Defects of Taste and Smell in Patients with Hypothyroidism

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Taste and smell functions were measured in 18 unselected patients with untreated primary hypothyroidism, and in 15 of the 18 patients after treatment with thyroid hormones. Before treatment, 9 of the 18 patients (50 per cent) were aware of some alteration in their sense of taste, and 7 of the 18 patients (39 per cent) were aware of some alteration in their sense of smell. Distortions of taste (dysgeusia) and smell (dysosmia) were frequent complaints among the untreated patients; dysgeusia was observed by 7 patients (39 per cent) and dysosmia by 3 patients (17 per cent). Median detection and recognition thresholds for four taste stimuli (salt (sodium chloride), sweet (sucrose), sour (hydrochloric acid) and bitter (urea), and for two smell stimuli (pyridine and nitrobenzene), were determined in each patient before and after treatment with thyroid hormones. Before treatment, decreased taste acuity (hypogeusia) for at least one stimulus was observed in 14 of the patients (83 per cent); the most common abnormalities were in the detection and recognition of bitter stimuli. Median detection thresholds for both smell stimuli were also markedly elevated (hyposmia) before therapy. Treatment with thyroid hormones largely reversed both the taste and smell defects. In one patient, taste and smell abnormalities were completely corrected after 16 days of treatment with thyroxine. This study indicates that taste and smell defects are common clinical abnormalities in primary hypothyroidism, and suggests that these defects may contribute to the anorexia and lack of interest in eating which are frequently observed.

Abnormalities of taste and smell sensations have been reported in a variety of endocrine disorders including adrenal cortical insufficiency [1,2], Cushing's syndrome [3], congenital adrenal hyperplasia [4], chromatin-negative gonadal dysgenesis [5], hypogonadotropic hypogonadism [6-8], various menstrual abnormalities [9] and pseudohypoparathyroidism [10]. Although various neurosensory disorders such as decreased auditory acuity and deafness [11-13], peripheral neuropathy [14] and mental changes [15,17] have been reported in patients with myxedema, no documentation of abnormalities in taste and smell acuity has been reported.

More than 50 years ago, McCarrison [18] observed that in the typical patient with hypothyroidism the "sense of taste and smell may be disturbed, although this is difficult to determine." Reduction in taste acuity has been reported after therapy with methimazole in
patients with hypothyroidism [19,20]. Whether this change was caused by a direct effect of the drug on taste sensation or by the production of hypothyroidism cannot be determined because indices of thyroid function were not provided. The ability to taste the bitter compounds, phenylthiocarbamide and propylthiouracil, is inherited as a probable mendelian autosomal recessive trait [21]. The incidence of nontasting is increased in congenital athyreotic cretins [22] and in certain patients with nodular goiter [23]. Pittman and Beschi [24] measured detection and recognition thresholds for four taste qualities in 10 subjects with hypothyroidism, and they could not demonstrate any consistent alterations.

In an effort to evaluate possible interrelationships between the thyroid hormones and taste and smell functions, these sensory systems were studied in 18 patients with untreated primary hypothyroidism and in 15 of the 18 patients after treatment with thyroid hormones. The results demonstrate that taste and smell functions are frequently and greatly impaired in hypothyroidism and that in the majority of patients these impairments appear to be reversed by hormonal replacement. Such abnormalities may contribute to the anorexia and decreased food intake often seen in this disorder and may contribute to their frequently observed lack of interest in eating.

