condition.

In November 1962 he complained of troublesome constipation, hoarseness and puffiness of the face. Physical examination revealed a heavy-set subject with signs of chronic bronchitis and emphysema. He appeared slow, had marked hoarseness, oedema of the eyelids and ptosis. The reflex return was slow. His thyroid was enlarged and estimated at 40 g, with a slightly nodular surface. In addition mild cardiac failure was found, and pyuria attributed to chronic prostatitis. Determination of the BMR was not found to be practicable because of dyspnoea.

Results of laboratory studies before and after stopping KI are shown in Figs. 2–5. Total serum iodine was more than 100 µg/100 ml.

Course after stopping KI. After one month he appeared euthyroid, and this condition was maintained. After two months his thyroid was no longer palpable, although
scintigram showed the gland to be still enlarged, but smaller than before. The uptake of 131I was normal.

At this point the patient asked for reinstitution of iodides, and medication was re-started in the same doses as before, under close supervision. During the ensuing 4 months he appeared to get along well. Control of BEI showed 7.9 µg/100 ml (high normal) and serum cholesterol was 265 mg/100 ml. After 4 months on iodides he again started to complain of facial puffiness, constipation, cold intolerance and depression. Clinically he was mildly hypothyroid. The BEI had fallen to 5.0 µg/100 ml and the serum cholesterol had risen to 357 mg/100 ml. Because he felt he could not get along without iodides, he was started on Na-l-thyroxine 0.2 mg daily.

He continued treatment with iodides and thyroxine for three months. His condition again improved, and he soon became euthyroid. BEI was 6.3 µg/100 ml and serum cholesterol 287 mg/100 ml. The PBI, however, was still high, 21 µg/100 ml.

No. 4, H. A., male aged 72 years. Asthmatic bronchitis for 12 years. For the last 10 years he had been taking KI every day, with a yearly consumption in excess of 500 g. In addition he was suffering from polyneuropathy of the lower extremities of unknown aetiology. He had never before shown any evidence of thyroid disease.

In 1958 and -59 nothing was said about his thyroid condition.

In June 1961 he was clinically hypothyroid, with typical skin and reflex changes. No definite goitre was found. Serum cholesterol was 455 mg/100 ml. BEI was 2.5 µg/100 ml and PBI 14.8 µg/100 ml. He weighed 65 kg.

KI was stopped, since iodide interfered with the thyroid function studies, but was not at that time held responsible for his hypothyroidism. In September 1961, still with no iodides, he was euthyroid with brisk reflexes and normal skin. His thyroid was probably normal. He weighed 60 kg. Serum cholesterol was 253 µg/100 ml, BEI 5.2 µg/100 ml and PBI 9.2 µg/100 ml. Thyroid uptake of 131I was normal. – Because the causal role of iodides in the production of his symptoms was still not recognized, he was again started on massive doses of KI, in January 1962. Before this, in October 1961, he had a slight myocardial infarction and later developed heart failure.

In October 1962 he was seen again and found to have progressive heart failure and flourishing myxoedema. He spent his day dozing in a chair by the stove and was very constipated. His thyroid was still hard to palpate and no definite goitre was found. He had palpebral and ankle oedema, but had normal reflex return and no ptosis, in contrast to the findings in June 1961. (This changing picture of myxoedema in the same patient is very interesting). He weighed 65 kg, and treatment with with KI was stopped for good.

The results of the laboratory studies before and after stopping iodides are shown in Figs. 2–5.

The results of the PBI determination was the same both with Zn(OH)2– and TCA-precipitation. Total serum iodine fell from 42 µg/100 ml to 11 µg/100 ml in one week.

– Thyrotrophin stimulation did not change the pattern of the 131I uptake. Thiocyanate administration one hour after the tracer dose was given, resulted in a fall of uptake from 7.6% of the dose at one hour, to 0 at two hours.

Course after stopping KI. Within 6 weeks he became euthyroid and lost 10 kg in weight. His bronchial and cardiac condition improved. After 7 months he was seen again; he was euthyroid and weighed 56 kg. No goitre was found. Serum cholesterol was 257 mg/100 ml and BEI 5.7 µg/100 ml. His heart and lungs were in a better condition than they had been for a very long time.
No. 5. G. K., female aged 56 years. She had suffered from asthma for more than 20 years. For the last 6–7 years she had been taking iodide-containing expectorants every day, and her yearly consumption amounted to 300 g KI. During the last 4 months before admission she had taken 200 g because of increasing respiratory distress. She had previously not had any known thyroid abnormality, and suffered from no important contributory disease.

