RADIOIODINE UPTAKE IN THE STUDY OF DIFFERENT TYPES OF HYPOTHYROIDISM IN CHILDHOOD

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The application of radioiodine tracer technics to the clinical study of thyroid disorders depends upon measurements of radioactivity over the thyroid gland, in the urine and in the blood. Various workers have attempted to determine: (1) the total amount of the administered I\textsuperscript{131} which has been trapped by the thyroid gland at the end of 24 hours or longer, or the rate of its accumulation by the gland;\textsuperscript{1-19} and (2) the rate of conversion of inorganic iodine into thyroid hormone as measured by (a) the discharge of I\textsuperscript{131} from the gland after the administration of KSCN or KI\textsuperscript{131-14} or (b) the ratio of protein-bound I\textsuperscript{131} to the total I\textsuperscript{131} of the plasma.\textsuperscript{15-19} Most workers have attempted to express the uptake by the thyroid gland in terms of the percentage of the dose of I\textsuperscript{131} administered, although technical difficulties frequently lead to considerable inaccuracy. The usefulness of the different methods depends upon the particular problem to be studied.

A number of workers have applied radioiodine tracer technics to study the effects of thyrotropic hormone upon thyroid function. Stanley and Astwood\textsuperscript{2} showed that in euthyroid patients, when the ability of the thyroid gland to take up iodine had been suppressed by thyroid medication, the capacity for I\textsuperscript{131} uptake could be restored by the administration of thyrotropic hormone (TSH). Querido and Stanbury,\textsuperscript{21} Werner et al.\textsuperscript{7} and Levy et al.\textsuperscript{22} measured the effect of TSH on the uptake of I\textsuperscript{131} in attempting to differentiate primary hypothyroidism from thyroid deficiency secondary to hypopituitarism.

Relatively few studies with radioiodine have been reported in children with hypothyroidism\textsuperscript{2, 3, 8, 13, 14} and there has been little attempt to correlate the findings with the clinical symptomatology or the degree of thyroid deficiency. The pioneer work of Hamilton et al.\textsuperscript{2} showed that in most cretins there was little or no uptake of I\textsuperscript{131} but that some "goitrous cretins" took up and retained large amounts of I\textsuperscript{131} in the enlarged glands. Stanbury and Hedges\textsuperscript{16, 14} showed that the administration of KSCN to a number of patients with sporadic cretinism who had large nodular goiters caused a rapid release of previously accumulated I\textsuperscript{131} from the glands indicating that there was a disability in the conversion of inorganic iodine into organic compounds. In the nongoitrous forms of hypothyroidism various workers have confirmed the finding of a low or absent uptake of I\textsuperscript{131}. However, it has been shown\textsuperscript{6, 7} that the uptake of I\textsuperscript{131} in hypothyroid patients varies from 1% to 15% of the administered dose, whereas 2% of supposedly euthyroid subjects take up less than 10%.
The present studies were undertaken in the hope that they might offer some explanation for the marked variations observed in the symptomatology of hypothyroid children, and perhaps shed light on differences in etiology. The clinical differences between congenital cretins and children with acquired hypothyroidism depend to a large extent upon the level of development which the patient has attained before the thyroid deficiency begins. However, one frequently observes marked differences in the clinical picture of untreated hypothyroid patients 2 or 3 years of age whose osseous development had advanced little if at all above the birth level, indicating that the deficiency has existed since birth. In such cases, it is often impossible to demonstrate differences in the degree of thyroid deficiency by the usual studies of circulatory changes, serum cholesterol, B.M.R. or even protein-bound iodine. It was realized that the study of J131 uptake sheds no light on the functional ability of the thyroid gland to secrete hormone. It seemed, however, that such a study might demonstrate the presence or absence of small amounts of thyroid tissue and that the existence of such tissue might be correlated with the relatively milder types of clinical symptoms. It was possible also that cases might be found in which thyroid deficiency was due to inability of the gland to synthesize hormone rather than to absence of the gland.

METHODS

Since it was anticipated that there would be slight, if any, uptake of 131I by most of the patients studied, it seemed impractical in view of the present inaccuracies of methods to attempt to calculate the radioactivity taken up by the gland as the percentage of the administered dose. It was considered that the demonstration of even small amounts of radioactivity persisting in the thyroid region for some days after all evidence of radioactivity had disappeared elsewhere in the body could be considered presumptive evidence of the presence of thyroid tissue. Accordingly all radioactivity was recorded in terms of counts/sec. Although the dose of 131I/kg. body weight was approximately the same in most patients, a comparison of counts/sec. retained in different patients gives only a crude relative measurement of the J131 accumulation.