**MATERIAL AND METHODS**

**Patients.** The subjects were 18 unselected patients with hypothyroidism from the Medical wards and outpatient departments of the Columbia Presbyterian, Francis Delafield, Montefiore and Queens General Hospitals, New York, New York, and from the Clinical Center, National Institutes of Health, Bethesda, Maryland. There were 3 men and 15 women, aged 28 to 71 years (mean = 54.9 years). The sex ratio and age distribution were similar to that noted previously in other samples of patients with hypothyroidism [25]. Before treatment, each patient exhibited signs and symptoms consistent with the disease [25]. Confirmation of hypothyroidism was made by measurements of serum thyroxine (T4) concentration (by the competitive protein-binding method of Murphy and Pattee [26]), by resin uptake of labeled triiodothyronine (T3) and by serum thyroid stimulating hormone (TSH) concentration (by the double antibody radioimmunoassay * [27,28]). Each patient had values of serum thyroxine which were below normal (Table I). The resin uptake of labeled triiodothyronine was below normal in 12 patients and the serum TSH level was above normal in each of the 13 patients tested (Table I).

Each patient studied was clinically hypothyroid [25]. In only one patient (Case 11) was the degree of hypothyroidism severe enough to prevent the patient from paying attention and cooperating optimally with the testing procedures. In all other instances satisfactory patient participation was obtained. In 13 of the 18 patients, hypothyroidism appeared to be idiopathic; in 2 patients it occurred 3 and 4 years after radioactive iodine treatment for hyperthyroidism; in 1 patient it was noted 13 years after subtotal thyroidectomy for hyperthyroidism; in 1 patient it occurred 10 years after an attack of thyroiditis; and in 1 patient it occurred after 3 years of lithium carbonate treatment for a manic-depressive psychosis.

Prior to and during this study no patient was receiving a drug or hormone previously noted to produce altered taste or smell [29-34]. Three patients had reported a transient loss of taste and smell during an earlier upper respiratory tract infection; however, each person had regained his normal taste and smell acuity prior to the loss experienced with the development of clinical hypothyroidism. One patient (Case 3) had an unilateral naso-pharyngeal mass for at least 1 year prior to study; biopsy specimen revealed this to be chronic inflammation of the nasal mucous membranes. All other patients, within a 3 month period prior to study, denied acute or chronic allergies, or traumatic or infectious processes involving the mouth, nasopharynx or nose. Although many of the patients had complicating diseases (Table I), none of them had previously been noted to be associated with the production of taste and smell defects. Examination of the head and neck performed at the time of each determination of taste and smell thresholds was within normal limits except, as noted previously, in Case 3.

Treatment for hypothyroidism was carried out in 13 patients with L-thyroxine (Synthroid®, Flint Laboratories), in 1 patient with L-triiodothyronine (Cytomel®, Smith Kline & French Laboratories) and in 1 patient with thyroid USP. The patients were studied after periods of treatment ranging from 16 days to 3 years, at which time thyroid function was reevaluated.

**Procedures.** Subjective changes in taste and smell sensation were evaluated before and after treatment with thyroid hormone by the presentation of a standard list of questions related to taste, smell and appetite. Patients were asked about changes in the amount of salt and sugar added to food and drink, and the presence of unusual or altered taste and smell sensations.

Detection and recognition thresholds for salt (sodium chloride), sweet (sucrose), sour (hydrochloric acid) and bitter (urea) were measured by a forced choice, three-stimulus drop technic [1,33]. All measurements were determined in the late morning or in the afternoon at least 1 hour after each patient had finished eating or smoking. Centuries, if worn, were removed [35] immediately before the test. Measurements of the 18 patients were taken by four different observers. Each patient was studied by only one observer.

Detection and recognition thresholds for the vapors of pyridine in water and nitrobenzene in mineral oil were also determined in each patient by a forced-choice, three-stimulus sniff technic [9]. Measurements of smell thresholds were made immediately after the conclusion of the measurements of taste acuity.

