SCHMIDT’S SYNDROME (THYROID AND ADRENAL INSUFFICIENCY): A REVIEW OF THE LITERATURE AND A REPORT OF FIFTEEN NEW CASES INCLUDING TEN INSTANCES OF CO-EXISTENT DIABETES MELLITUS*†


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I. INTRODUCTION

In 1926, M. B. Schmidt (119) described two patients with non-tuberculous Addison’s disease and chronic lymphocytic thyroiditis. Although neither of these patients had clinical signs of hypothyroidism, the coexistence of adrenal and thyroid insufficiency has come to be known as Schmidt’s syndrome.

Not only have subsequent reports documented the association of myxedema and non-tuberculous Addison’s disease, but other endocrine disorders, particularly diabetes mellitus, have been described in Addisonian patients with a great enough frequency to suggest more than a chance relationship of these endocrinopathies.

This review of Schmidt’s syndrome and the concurrence of adrenal insufficiency with other endocrine abnormalities is based upon a summary of pertinent published reports, upon our own studies of 15 patients with Addison’s disease and thyroid dysfunction, several of whom also had diabetes mellitus, and upon a review of the histologic findings in 24 autopsies of patients with Addison’s disease of tuberculous or of idiopathic origin.

II. REVIEW OF THE LITERATURE

Detailed discussion in this section has been limited to publications of particular significance. Table I contains a listing of previous case reports and clinical studies on the association of adrenal insufficiency and thyroid dysfunction, as well as articles dealing with the finding at autopsy or by biopsy of thyroid lesions in patients with Addison’s disease.
The most extensive study of adrenal antibodies is that of Blizard et al (10, 11). Adrenal antibodies were found in 16 (53%) of 31 patients with Addison's disease, but in none of 15 patients with either Cushing's disease or virilizing adrenal hyperplasia. Data were not always available to indicate whether the adrenal insufficiency was caused by tuberculosis, sarcinoma, amyloidosis, histoplasmosis, or idiopathic atrophy. Seven of 6 patients with Addison's disease and adrenal antibodies also had thyroid antibodies which were detected by the Coons method applied to unfixed thyroid tissue. It was felt, however, that the two antibodies must be distinct as 22 patients with Hashimoto's disease had no adrenal antibodies. In a subsequent report, Blizard and Kyle (11) found adrenal antibodies in the serum of 36 of 67 Addisonian patients studied by the indirect Coons method. Complement-fixing antibodies were found in 24 of these 35 patients. These antibodies were organ specific, but not species specific. Twenty-two of these Addisonians also had circulating anti-thyroid antibodies as measured by the indirect Coons test using unfixed thyroid slices. Eight of the 36 with adrenal antibodies also had circulating antibodies to the intercalated ducts of submaxillary and parotid salivary tissue. None of these patients had Sjögren's syndrome. Blizard and Kyle also demonstrated that the antigen with which the circulating antibody reacts is in both the microsomal and mitochondrial fractions of tissue. They point out that although many of the criteria needed to classify "idiopathic" Addison's disease as an auto-immune process have been established, the role of the circulating antibodies has not been determined. Such antibodies may only reflect the disease process and not be etiologically related to it.

Anderson, in a recent review of the subject of autoantibodies in man (2), mentions a patient with Addison's disease whose serum reacted with adrenal but not with thyroid extract. Of interest was another patient with Hashimoto's disease whose serum contained antibody to thyroid and adrenal and who developed Addison's disease several months later.

Colover and Glynn, in 1958, reported the development of extensive adrenal inflammatory changes in rabbits immunized with adrenal tissue in Freund's adjuvant, but no search for specific antibody was carried out (25). In 1960, Steiner et al (129) injected either pooled adrenal extract or isologous adrenal into guinea pigs and found focal adrenalitis in six of eleven homoinmune and ten of twelve isoinmune animals. One of the latter group showed thyroiditis also.

Witebsky (143) and Milgrom et al (93) were successful in eliciting the formation of serum antibodies by injection of homologous adrenal tissue in animals. Furthermore, animals immunized in this fashion often showed inflammatory lesions in the adrenals, especially in the inner cortical area. While there can be no question about the occurrence of significant adrenalitis and the development of organ-specific humoral antibody in rabbits and guinea pigs given suspensions of homologous or isologous adrenal tissue, the significance of these findings in terms of human disease is far from clear. Indeed, Terplan, Witebsky, and Milgrom (137) pointed out the fact that the histologic lesions correlate very poorly with serologic data in their animals. Of perhaps more importance is their further observation of occasional adrenal lesions in control animals given only Freund's adjuvant or suspensions of tissues other than adrenal. Their conclusion, that the adrenal inflammation in experimental animals injected with adrenal tissue cannot be related exclusively to a specific immune response, seems fully justified.