In April 1962 she appeared euthyroid and had no complaints except about her asthma. The important finding was an enlarged thyroid gland, estimated to weigh 40 g and firm. Suspecting that her goitre might have been caused by iodides, KI was withdrawn. Figs. 2–5 show the laboratory findings before and after stopping KI. Total serum iodide was 30 µg/100 ml.

Course after stopping KI. The goitre disappeared within two months, and the gland attained a normal consistency. The patient was last seen 4.5 months after KI was stopped. At that time she was euthyroid and had a thyroid gland that was normal to palpate. Her asthma was unchanged, but she did not miss the iodides.

DISCUSSION

There appears to be little doubt that the iodine intake was the direct cause of the goitre and/or hypothyroidism in all cases. After stopping iodine intake, manifestations of goitre and hypothyroidism reverted completely to normal within 1–2 months, followed by a short period of slight thyroid hyperactivity, after which the gland returned to normal, leaving no signs of thyroid abnormality. Reinstitution of iodides produced a relapse of symptoms whenever this was tried. The clinical course is in agreement with that reported in the literature.

Particular clinical features of the syndrome deserve more detailed consideration:

The hypothyroidism develops gradually. This feature is well demonstrated in patient A. U., who was examined three times within 7 months. The initial sign was goitre, and later hypothyroidism developed. It apparently takes several months for myxoedema to develop, and during this period various clinical conditions, from goitre via mild hypothyroidism, may be observed. It is also interesting to note how long it takes for the inhibitory effect to become evident. Four of our patients had been followed for years while using KI, and had shown no signs of thyroid inhibition. The above clinical features point to the conclusion that we are concerned with some kind of exhaustion reaction from the thyroid, in response to high and prolonged iodine administration.

The situation seems to be different once thyroid inhibition has been manifest. On reinstitution of iodides, it now takes only a few weeks or months before signs of hypothyroidism are evident, whereas the same patient previously had been able to tolerate iodide loads for years without any ill effect. Both H. A., A. B. and B. J. demonstrate this point clearly. Previous episodes thus

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seem to condition the gland to the inhibitory effect of iodides. The phenomena here called "exhaustion" and "conditioning" have not previously been commented upon in the literature, although Nixon (1957) reports a case with four episodes of iodine myxoedema in 5 years.

The size of the thyroid gland varied considerably in our patients, and bore no relationship to the severity of the hypothyroidism. Thus G. K. had a goitre with only borderling hypothyroidism, while H. A. had myxoedema with no goitre. The goitre was usually small, in only one case larger than 50 g. It usually had a firm consistency with a somewhat irregular surface, but no distinct nodules. In A. U. it was larger and softer. This erratic nature of the goitre was also noted by Morgans & Trotter (1953), who in one patient found a gland similar to the one usually found in Hashimoto's thyroiditis, and in another no palpable gland at all, while both patients had clinical and biochemical evidence of hypothyroidism. In the case of Dimitriadou & Fraser (1961) the goitre weighed 160 g, and the infants described by Martin & Rento (1962) also had large goitres. In the majority of cases reported, however, the goitre has been of moderate size. The palpation of the gland thus seems to give little information of diagnostic significance.

It has been very satisfactory to observe the beneficial effect on the cardiorespiratory condition of several of our patients as they reached a euthyroid state. This contrasts with the finding of Burrows et al. (1960) in one patient, and it represents an interesting comment on the widely-accepted treatment of patients with chronic cardiorespiratory failure with radioiodine in order to make them hypothyroid.

Conditions for the syndrome to develop.

First of all, the syndrome may develop in normal thyroid glands. None of our patients had had thyroid disorders previously, nor did this develop subsequently during the period of observation. It is evident from the literature, however, that the syndrome has been described several times in patients with pre-existing thyroid disorders. Bell (1953) was the first to report the syndrome in patients with normal glands. According to Oppenheimer & McPherson (1961), 23 cases with previously normal thyroids had been reported to that time, and the majority of cases reported later had normal glands. Pre-existing thyroid disease was found by some authors (Caplin et al. 1961; Dimitriadou & Fraser 1961; Hydovitz & Rose 1956; Laroche & Hirsch 1960; Lukens 1961; Vanderlaan 1956). In conclusion it may be said, that in the majority of cases, the syndrome has developed in previously normal thyroid glands.

In this connection it should be mentioned that the presence of asthma does not seem to be a prerequisite for the syndrome to develop (Martin & Rento 1962; Mornex et al. 1960).

The nature of the ingested iodine does not seem to be of importance. Bron-
Table 1.
Consumption of KI by 100 asthmatic patients.