After hormonal replacement therapy, subjective reports

* Performed by Bio-Science Laboratories, Van Nuys, California.
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr) and Sex</th>
<th>Serum T4 (µg/100 ml)</th>
<th>T4 Resin Uptake (fraction of normal)</th>
<th>Serum Thyroid Stimulating Hormone (µU/ml)</th>
<th>Associated Diseases</th>
<th>Drugs</th>
<th>Subjective Symptoms (duration)</th>
<th>Probable Etiology of Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42, F</td>
<td>2.7</td>
<td>0.80</td>
<td>30</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Decreased hearing and herniated nucleus pulposus (3 mo)</td>
</tr>
<tr>
<td>2</td>
<td>73, F</td>
<td>&lt;1.0</td>
<td>0.67</td>
<td>...</td>
<td>Idiopathic cerebellar degeneration</td>
<td>Chlordiazepoxide</td>
<td>Nausea and decreased appetite (6 mo) and hyposmia (10 yr)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>51, M</td>
<td>&lt;1.0</td>
<td>0.87</td>
<td>&gt;90</td>
<td>Inflammatory nasopharyngeal mass</td>
<td>None</td>
<td>Decreased appetite, hyposmia and dysgeusia (6 mo)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>61, F</td>
<td>1.4</td>
<td>0.75</td>
<td>...</td>
<td>Decreased hearing and bronchiectasis</td>
<td>None</td>
<td>Dysgeusia (2 yr)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>42, F</td>
<td>&lt;1.0</td>
<td>0.56</td>
<td>&gt;90</td>
<td>Carcinoma of cervix</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>52, F</td>
<td>0.5</td>
<td>...</td>
<td>34</td>
<td>None</td>
<td>None</td>
<td>Decreased appetite (6 mo)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>48, F</td>
<td>2.8</td>
<td>1.00</td>
<td>...</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>62, F</td>
<td>2.3</td>
<td>0.66</td>
<td>70</td>
<td>None</td>
<td>Imipramine</td>
<td>Decreased appetite, hyposmia and dysgeusia for citrus fruits (6 mo)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>40, F</td>
<td>2.4</td>
<td>...</td>
<td>&gt;90</td>
<td>Tuberculosis (treated) and multiple food allergies</td>
<td>None</td>
<td>Decreased appetite, hyposmia and dysgeusia (3 mo)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>55, F</td>
<td>0.8</td>
<td>...</td>
<td>75</td>
<td>Decreased hearing</td>
<td>Chlordiazepoxide and ferrous sulfate</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>69, F</td>
<td>1.1</td>
<td>...</td>
<td>34</td>
<td>Bilateral hearing loss and hypertension</td>
<td>Metyldopa and chlordiazepoxide</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

TABLE I  Clinical Summary of 18 Patients with Untreated Hypothyroidism
DEFECTS OF TASTE AND SMELL IN HYPOTHYROIDISM—McCONNELL ET AL.

### RESULTS

#### Subjective Responses Before Treatment. Taste:
Of the 18 patients, 9 patients (50 per cent) were subjectively aware of some alteration in their sense of taste at the time they were first examined; 8 patients (44 per cent) noted a diminution of taste acuity (hypogeusia); and 7 patients (39 per cent) noted some distortion in their sense of taste (dysgeusia). Both symptoms appeared together in 6 of the patients (33 per cent). Only 1 patient (Case 4) complained of dysgeusia not accompanied by hypogeusia. The hypogeusia was generally characterized by the patient's preferring to add more salt and/or sugar than usual to his food in order to obtain the usually desired salty or sweet taste.

Symptoms of dysgeusia included a persistent foul, metallic or bitter taste in the mouth when no oral stimuli were present (phantogeusia) or complaints that normal items of food tasted rancid or spoiled (cacogeusia). In none of the patients were subjective alterations of taste acuity noted to precede the other symptoms of hypothyroidism. Generally the gustatory symptoms developed concomitantly with other clinical symptoms of hypothyroidism or within several months thereafter. Appetite was decreased in 8 of the patients (44 per cent).

#### Subjective Responses Before Treatment. Smell:
Of the 18 patients, 7 patients (39 per cent) reported alterations in their sense of smell. Six patients (33 per cent) noted decreased smell acuity (hyposmia) and they complained that most foods tasted bland or pasty. Three patients (17 per cent) noted a distorted sense of smell (dysosmia). Both of these symptoms were present in 3 patients (17 per cent).