131I without carrier was injected intravenously into a vein of the arm or leg to avoid contamination of the skin of the neck which might occur if the infants were given the iodine orally and to obviate differences in gastrointestinal absorption. The dose was generally 1 microcurie/kg. body weight, although in some of the earlier cases 1.75 microcuries/kg. were given. Counts were made with a Victoreen Geiger Muller tube having an end window covered with mica and were recorded on a Tracerlab Autoscaler. A radiolead standard was used to check the constancy of the counter. The counter was centered over the neck just above the episternal notch and held in close proximity to but not touching the skin. To obtain the background of 131I in the general circulation, counts were taken similarly with the tube placed over the anterior thigh a short distance above the knee at a point where the circumference was approximately that of the neck. Counts were taken immediately after injection of 131I and at intervals of 10 to 15 min. during the 1st hr. They were then repeated hourly until the 4th to 6th hr. and again at 24 hr. Thereafter, the counts were taken at daily intervals until radioactivity had been absent over the thigh for one or more days. All counts were corrected for the room background and for the rate of disintegration of 131I.

In some cases 5 or 6 days after the first count when radioactivity over the thigh had disappeared 25 or 30 mg. thyrotropic hormone* (10 U.S.P. units) were given intramuscularly in a single dose on 1 or 2 successive days. Forty-eight hours later 131I was again administered intravenously and the uptake measured.

TYPES OF CURVES

Normal Uptake: Chart 1 shows the uptake curves of normal children who had received no thyroid therapy. The curves represent the counts over the neck minus the

* Gratitude is due the Armour Laboratories for a generous supply of lyophilized thyrotropin.
counts over the thigh plotted against the time following the injection of $^{131}$I. Both counts were corrected for the rate of disintegration of $^{131}$I. The counts over the thigh, representing the $^{131}$I in the general circulation, generally fell progressively and disappeared after 24 to 48 hours. Over the neck the counts rose fairly rapidly during the first six hours and then more slowly, reaching a plateau of 30 to 150 counts per second at 24 to 48 hours. When corrections were made for disintegration the counts over the neck remained high for many days showing only a gradual decline. It is apparent that there was a considerable variation in the height of the plateau, representing the total accumulation of radioiodine. The curves are in essential agreement with findings of other workers.
CHART 2. Measurements of radioactivity after intravenous injection of tracer dose of I\textsuperscript{131}. Upper curves showing disappearance of radioactivity over neck simultaneously with its disappearance elsewhere in body indicate absence of any thyroid tissue capable of trapping iodine. Lower curves showing persistence of radioactivity over neck long after it has disappeared elsewhere in body indicate presence of some thyroid tissue capable of taking up and retaining iodine.

No Uptake: In Chart 2 the upper two curves are the type which the authors believe indicate the absence of any significant uptake of radioiodine by the thyroid gland. Both the counts over the neck and those over the thigh (corrected for disintegration) were plotted against time. It is seen that the counts over the thigh began to fall promptly, due to disappearance of the iodine from the circulation. However, the counts over the neck rose during the first few hours and then fell, approaching those of the thigh and disappearing at about the same time in 24 to 48 hours. It is probable that the early elevation of the neck count is due to salivary excretion of I\textsuperscript{131} in the esophagus and the authors have been able to demonstrate a high degree of radioactivity in the saliva. The still higher count over the stomach is probably due to the presence of I\textsuperscript{131} in saliva and gastric juice.

Slight Uptake: In contrast, the lower curves of chart 2 show small counts over the neck persisting for many days after all radioactivity disappeared from the thigh and other parts of the body. It is believed that the persistence of such a count indicates the presence of a small amount of thyroid tissue capable of taking up iodine.

Selection of Cases

Studies of I\textsuperscript{131} uptake have been made on 34 patients who had definite clinical and biochemical signs of hypothyroidism. Fourteen of these patients who had been treated previously with desiccated thyroid or were receiving it at the time of the study showed no uptake of I\textsuperscript{131}. Nine of the 14 were retested 48 hours after the injection of 30 mg. thyrotropic hormone and were again found to have no uptake. Since it was considered impossible to conclude whether some functioning thyroid tissue may have been present originally and undergone atrophy as a result of long continued treatment, these cases were excluded from the present study. Of the remaining 20 cases to be reported, 16 had
never received thyroid medication, but four patients (10, 11, 13 and 20) who were able to accumulate $I^{131}$ in spite of treatment are included.