<table>
<thead>
<tr>
<th>Grams KI per year</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or negligible</td>
<td>58</td>
</tr>
<tr>
<td>less than 50</td>
<td>13</td>
</tr>
<tr>
<td>50-100</td>
<td>6</td>
</tr>
<tr>
<td>100-200</td>
<td>9</td>
</tr>
<tr>
<td>200-300</td>
<td>5</td>
</tr>
<tr>
<td>300-400</td>
<td>3</td>
</tr>
<tr>
<td>400-500</td>
<td>6</td>
</tr>
</tbody>
</table>

Chography (Mornex et al. 1960) may be the cause, as may Felsol, a combined preparation containing 30 mg of iodopyrin per dose. There is reason to believe that the effect of Felsol on the thyroid gland is a pure iodide effect (Brownstone & Pitt-Rivers 1959). In the great majority of cases inorganic KI was the causative agent.

The dose of iodine ingested and the period of administration need closer scrutiny. Our patients were all taking large amounts of KI, and they were taking it every day over a period of years.

In order to get an impression of the pattern of iodine consumption in Akershus county, 100 consecutive cases of asthma or chronic bronchitis as their main or contributory diagnosis were interviewed and examined by the author. The 5 cases reported were included in this group. The age of the patients varied from less than one year to 75 years, and the duration of their disease from acute cases up to 50 years. Only 10 of the patients had had their asthma for less than one year.

Table 1 shows the amounts of iodine ingested. Only 9 patients had been taking more than 300 g of KI per year.

Equally important is the question of regularity of consumption. Of the 100 patients, 90 were taking their medicine intermittently, with intervals of one to several weeks, often many times a year. Only 10 patients were taking it continually, every day the whole year round. Four of these patients used very small doses, mostly in the form of Felsol.

Only 6 patients belonged to both groups, i.e. they were using large doses without interruption. All the 5 patients with iodine hypothyroidism described above were among these 6!

Similar information regarding regularity, dose and time are very scanty in
the literature. Two authors (Folliers 1960; Rubinstein & Oliver 1957) have the impression that most asthmatics take their medicine intermittently. The necessary doses, according to reported cases, are in most instances large, but doses as small as 150 mg iodopyrin daily have been reported as being capable of causing the condition (Ezrin et al. 1961; Morgans & Trotter 1959). As for the time necessary for the syndrome to become evident, the quoted figures are usually smaller than in the present material, from 6 months (Toguchi & Skillman 1960) up to several years. Many authors (Mornex et al. 1960; Oppenheimer & McPherson 1961; Rubinstein & Oliver 1957; Toguchi & Skillman 1960) have found large iodine intake by the patients, and according to Oppenheimer & McPherson (1961) only 3 out of 23 cases reviewed had been using iodine for less than one year.

In conclusion, it can be said that in the majority of cases high and prolonged exposure to iodine has been encountered, although there are exceptions to this rule, even in patients with no evidence of pre-existing thyroid disorders. The inhibitory effect of iodine can therefore be regarded as an unpredictable event in a few cases, namely those who have been using iodine for only some months and in moderately large doses. To expect and prevent this development in such patients is at the present time outside our ability. On the other hand, our own experience, supported by a body of evidence from the literature, leads us to believe that high and prolonged exposure to iodine carries a considerable risk of developing iodine goitre and hypothyroidism. The practical consequence of this must be that these patients stop iodine medication for 2–4 weeks several times a year, starting from the time they begin this form of treatment.

In accordance with the above view, we believe that the syndrome of iodine inhibition of the thyroid gland is rare only because marked and prolonged exposure to iodine is rare.

The mechanism of iodine inhibition.