#### Other sensory symptoms:
Of the 18 patients, 6 patients (33 per cent) noted decreased auditory acuity; in 3 patients (17 per cent) this symptom appeared long before the onset of hypothyroid symptoms and may have been unrelated to their changes in thyroid function. One patient (Case 2) suffered from cerebellar ataxia and titubation of the head; this symptom appeared 10 years before the onset of hypothyroidism and was classified as idiopathic. None of the patients complained of symptoms compatible with peripheral neuropathy.

#### Objective Measurements Before Treatment. Taste thresholds:
Table II shows detection and recognition thresholds for taste and smell in each of the 18 patients studied before treatment. Medians for the patient group were determined for each taste quality and compared with similar values obtained previously in normal volunteers. Both the median detection and the median recognition thresholds for the sour and sweet tastes were significantly lower (p < 0.001) in these patients than in normal volunteers. The increases in detection and recognition thresholds for the sour and sweet tastes were approximately 1.5 times greater than those for normal values. The increases in detection and recognition thresholds for the salty taste were significantly greater than those for the sour and sweet tastes. The increases in detection and recognition thresholds for the bitter taste were significantly less than those for the sour and sweet tastes. The increases in detection and recognition thresholds for the pungent taste were significantly greater than those for the sour and sweet tastes. The increases in detection and recognition thresholds for the metallic taste were significantly greater than those for the sour and sweet tastes. The increases in detection and recognition thresholds for the rancid taste were significantly greater than those for the sour and sweet tastes. The increases in detection and recognition thresholds for the spoiled taste were significantly greater than those for the sour and sweet tastes.

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<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Detection Threshold (mmol/L)</th>
<th>Recognition Threshold (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>71</td>
<td>0.90</td>
<td>3.0</td>
</tr>
<tr>
<td>13</td>
<td>64</td>
<td>2.1</td>
<td>140</td>
</tr>
<tr>
<td>14</td>
<td>64</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>15</td>
<td>62</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>16</td>
<td>47</td>
<td>1.8</td>
<td>0.7</td>
</tr>
<tr>
<td>17</td>
<td>57</td>
<td>&lt;1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>18</td>
<td>57</td>
<td>6.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table II: Detection and recognition thresholds for taste and smell in each of the 18 patients studied before treatment.
bitter qualities were above the upper limit of normal, as was the median recognition threshold for sodium chloride. The median detection threshold for sodium chloride was at the upper limit of normal whereas both thresholds for sucrose were within normal limits.

Decreased acuity for at least one taste stimulus occurred in 15 of the 18 patients (83 per cent). Eight patients (44 per cent) had elevated detection thresholds for salt, and 9 patients (50 per cent) had elevated recognition thresholds for salt. For the other qualities, the respective percentages demonstrating abnormal thresholds were: sucrose, 3 patients (17 per cent) with elevated detection and recognition thresholds; hydrochloric acid, 11 patients (61 per cent) with elevated detection and 12 patients (67 per cent) with elevated recognition thresholds; and urea, 13 patients (72 per cent) with elevated detection and 14 patients (78 per cent) with elevated recognition thresholds. Three patients have normal thresholds for each taste quality tested. No patient exhibited ageusia* for any taste quality.

\* Ageusia is operationally defined as inability to detect or recognize a saturated solution of sodium chloride or sucrose, 0.5N hydrogen chloride, or 5M urea [34,37].

Smell thresholds: Median detection thresholds were elevated above normal for both vapors tested (Table II). Median recognition thresholds both for pyridine and nitrobenzene were at the upper limits of the normal range. Decreased detection acuity for at least one olfactory stimulus was measured in 14 of the 17 patients (82 per cent). Of the 17 patients, 14 patients (82 per cent) also had elevated detection and 7 patients (41 per cent) had elevated recognition thresholds for pyridine; 13 patients (76 per cent) had elevated detection and 6 patients (35 per cent) had elevated recognition thresholds for nitrobenzene. Three patients could not recognize absolute nitrobenzene (recognition anosmia*).