**RESULTS**

"Congenital" Hypothyroidism: Table 1 lists 14 patients who had symptoms of hypothyroidism dating from birth or before the age of 12 months. Eight of these showed no measurable uptake of $I^{131}$, 4 (Cases 9, 10, 11, 12) showed small uptakes amounting to a retention over the neck of 3 to 16 counts/second, 2 (Cases 13 and 14) had normal uptakes of 90 and 95 counts/second. Two of the patients (Cases 10 and 13) showing uptakes had received thyroid previously and one (Case 11) was receiving it at the time of study. In the 8 cases (Cases 1, 2, 6, 9, 10, 11, 12, 14) in which the uptake of $I^{131}$ was again measured after the administration of TSH, there was no increase.

The cases were reviewed to determine whether variations in the history and symptomatology of the disorder were correlated with differences of uptake of $I^{131}$. In the eight cases in which there was no uptake of $I^{131}$ (Cases 1 to 8) marked symptoms of typical cretinism were apparently present from birth or the early months of life. In addition to

<table>
<thead>
<tr>
<th>Case</th>
<th>Onset of Symptoms</th>
<th>Age of Diagnosis</th>
<th>Condition when Studied</th>
<th>Thyroid Gland</th>
<th>Previous Thyroid Treatment</th>
<th>$I^{131}$ Uptake</th>
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<tr>
<td></td>
<td></td>
<td>Chron. Age</td>
<td>Bone Age</td>
<td>Chol. mg./100 cc.</td>
<td>Without TSH</td>
<td>After TSH</td>
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<tr>
<td>1*</td>
<td>Birth 2 mo.</td>
<td>2 mo. &lt;Birth</td>
<td>Ch 204</td>
<td>Not Palpable</td>
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<td>2</td>
<td>* 3 mo.</td>
<td>3 mo. &lt;Birth</td>
<td>Ch 160</td>
<td>* *</td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>* 4 mo.</td>
<td>4 mo. &lt;Birth</td>
<td>Ch 140</td>
<td>* *</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>* 4 mo.</td>
<td>4 mo. &lt;Birth</td>
<td>Ch 216</td>
<td>* *</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>* 8 mo.</td>
<td>8 mo. &lt;Birth</td>
<td>Ch 195</td>
<td>* *</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>* 8 mo.</td>
<td>8 mo. &lt;Birth</td>
<td>* *</td>
<td>0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7*</td>
<td>* 24 mo.</td>
<td>24 mo. &lt;Birth</td>
<td>Ch 250</td>
<td>* *</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>* 20 mo.</td>
<td>20 mo. 3 mo.</td>
<td>Ch 766</td>
<td>* *</td>
<td>0</td>
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</tr>
<tr>
<td>9</td>
<td>&lt;1 yr.</td>
<td>21 mo. 4 mo.</td>
<td>Ch 474</td>
<td>* *</td>
<td>4 5.5</td>
<td></td>
</tr>
<tr>
<td>10*</td>
<td>&lt;6 mo.</td>
<td>24 mo. &lt;3 mo.</td>
<td>Ch 448</td>
<td>* *</td>
<td>16 8</td>
<td></td>
</tr>
<tr>
<td>11*</td>
<td>&lt;1 yr.</td>
<td>21 mo. 8½ yr.</td>
<td>Ch 240</td>
<td>* *</td>
<td>5.5 6.5</td>
<td></td>
</tr>
<tr>
<td>12*</td>
<td>3 mo.</td>
<td>4½ yr. 9-12 mo.</td>
<td>Ch 344</td>
<td>* *</td>
<td>3 3.1</td>
<td></td>
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<tr>
<td>13*</td>
<td>Birth 11 mo.</td>
<td>3 yr. 9 mo.</td>
<td>Normal Size</td>
<td>32 mg./day disc.‡ 2 mo. previously</td>
<td>50 40</td>
<td></td>
</tr>
<tr>
<td>14*</td>
<td>Birth 6½ yr.</td>
<td>6½ yr. 1½ yr.</td>
<td>Enlarged</td>
<td>None</td>
<td>95 92</td>
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* Case histories appended.
† Patient had received 16 to 32 mg. desiccated thyroid daily during January at age of 21 mo.; study made in April.
‡ Received desiccated thyroid 32 mg. daily from 11 to 34th month; no treatment for 10 days prior to study.
§ "Counts/sec." indicates the count (corrected for disintegration) persisting over the neck after radioactivity had disappeared over the thigh.
coldness and circulatory mottling of the skin and constipation these patients at an early age had puffy myxedema of the face and large thickened tongues. In six cases the cretinoid appearance was so obvious that the diagnosis was made between the ages of 2 and 8 months. In the other 2 cases (Nos. 7 and 8) the clinical picture was also characteristic but the diagnosis was not made until the second year of life due to the fact that the infants were not taken to a physician.