Theoretically, iodine might be able to interfere at all stages in the thyroidal iodine cycle, from the trapping of iodide to the release of hormone. Iodine has been found to slow hormone release in thyrotoxic patients, and in subjects made hyperthyroid by exogenous thyrotrophin, but not in normal subjects (Greer & deGroot 1956; Solomon 1956). On the other hand, even in normal glands iodine is able to interfere with the hormone synthesis, as mentioned in the introduction. It is therefore not surprising that study of patients with iodine myxoedema has demonstrated a major defect in hormone synthesis. More specifically, the organic binding of iodine is hampered to a very high degree. Iodine is trapped by the gland, but further binding does not take place or happens on a very limited scale, as demonstrated by autoradiography and thiocyanate block (Paley et al. 1958; Paris et al. 1960).
The shape of the uptake curve may also point to the presence of an undisturbed iodide trapping mechanism in the presence of diminished organic binding: a high initial uptake which later falls slowly and proportionally to the disappearance of iodide from other tissues in the body (Paris et al. 1960). This feature was demonstrated by our patients H. A. and A. B., but not found in the others. The explanation is that the shape of the curve depends on the time that has passed since inhibition has ceased. With time, it approaches normal (Fig. 5). The shape of the uptake curve is not therefore of any diagnostic significance without knowledge of the time factor. More informative is the finding of relatively high initial uptake values (1 and 2 hours) in the presence of a greatly expanded extrathyroidal iodide pool. This points to an enormous extraction of stable iodide from the blood into the thyroid gland (Paley et al. 1958; Toguchi & Skillman 1960), and is due to compensatory thyrotrophin stimulation. The same pituitary secretions are responsible for the goitre, and would produce the histological picture of a hyperactive gland. This was also found in two of our patients in whom biopsy was performed, and in most of the cases reported by others (Mornex et al. 1960; Paley et al. 1958; Paris et al. 1960; Toguchi & Skillman 1960; Turner & Howard 1956). Colloid goitre has been found (Burrows et al. 1960) but may represent a pre-existing disorder. The above evidence of pituitary hyperactivity does not support an inhibitory action of iodide on the pituitary gland itself.

The elevation of the PBI.

All patients with iodine myxoedema have elevated values of PBI in the presence of low values of BEI, pointing to the presence of some iodinated substance in the blood that is not hormonally active. It is well known from the work of Danowski et al. (1950) that massive doses of iodide increase the PBI, irrespective of the effect on the thyroid gland itself. The cause of this »Danowski effect« is still not clear (Danowski, 1963, personal communication).

In order to study the PBI in euthyroid asthmatic patients receiving comparable doses of KI, serial determinations were done after stopping the iodine medication (Fig. 7). In all patients there was an increase in PBI of the same order as in patients with iodine myxoedema, and this increase persisted for a similar period of time. KI was also given to one patient with primary myxoedema and an initial PBI-value of 1.5 μg/100 ml. This patient also had a greatly increased PBI, without any change in his thyroid condition (Fig. 7).

The findings indicate, that an increase in PBI is a uniform feature in subjects using iodide in comparatively large doses, and is thus not confined to patients who develop myxoedema or goitre; and further, that this increase may also take place in subjects with very inactive thyroid glands (primary myxoedema).

Although an increase in the PBI may be caused by the same mechanism in
Serum protein-bound iodine of 5 euthyroid patients with asthma and 1 patient with primary myxoedema after stopping iodine, which had been given for several weeks in a dose of 1.5 g KI daily.

iodine myxoedema as in euthyroid subjects, other possibilities cannot be excluded. If the block in hormone synthesis caused by iodine is not complete, which is certainly the case as this would be incompatible with life, some iodine would be available throughout the cycle, giving rise to more or less normal products of the thyroid gland. Thus Paley et al. (1958) in their careful study calculated that in the presence of a greatly enlarged thyroidal iodine pool, as found in the syndrome, as little as 0.1% of the iodine in the gland would be necessary to secure a normal production of thyroid hormone. A «leak» of this small magnitude would be very difficult to detect with our present tools.

The present material may shed some light on the question whether the iodine-inhibited gland in addition to small amounts of hormones also produces other products that may increase the PBI. Thus the biochemical findings in H. A. and A. U. tend to exclude iodotyrosines as the cause of the PBI elevation, since the values were the same both with Zn(OH)$_2$- and TCA-precipitation. Furthermore, the results of the thyroxine medication in patient A. B. indicate that whatever the nature of the substance that elevate the PBI, it is
not dependent on pituitary stimulation, as it was still present in large amounts during pituitary suppression with exogenous thyroxine.

In conclusion: the chemical composition of the substance responsible for the elevation of the PBI in this syndrome still awaits clarification, as does its eventual role in the pathogenesis. Our own results are all compatible with the view that it may be due to extrathyroidal iodination of serum proteins.

Final remarks.

We know that some subjects under certain circumstances develop iodine myxoedema. We also partly know how, but not why this happens. The factors governing the fate of the gland working under heavy iodine loads are poorly understood. Increased sensitivity to iodine in susceptible subjects has been demonstrated (Paris et al. 1960), but not confirmed (Dimitriadou & Fraser, 1961). Some evidence points to the possibility that the compensatory thyrotrophin stimulation, elicited by decreasing amounts of circulating thyroid hormone, may render the gland more sensitive to the inhibitory effect of iodine, thus setting up a vicious circle (Childs et al. 1950; Paley et al. 1958; Stanley 1949).

Future investigations should prove (or disprove) the contention that high and prolonged intake of iodine usually leads to thyroid hypofunction, and throw further light on the intrathyroidal mechanisms operating under these conditions.

REFERENCES


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