**Subjective Responses After Therapy.** Taste: Subjective responses and taste and smell thresholds obtained in 15 of the 18 patients after replacement therapy are shown in Table III. Of those patients with hypothyroidism who initially reported decreases in appetite, all had experienced an increase in appetite at the time of follow-up examination. Six of the nine
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Treatment Schedule</th>
<th>Dose (µg/day)</th>
<th>Duration of Follow-up (days)</th>
<th>Serum T4 (µg/100 ml)</th>
<th>Serum Thyroid Stimulating Hormone (µU/ml)</th>
<th>Subjective Symptoms</th>
<th>Taste Thresholds*</th>
<th>Smell Thresholds*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sodium Chloride (mmole/liter)</td>
<td>Sucrose (mmole/liter)</td>
</tr>
<tr>
<td>1</td>
<td>Thyroxine 300</td>
<td>60</td>
<td>...</td>
<td>...</td>
<td></td>
<td>Taste returned to normal</td>
<td>30/30</td>
<td>30/30</td>
</tr>
<tr>
<td>2</td>
<td>Triiodothyronine</td>
<td>5-25</td>
<td>35</td>
<td>...</td>
<td></td>
<td>Increased appetite and dysosmia for fried foods</td>
<td>30/60</td>
<td>6/12</td>
</tr>
<tr>
<td>3</td>
<td>Thyroid, USP 30-150 mg</td>
<td>170</td>
<td>2.9</td>
<td>...</td>
<td></td>
<td>Increased appetite, taste returned to normal and persistent mild hypoplasma</td>
<td>60/60</td>
<td>30/30</td>
</tr>
<tr>
<td>4</td>
<td>Thyroxine 50-100</td>
<td>160</td>
<td>7.3</td>
<td>...</td>
<td></td>
<td>Taste returned to normal</td>
<td>60/90</td>
<td>30/30</td>
</tr>
<tr>
<td>5</td>
<td>Thyroxine 250</td>
<td>120</td>
<td>5.5</td>
<td>4.4</td>
<td></td>
<td>None</td>
<td>30/30</td>
<td>30/30</td>
</tr>
<tr>
<td>6</td>
<td>Thyroxine 100</td>
<td>120</td>
<td>0.7</td>
<td>27.0</td>
<td></td>
<td>Increased appetite</td>
<td>30/60</td>
<td>12/30</td>
</tr>
<tr>
<td>7</td>
<td>Thyroxine 100-200</td>
<td>90</td>
<td>4.1</td>
<td>2.6</td>
<td></td>
<td>None</td>
<td>6/60</td>
<td>30/30</td>
</tr>
<tr>
<td>8</td>
<td>Thyroxine 50-200</td>
<td>130</td>
<td>9.2</td>
<td>6.6</td>
<td></td>
<td>Increased appetite and persistent dysgeusia for citrus fruits increased appetite, taste and smell returned to normal</td>
<td>6/60</td>
<td>6/6</td>
</tr>
<tr>
<td>9</td>
<td>Thyroxine 300</td>
<td>120</td>
<td>10.0</td>
<td>12.0</td>
<td></td>
<td>Increased appetite and smell switched to normal and persistent mild hypoplasma</td>
<td>12/60</td>
<td>30/30</td>
</tr>
<tr>
<td>10</td>
<td>Thyroxine 12.5-25</td>
<td>160</td>
<td>4.5</td>
<td>&lt;4.0</td>
<td></td>
<td>Increased appetite, persistent dysgeusia and hypoplasma</td>
<td>12/12</td>
<td>9/90</td>
</tr>
<tr>
<td>11</td>
<td>Thyroxine 12.5-100</td>
<td>160</td>
<td>4.9</td>
<td>19.0</td>
<td></td>
<td>None</td>
<td>60/60</td>
<td>60/60</td>
</tr>
<tr>
<td>12</td>
<td>Thyroxine 200</td>
<td>3 yrs</td>
<td>...</td>
<td>...</td>
<td></td>
<td>Increased appetite, taste returned to normal and mild hypoplasma</td>
<td>30/60</td>
<td>30/30</td>
</tr>
<tr>
<td>13</td>
<td>Thyroxine 100</td>
<td>55</td>
<td>4.0</td>
<td>&lt;2.0</td>
<td></td>
<td>Smell returned to normal</td>
<td>6/60</td>
<td>30/30</td>
</tr>
<tr>
<td>14</td>
<td>Thyroxine 200</td>
<td>16</td>
<td>3.0</td>
<td>...</td>
<td></td>
<td>Increased appetite, taste and smell returned to normal</td>
<td>12/12</td>
<td>30/30</td>
</tr>
<tr>
<td>15</td>
<td>Thyroxine 100-200</td>
<td>60</td>
<td>5.0</td>
<td>8.1</td>
<td></td>
<td>Persistent mild hypoplasma</td>
<td>30/30</td>
<td>12/12</td>
</tr>
</tbody>
</table>