In the four patients who showed a slight uptake of $^{131}I$ (Cases 9, 10, 11, 12) the history indicates a somewhat slower, more insidious onset of symptoms, and three of the children did not present the grotesque, puffy appearance typical of cretins. Nevertheless, the fact that prior to treatment two of these patients had an osseous development of less than six months and that the other two showed typical epiphyseal dysgenesis in the head

<table>
<thead>
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<th>TABLE 2</th>
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<td>CASES OF ACQUIRED HYPOTHYROIDISM</td>
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<table>
<thead>
<tr>
<th>Case</th>
<th>Onset of Symptoms (yr.)</th>
<th>Age of Diagnosis (yr.)</th>
<th>Condition when Studied</th>
<th>Thyroid Gland</th>
<th>Thyroid Treatment</th>
<th>$^{131}I$ Uptake counts/sec.</th>
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<tbody>
<tr>
<td>15</td>
<td>3-4</td>
<td>5½</td>
<td>Chron. Age (yr.)</td>
<td>3</td>
<td>Not Palpable</td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>3-4</td>
<td>8</td>
<td>Bone Age (yr.)</td>
<td>4</td>
<td>Palpable</td>
<td>15.5</td>
</tr>
<tr>
<td>17</td>
<td>3-4</td>
<td>12½</td>
<td>Chol. mg./100 cc.</td>
<td>400</td>
<td>None</td>
<td>3.5</td>
</tr>
<tr>
<td>18</td>
<td>5-6</td>
<td>11</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>4.0</td>
</tr>
<tr>
<td>19</td>
<td>10-12</td>
<td>15</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.7</td>
</tr>
<tr>
<td>20</td>
<td>1-4</td>
<td>12½</td>
<td>Adult</td>
<td>*</td>
<td>Receiving 90 mg./day</td>
<td>18.5</td>
</tr>
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* Case histories appended.
† "Counts/sec." indicates the count (corrected for disintegration) persisting over the neck after radioactivity had disappeared over the thigh.

of the femur and other early centers indicates that the thyroid deficiency had begun in the early months of life.23

Two patients (Cases 13 and 14) who had definite evidences of hypothyroidism dating from birth or shortly thereafter showed normal uptakes of $^{131}I$. In Patient 13 a thyroid gland of normal size and consistency was palpated. Patient 14 had a thyroid gland which was firm and enlarged to 1½ the normal size. The enlargement was not discovered until she was 6 years of age but may have been present from birth since it was visible only when she tilted back her head.

Acquired Hypothyroidism: Table 2 shows the findings in six patients who had the acquired type of hypothyroidism. Five of these patients had not been treated prior to the study, and one (No. 20) had received thyroid therapy for 14 years. The "time of onset" of the thyroid deficiency was based on the history and on the facts that growth and development had been entirely normal up until this time, that osseous development had advanced only very slightly beyond the time indicated, and that dysgenesis of the earlier epiphyseal centers was absent.

Five of the patients (Cases 16 to 20) showed a definite but small uptake of $^{131}I$ ranging from 3.5 to 18.5 counts/second. The administration of TSH caused no increase
in the uptake when a second injection of I\textsuperscript{131} was given 48 hours later. The sixth patient (No. 15) showed no uptake of I\textsuperscript{131} when first studied, but 48 hours after the administration of 30 mg. TSH there was a normal rapid uptake of I\textsuperscript{131} causing a maximum count of 80/sec. This patient differed from the other ones in the fact that the thyroid deficiency was of shorter duration, probably about 1\frac{1}{2} years in contrast to 4 to 8 years in the other cases.