* Numerator of fraction is detection threshold; denominator is recognition threshold.
Objective Measurements After Treatment. Taste and smell symptoms after therapy.

**Smell thresholds:** Median detection and recognition thresholds for pyridine and nitrobenzene improved after treatment but did not return completely to normal. Median recognition thresholds for both pyridine and nitrobenzene, at the upper limits of the normal range before treatment, decreased further after treatment. For pyridine, abnormal detection thresholds were improved in 9 patients and unchanged in 4; this improvement was significant compared with pretreatment values by the method of paired comparisons (p < 0.01). For pyridine, improvement in recognition thresholds occurred in each of the six patients in whom this value was abnormal before treatment; this improvement was also significant by paired comparisons (p < 0.001). For pyridine, abnormal detection thresholds returned to normal levels in 4 of the 14 patients, whereas recognition thresholds returned to normal in each of the 6 patients in whom this value had been previously abnormal. For nitrobenzene, detection thresholds improved in nine patients, were worse in one and without change in one other after treatment; this improvement was significant (p < 0.01). Abnormal recognition thresholds for nitrobenzene significantly improved (p < 0.001) in each of the seven patients. For nitrobenzene, abnormal detection thresholds returned to normal in each of the six patients (p < 0.01).

The effect of therapy upon taste and smell thresholds is summarized in Table IV. Generally, taste thresholds for sodium chloride and sucrose improved more completely than those for urea and hydrogen chloride during the time period studied. Both subjective and objective improvement occurred as early as 16 days after initiation of therapy (Case 16).
Representative Case

Figure 1 illustrates the effect of treatment upon the taste detection thresholds for sodium chloride and urea in Case 7. After 57 days of treatment with thyroxine (Synthroide) at a dose of 100 μg/day, the patient's serum T4 concentration increased from 2.8 to 3.2 μg/100 ml (normal 3.0 to 7.0 μg/100 ml). During this period her detection threshold for sodium chloride, which was 90 mmol/liter before initiation of therapy, remained unchanged, whereas that for urea decreased from 2,000 to 500 mmol/liter. At this point the daily dose of thyroxine was doubled and after 33 additional days of therapy, the serum T4 concentration level had risen to 4.1 μg/100 ml. During this latter period the detection thresholds for both sodium chloride and urea became normal, 6 mmol/liter and 90 mmol/liter, respectively.

Serum Concentrations of Vitamin A Before Treatment. Serum concentrations of vitamin A, retinol-binding protein and prealbumin were measured in the patients with untreated hypothyroidism using methods previously described [37] and are expressed as (mean ± 1 standard error of the mean). As in an earlier study [37], serum concentrations of vitamin A in the patients with hypothyroidism (68.6 ± 5.0 μg/100 ml) were significantly higher (p <0.001) than in the previously reported normal subjects (50.1 ± 1.5 μg/100 ml); those of retinol-binding protein (50.3 ± 6.4 μg/ml) and of prealbumin (255 ± 27 μg/ml) were entirely normal. Patients with hypothyroidism who had normal recognition thresholds for either salty, sweet, sour or bitter stimuli did not differ from patients with hypothyroidism who had abnormal recognition thresholds for any of these taste stimuli with respect to the serum concentrations of vitamin A, retinol-binding protein or prealbumin.

The serum concentrations of zinc were determined in three patients with untreated hypothyroidism (Cases 14, 15 and 16) by methods previously described [38] and the values obtained, 62, 69 and 57 μg/100 ml, respectively, were decreased below the levels of 92 ± 2 μg/100 ml (mean ± 1 standard error of the mean) found in normal subjects [38].

COMMENTS

The patient with hypothyroidism who presents with apathy, listlessness and anorexia is a familiar clinical entity. Diminished food intake has been commonly attributed to weakness, lack of energy or loss of interest in the environment. The present finding that defects in taste and smell are observed is significant number of patients with hypothyroidism may provide an additional explanation for this lack of food intake. When food tastes bland or unpleasant, or previously favored food items provide little of their usual satisfaction, there may be less impetus for the patient with hypothyroidism to eat. In a case report of psychosis due to myxedema in 1920 [39], mention was made that the patient would "spoil the food by putting salt in it," when in reality she may have been attempting to make the food more appetizing to her.

The high frequency of disturbances in taste and smell in untreated patients with hypothyroidism suggests that more attention should be paid to this symptom complex in evaluating patients with thyroid disease. In the present series of patients, questioning revealed that fully half were aware that their taste abilities had changed and were defective; objective measurements indicated that more than 80 per cent of them had some abnormality. Defects of smell were less common than those of taste although the two defects occurred together in a high proportion of the cases. Interestingly, none of this information had...
been elicited from these patients in any prior clinical or laboratory examination.

Taste and smell disturbances did not appear to precede other clinical symptoms of hypothyroidism. These disturbances generally improved after institution of replacement therapy with thyroid hormone and in many instances returned completely to normal. Patients were studied at various intervals after initiation of therapy and at various dosage levels of thyroid hormones; it is possible that further improvement in taste and smell sensations might have occurred with either more prolonged treatment or with larger doses of thyroid hormones. Indeed, this appears to be the case with the patients followed for longer intervals on therapy. These results indicate that disturbances of taste and smell are related in some manner to reduced thyroid function and that thyroid hormones are important in maintaining normal taste and smell functions.

The subjective taste and smell changes most commonly observed in patients with untreated hypothyroidism were those of dysgeusia and dysosmia. The most commonly observed deficit in taste acuity was loss of taste for bitter stimuli. This loss has previously been observed in other patients in whom hypogeusia developed after several metabolic defects [29,33,34]. The taste affected to the least extent in patients with hypothyroidism was that for sweet stimuli. The relative retention of sweet taste in the face of loss of other taste qualities has also previously been observed in a number of patients in whom hypogeusia developed secondary to several other etiologic factors [40]. The basis for this relative retention may be either metabolic or may be related to the relatively large number of taste buds subserving the sweet taste quality in the oral cavity in man [40].

The pathogenesis of the defects in taste and smell sensations noted here in patients with hypothyroidism is not known. As with other diseases, the effects of thyroid hormone may be manifested at the taste receptor itself, in the nerves or in the synapses carrying taste information from the receptor to the brain, in the brain where the taste messages are received and integrated, or in some combination of these three systems. Taste buds from patients with hypothyroidism have not as yet been systematically compared with those of normal subjects; thus it is not possible to specify any precise anatomic defects. It will be of interest to determine whether defects of taste and smell are restricted to patients with primary hypothyroidism or whether they are also observed in patients with hypothyroidism secondary to pituitary or hypothalamic disease.