DISCUSSION

In this study the authors have assumed that after the administration of I\textsuperscript{131} the persistence of radioactivity over the neck for several days or longer after it can no longer be detected elsewhere in the body is evidence that some thyroid tissue is present. Although the amount of radioactivity retained is shown in the tables as "counts/second," the patients were classified merely as those having "no uptake," "small uptake" or "normal uptake," realizing that with this technic minor differences in the count may depend upon factors other than the amount of iodine-accumulating thyroid tissue present. In a patient who has previously been treated the absence of I\textsuperscript{131} uptake over the neck even after TSH does not prove that functioning thyroid is entirely lacking, since the uptake may be suppressed by the administration of thyroid or iodine, or the gland may have undergone atrophy as the result of long continued treatment. Since all patients having no uptake who had received thyroid or iodine were excluded, it is probable that the patients reported here as showing no retention of I\textsuperscript{131} were actually lacking in functioning thyroid tissue.

The 20 patients studied all showed marked hypothyroidism. In spite of the fact that no differences in the degree of deficiency could be detected by studies of the circulation, serum cholesterol or B.M.R., 9 patients showed no uptake of I\textsuperscript{131}, 9 had a small uptake and 2 a normal uptake. Unfortunately the authors were unable to make measurements of the protein-bound iodine of the serum or of the PBI\textsuperscript{131}.

The four patients believed to have the congenital form of the disorder who took up small amounts of I\textsuperscript{131} (Cases 9, 10, 11, 12) differed from those who showed no retention in that the clinical picture had developed more slowly and insidiously and that the typical myxedematous, cretinoid facies were absent. This suggests that the more typical cretins were born without any thyroid tissue while those with milder symptoms may have had small amounts with sufficient activity to delay the development of the clinical picture during the earliest months of life. The absence of increased uptake of I\textsuperscript{131} after the injection of thyrotropic hormone indicates that the thyroid tissue present was not capable of responding to stimulation.

The two patients who took up normal amounts of I\textsuperscript{131} are of special interest. The histories, the occurrence of epiphyseal dysgenesis in the early centers and the marked immaturity of osseous development indicated that the thyroid deficiency had been present from birth or the earliest months of life. Patient 13 apparently had a thyroid gland of normal size and consistency while Patient 14 had a goiter of moderate size which may or may not have been present since birth. There was no indication of iodine deficiency in either case. Apparently the thyroid gland was unable either to convert inorganic iodine to thyroxine or to secrete the hormone if it were formed. Stanbury\textsuperscript{13,14} studied three siblings and a child in another family with marked congenital hypothyroidism, who had developed large nodular goiters at the ages of 7 to 13 years. They lived on the Atlantic seaboard and received diets abundant in iodine. In each case large amounts of I\textsuperscript{131} were accumulated by the goiter. However, the oral administration of 1 or 2 gm. KSCN 4 to
27 hours after the $^{131}I$ was given caused a sudden decrease in the radioactivity of the gland. He interpreted this as indicating that the inorganic iodine in the thyroid had not been bound into an organic compound and was released by the KSCN. In Patient 13 the effects of KSCN were not studied, but in Patient 14 the authors failed to demonstrate the rapid release of radioactivity from the gland described by Stanbury. This patient was given 0.5 gm. KSCN five hours after the administration of $^{131}I$. The count which was 94 per second showed no decrease and at the 18th hour the administration of 1.5 gm. again failed to cause a decrease. Seven days later the uptake of $^{131}I$ was measured 48 hours after the administration of 30 mg. TSH. The uptake did not differ materially from the first study. On this occasion the oral administration of 1.5 gm. KSCN $3\frac{1}{2}$ hours after $^{131}I$ caused only a transient small decrease in the neck count. The authors have no explanation of these findings.

In five of the cases of acquired hypothyroidism (Cases 16 to 20) the uptake of $^{131}I$ indicated that small amounts of thyroid tissue were present, in spite of the fact that the gland could not be palpated. However, the thyroid glands were apparently incapable of responding to stimulation with thyrotropic hormone in the doses given. Patient 15 had no uptake of $^{131}I$ on the first test but after the administration of thyrotropic hormone showed a normal uptake and a clinical response consisting of increased pulse rate and general activity lasting for 4 or 5 days. This suggests that the hypothyroidism may have been due to deficiency of thyrotropic hormone rather than to a primary disorder of the thyroid gland. Werner and other\textsuperscript{31,32} believe that absence of response to thyrotropic hormone indicates a primary disturbance of the thyroid gland while a positive response is evidence that hypothyroidism is secondary to pituitary dysfunction. Certainly if there were a pituitary disturbance in this patient, it must have been limited to a specific deficiency of thyrotropin since she showed no other signs of hypopituitarism and during the past four years thyroid therapy has brought about entirely normal growth and development, a result which does not occur in the usual cases of generalized hypopituitarism. The hypothyroidism was of much shorter duration in this patient than in any of the other cases of acquired type studied. It is possible that in some of the other cases of longer duration the initial failure may have been due to deficiency of thyrotropic hormone and subsequently the gland may have atrophied to a degree when it was no longer capable of responding to stimulation.