To explore possible mechanisms underlying taste and smell deficits in patients with hypothyroidism, three types of studies have been performed. First, measurements were made of the serum concentrations of vitamin A, retinol-binding protein and prealbumin in hypothyroid and normal subjects. Disturbances in vitamin A have been described in patients with hypothyroidism [41]. Furthermore, taste sensations in experimental animals have been shown to be altered by vitamin A deficiency [42,43]. The elevated serum concentrations of vitamin A and the normal concentrations of the serum transport proteins, retinol-binding protein and prealbumin, in the patients with untreated hypothyroidism make it unlikely that changes in taste sensations in this disorder are related to disturbances in vitamin A metabolism. Second, measurements were taken of zinc concentrations in the serum of three of the patients with untreated hypothyroidism because of the observation that lowered serum zinc levels have been associated with decreased taste acuity in a variety of clinical conditions [30]. The finding that zinc levels in the serum of these three patients were decreased requires extension and confirmation before a significant role can be attributed to this metal in the symptom complex of thyroid disease. Further studies are in progress on this point.

Third, a suitable animal model has been developed to better understand the taste and smell abnormalities in thyroid disease. Defects similar to those observed in patients with hypothyroidism have recently been reproduced in Holtzman rats who were rendered hypothyroid with large doses of radioactive iodine [44]. These animals, when offered a choice between water and a test solution to drink ad libitum, reject the bitter stimulus of a urea solution less often than do normal animals and drink less of a sweet solution of sucrose than do normal animals. The animals with hypothyroidism also drink relatively more saline solution than water than do normal animals. Abnormalities can be corrected within 2 to 3 weeks by daily intraperitoneal injections of thyroxine. The significant, reversible defects produced in laboratory animals with hypothyroidism are well suited for experiments to elucidate the nature of the symptom complex in man.

Changes in peripheral, sensory and motor nerve function and in synaptic delay have commonly been observed in patients and in animals with untreated hypothyroidism [45–50]. These changes have been manifested by paresthesias in 42 to 83 per cent of the patients [4], by decreased peripheral sensation in 60 per cent of the patients [46], by impairment in vibratory sensation [47], by prolonged ankle jerks [48,49] and by slowed neural conduction velocity [50]. These changes have been related to mucinous or myxedematous deposits in the endoneurium [47]...
and perineurium [46,51] by altered myelin formation [45,46], by specific impairment of the neurons carrying vibratory impulses [47] and by abnormalities of the contractile substance of individual muscle fibers [47]. Whatever the cause, these changes generally return to normal after treatment with thyroid hormone [46].

Changes in visual and auditory cortical evoked potentials in animals [52] and in the electroencephalograms of animals and patients with untreated hypothyroidism [46,53-56], have previously been observed. These electroencephalographic changes include decreased amplitude [46,53-56] and a slowed alpha rhythm [46]. Impaired cerebellar function with ataxia has been observed in one fourth to one third of the patients studied [45]. The basis of these central defects is also unclear. Round bodies containing glycogen and called "neural myxedema bodies" have been found in the cerebellum of patients with myxedema and ataxia [51]. In addition, decreased cardiac output, cerebral blood flow, cerebral oxygen and glucose consumption, and increased cerebrovascular resistance occurs [57].

In the newborn animal, hypothyroidism produces a reduced rate of brain growth [58] and retarded neurochemical maturation [59-61]. Decreased capillary density in the brain occurs which reduces the area of capillary surface available for substrate and metabolic product exchange and increases the mean capillary distance for diffusion and transport [62]. Despite these severe defects, however, replacement therapy with thyroid hormone commonly restores central nervous system function to normal when it is started sufficiently early.

Apparently, disturbances in taste and smell are only a part of the sensory changes which may be observed in hypothyroidism. The role that thyroid hormones play in taste and smell sensations will be of interest not only in our understanding of the various clinical manifestations of hypothyroidism but also in our knowledge of the specific action these hormones play generally in sensory functions.

REFERENCES

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