The studies reported suggest that in congenital hypothyroidism due to defective development of the gland there are differences in the degree of the defect. In patients in whom no thyroid tissue can be demonstrated clinical symptoms appear earlier and are more striking than in patients in whom a small amount of tissue capable of accumulating iodine can be found. In addition some patients who have unquestionable signs of hypothyroidism and live in regions where iodine is abundant can be shown to have thyroid glands which are either of normal size or enlarged and which are capable of taking up iodine normally but are unable to secrete adequate amounts of hormone. Additional studies of the dysfunction are being made.

\textbf{Abstracts of Illustrative Histories}

\textbf{Patients with Marked Symptoms of Cretinism From Birth and No Uptake of $^{131}I$}

Case 1. It was noted at birth that the infant had a peculiar bloated appearance with puffy features, short fat neck and depressed nasal bridge. The tongue was thick and protruded so that he had difficulty breathing and feeding. His hands and feet were always cold and the skin was dry, dusky and
mottled. The bowels were always constipated. When examined at 2 mo., he presented a typical cretinoid appearance. The epiphysial development was less than normal for a newborn infant and there was characteristic dysgenesis of the cuboid of the foot.

Case 7. From the time of birth, the child was inactive, and his skin was dusky, mottled and cold. He was chronically constipated. An umbilical hernia was present. He took his feedings poorly and grew and gained very little. He took little interest in his environment. The first tooth erupted at 21 mo., and he was unable to sit alone at 2 yr. When first examined at 2 yr., he presented a characteristic cretinoid appearance. The height age was 5 mo. His osseous development had not progressed beyond the birth level and there was dysgenesis of the epiphyses at the knee.

Patients with Insidious Onset of Symptoms of Hypothyroidism During Early Months and Slight Uptake of I\[127\]

Case 10. This boy was slow in his growth and development. He sat alone at 14 mo., cut his first tooth at 17 mo. and began to walk at 23 mo. At 20 mo., his osseous development was that of a newborn infant. However, he had always been fairly alert and active, and numerous photographs showed that he did not have a cretinoid facies and was not puffy or myxedematous. Thyroid treatment with doses of \[1/4\] to \[1/2\] gr. daily was given at 21 mo. for a few weeks, but it was discontinued 2 mo. prior to the I\[127\] study. The serum cholesterol was 448 mg./100 cc.

Case 11. This child was considered normal and showed nothing unusual in the character of her features, skin or color until she was about 1 yr. of age. However, no teeth erupted until she was 13 mo. After she was 1 yr. of age, she became progressively more apathetic and ceased to grow or develop. A second tooth erupted at 15 mo. but no more appeared until the 21st mo. At the age of 21 mo. her height age was 10 mo., bone age 6 mo. Her features were not coarse or cretinoid. Thyroid therapy was begun at this time and caused marked clinical response with accelerated growth and development. The I\[127\] study made when she was 8 1/4 yr. old showed a moderate uptake in spite of the fact that she had been receiving thyroid 1/2 gr. daily for the past 6 1/4 yr.

Case 12. The patient seemed normal at birth. At 3 mo. it was noted that the skin had a yellowish tinge. She sat alone at 7 mo. and walked at 18 mo., but she was relatively inactive and tired easily. The first teeth erupted at 14 mo. At 2 yr. she became chronically constipated. After 3 yr. the mother noticed that she was growing very little. When examined at 4 yr., 10 mo., she did not have characteristic cretinoid features but had an infantile type of naso-orbital development. Her height age was 3 yr. The osseous development showed scattering between the levels of 9 mo. and 3 yr. with an average development of 9 to 12 mo. All the postnatal centers including the head of the humerus (3 mo.) and the head of the femur (9 mo.) showed dysgenesis.

Patients with Onset of Hypothyroidism in Early Months Who Had Normal or Enlarged Thyroid Glands and Showed Normal Uptake of I\[127\]

Case 13. This boy had been slow in his growth and development. The first tooth had erupted at 13 mo.; he sat alone at 13 mo. and walked at 18 mo. He had had a poor appetite but was not constipated. His features had never become puffy or cretinoid. When he was examined elsewhere at 11 mo. his height age was 5 mo. and no postnatal centers had ossified. From 11 to 34 mo. he was treated daily with 1/2 gr. of desiccated thyroid or less. When he was studied at 2 yr., 11 mo., his height age was 2 yr. and his bone age was 9 mo. At that time thyroid had been omitted for 10 days, and there were circulatory changes and coolness of the skin suggestive of hypothyroidism but there was no myxedema. The serum cholesterol was 420%. A number of examiners thought that his thyroid gland was of normal size and consistency. Certainly no goiter was visible or demonstrable on roentgenographic examination of the mediastinum. Following the demonstration of a normal uptake of I\[127\] he was allowed to continue without thyroid therapy for another 7 wk. in order to establish the diagnosis more conclusively, at the end of which the cholesterol had risen to 460 mg./100 cc.

Case 14. There was no history of any thyroid disturbance in the family and the patient had 2 normal siblings. She had always lived in Baltimore and had taken a normal diet. She seemed normal at birth but during the 1st 2 wk. of life had a severe attack of epidemic diarrhea of the newborn infant with jaundice. The first teeth did not erupt until she was 15 mo. old, and she did not walk until the age of 2 yr. She grew slowly. She was relatively inactive and phlegmatic and was
constipated. Her color was always pale and slightly yellowish. When she was 6 yr. old an enlarge-
ment of the thyroid was noticed for the first time. When she was examined at the age of 6 1/4 yr.,
her height age was 3 yr. and her bone age 1 3/4 yr. There was dysgenesis of the heads of the femora
and humeri. Her skin was pale and cool and the musculature flabby. There were no signs of
myxedema. The serum cholesterol was 420 mg./100 cc. The thyroid gland was diffusely enlarged and
firm, about 1 1/2 times the normal size, but it was apparent only when she tilted back her head. After
diagnostic studies were completed an excellent therapeutic response to desiccated thyroid confirmed
the original impression of hypothyroidism.

Patient with Acquired Hypothyroidism of 1 1/2 Years' Duration Who Showed No Uptake of
\( ^{131}I \) Before TSH and Normal Uptake After Its Administration

Case 15. The child had grown and developed normally and had been active, energetic and alert
with regular bowels and good color up until the age of 4 yr. At that time her appetite became poor
and she stopped gaining. She became sluggish and apathetic. Her color became pasty; the skin cold
and dry; the bowels constipated. When she was examined at the age of 5 1/2 yr., her height age was
4 yr., bone age 3 1/2 yr., mental age 5 10/12 yr. She was placid and inactive. The skin was cool and
pale with circulatory mottling. She was slender and showed no puffiness or myxedema. The serum
cholesterol ranged between 618 and 467 mg./100 cc.; the B.M.R. was \(-28\%\). \(^{131}I\) studies were made
before starting treatment. Subsequently thyroid therapy has resulted in entirely normal growth and
development.

Patient with Acquired Hypothyroidism of 4 to 5 Years' Duration Who Had
No Uptake of \(^{131}I\) Before or After TSH

Case 18. This boy had been entirely normal and was lively and energetic until he was 5 yr. of
age. The first dentition, walking and talking had occurred at the average time. He had had good
color and regular bowels. Linear growth had been normal until 5 yr. after which it gradually
slowed, although his short height did not attract attention until he was 9 yr. After 5 yr. he gradu-
ally became less energetic and was constipated. His color became pale and his skin dry and cool.
None of the deciduous teeth were lost until he was 10 yr. old. Because of his pallor he was treated
for anemia between the ages of 9 and 11 yr. When he was examined at 11 1/4 yr. he was slow and
apathetic. His skin was cold, pale, slightly yellowish. The tissues were loose and flabby although
there was no obvious myxedema. The height age was 6 3/4 yr., the bone age 6 1/2 yr. with suggestions
of epiphyseal dysgenesis in some of the 4 yr. centers, but not in the earlier ones.

SUMMARY

A method for demonstrating small uptakes of radioiodine by the thyroid gland has
been described. The study suggests that in some cases of cretinism iodine-accumulating
thyroid tissue may be completely absent while in others a small amount may be present.
In cretins in whom a small amount of thyroid tissue can be demonstrated, the symptoms,
even though appearing during the first year of life develop more insidiously. In cases of
hypothyroidism developing later in childhood, small amounts of thyroid tissue capable of
taking up iodine usually can be demonstrated.

In addition to the cases of hypothyroidism in which there is absence of the gland or
marked diminution in the amount of thyroid tissue, two patients (Nos. 13 and 14) with
definite hypothyroidism showed a normal uptake of \( ^{131}I \). One of those patients had a
thyroid gland of normal size, the other a moderately enlarged gland. They lived in
regions in which there was no likelihood of deficient iodine intake (see Addendum).

One patient (No. 15) with acquired hypothyroidism took up no iodine when first
studied but after injection of thyrotropic hormone showed a normal uptake. The problem
of whether acquired hypothyroidism may be due to deficiency of thyrotropic hormone is
discussed.
ADDENDUM

Since the completion of this paper a number of other patients with congenital hypothyroidism whose thyroid glands were capable of accumulating iodine normally have been discovered. The cause of this type of hypothyroidism and the subsequent development of goiter and neoplasm when treatment is inadequate will be the subject of a subsequent report.

REFERENCES

Fijación de Yodo Radioactivo en el Estudio de Diferentes Tipos de Hipotiroidismo en la Infancia

Este trabajo se realizó buscando una explicación a las desviaciones tan marcadas de la sintomatología de niños hipotiroides así como para tratar de aclarar las diferencias etiológicas. Las divergencias clínicas entre cretinos congénitos y niños con hipotiroidismo adquirido, dependen en gran parte del grado de desarrollo del paciente antes de iniciarse el trastorno glandular; sin embargo, a menudo se observan diferencias notables en el cuadro clínico de hipotiroides no tratados, de dos a tres años de edad, con desarrollo óseo apenas sobrepasando al del nacimiento, lo que indica que la deficiencia existe desde el nacimiento; en estos casos es imposible a menudo demostrar las deficiencias tiroideas por los métodos comunes de estudio de cambios circulatorios, colesterol sanguíneo, metabolismo basal y del yodo proteico. Se acepta que la investigación de la fijación del yodo radioactivo no demuestra la capacidad funcional de la tiroides para secretar hormona, pero sí podría demostrar la presencia o ausencia de tejido tiroideo; y la existencia de tal tejido, determinar las manifestaciones de los cuadros clínicos discretos; asimismo podrían hallarse casos con deficiencia tiroidea debida más a la incapacidad de la glándula para sintetizar la hormona que a la ausencia misma de esta glándula.

El estudio de la fijación del yodo radioactivo se hizo en 34 pacientes con signos clínicos y bioquímicos definidos de hipotiroidismo; los autores asumieron que después de la administración de yodo radioactivo (I'131), la persistencia de radioactividad en la región tiroidea tras de varios días de no encontrarse en otro sitio del organismo, demostraría la presencia de alguna porción de tejido tiroideo.

Los autores describen el método para investigar la fijación del yodo por la glándula tiroidea.

El estudio sugiere que en algunos casos de cretinismo se puede encontrar pequeña cantidad del tejido tiroideo y que en otros puede no hallarse en absoluto; en los primeros aparecen los síntomas insidiosamente aún dentro del primer año de vida; en casos de hipotiroidismo de aparición durante la infancia, generalmente se encuentra tejido tiroideo capaz de fijar el yodo.

Dos casos de hipotiroidismo definido mostraron una fijación normal de yodo radioactivo; uno de ellos mostró una tiroides de tamaño normal y el otro moderadamente crecida; ambos vivían en regiones sin posibilidades de fijación deficiente de yodo (casos números 13 y 14).

Otro caso con hipotiroidismo adquirido no absorbió yodo durante el primer estudio pero tras de una inyección de hormona tirotropica tuvo una respuesta normal.

Se discute el problema de si el hipotiroidismo adquirido se debe a la deficiencia de la hormona tirotópica.

The Johns Hopkins Hospital
RADIOIODINE UPTAKE IN THE STUDY OF DIFFERENT TYPES OF HYPOTHYROIDISM IN CHILDHOOD

SAMUEL H. SILVERMAN and LAWSON WILKINS

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