III. METHODS EMPLOYED IN THE PRESENT STUDY

A. Clinical Material

This study resulted from the observation of a patient (Case #1, Table II) with Addison's disease, thyroid dysfunction, and diabetes mellitus. From Johns Hopkins Hospital and clinic records, it was possible to locate twelve additional patients with multiple endocrinopathy. Eleven of the 13 were admitted to the Metabolic Unit of the hospital for study, and two were followed closely in the Outpatient Department. In the course of the study, two additional patients (Cases #11 and #12) were observed and included in the study. Data and serum for Case #11 were supplied by Dr. A. Asadi, and for Case #12, Dr. William Engstrom supplied information and serum.

As is shown in Table II, there were nine females and six males, ranging from 10 to 58 years of age. Clinical studies included serologic tests, liver function tests, electrolyte determinations, roentgenograms, and skin tests for tuberculosis and fungal diseases. Because neither tuberculosis nor any other etiologic agent causing the Addison's disease could be determined in the first 12 patients, they were adjudged to have idiopathic adrenal atrophy. Patients 13, 14, and 15, appearing at the bottom of Table II, have Addison's disease presumably as a result of sarcoidosis (Case #13) and of tuberculosis (Cases #14 and 15). Careful attention was paid to any history of allergic reactions in the patient and to the familial incidence of hypersensitivity and endocrine disorders. Spe-
<table>
<thead>
<tr>
<th>No.</th>
<th>Initial</th>
<th>J.H.H. sl. number</th>
<th>Sex</th>
<th>Race</th>
<th>Age on set of symptoms</th>
<th>Age at time of study</th>
<th>Type of disease</th>
<th>Order of onset</th>
<th>Old tuberculin skin test</th>
<th>Adrenal</th>
<th>Thyroid</th>
<th>Non-specific</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>W.B.</td>
<td>135736</td>
<td>M</td>
<td>W</td>
<td>43</td>
<td>11</td>
<td>Idiopathic</td>
<td>++++</td>
<td>T A D</td>
<td>Negative</td>
<td>3+</td>
<td>1:40</td>
<td>73 units (high)</td>
</tr>
<tr>
<td>2</td>
<td>E.R.</td>
<td>734655</td>
<td>F</td>
<td>W</td>
<td>58</td>
<td>40</td>
<td>Idiopathic</td>
<td>0</td>
<td>T A</td>
<td>Negative</td>
<td>5+</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>3</td>
<td>V.W.</td>
<td>379718</td>
<td>F</td>
<td>C</td>
<td>41</td>
<td>39</td>
<td>Idiopathic</td>
<td>++</td>
<td>A D T</td>
<td>Negative</td>
<td>4+</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>4</td>
<td>E.R.</td>
<td>830158</td>
<td>M</td>
<td>W</td>
<td>15</td>
<td>14</td>
<td>Idiopathic</td>
<td>+++</td>
<td>A A D T</td>
<td>Negative</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>L.A.</td>
<td>356114</td>
<td>F</td>
<td>W</td>
<td>52</td>
<td>45</td>
<td>Idiopathic</td>
<td>++</td>
<td>A D T</td>
<td>Negative</td>
<td>3+</td>
<td>0</td>
<td>4+</td>
</tr>
<tr>
<td>6</td>
<td>J.E.</td>
<td>726097</td>
<td>F</td>
<td>W</td>
<td>46</td>
<td>45</td>
<td>Idiopathic</td>
<td>0</td>
<td>A T</td>
<td>Negative</td>
<td>3+</td>
<td>4+</td>
<td>4+</td>
</tr>
<tr>
<td>7</td>
<td>H.S.</td>
<td>972033</td>
<td>F</td>
<td>W</td>
<td>16</td>
<td>10</td>
<td>Idiopathic</td>
<td>+++</td>
<td>A D T</td>
<td>Negative</td>
<td>5+</td>
<td>4+</td>
<td>5+</td>
</tr>
<tr>
<td>8</td>
<td>M.D.</td>
<td>277824</td>
<td>M</td>
<td>W</td>
<td>50</td>
<td>28</td>
<td>Idiopathic</td>
<td>+</td>
<td>A T D</td>
<td>Negative</td>
<td>6+</td>
<td>4+</td>
<td>4+</td>
</tr>
<tr>
<td>9</td>
<td>R.M.</td>
<td>177612</td>
<td>F</td>
<td>W</td>
<td>57</td>
<td>57</td>
<td>Idiopathic</td>
<td>+++</td>
<td>A D D</td>
<td>Negative</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>M.S.</td>
<td>655072</td>
<td>F</td>
<td>W</td>
<td>35</td>
<td>35</td>
<td>Idiopathic</td>
<td>+++</td>
<td>A D D</td>
<td>Negative</td>
<td>6+</td>
<td>4+</td>
<td>3+</td>
</tr>
<tr>
<td>11</td>
<td>L.A.</td>
<td>567121</td>
<td>F</td>
<td>W</td>
<td>33</td>
<td>33</td>
<td>Idiopathic</td>
<td>T</td>
<td>A</td>
<td>Negative</td>
<td>3+</td>
<td>2+</td>
<td>3+</td>
</tr>
<tr>
<td>12</td>
<td>C.S.</td>
<td>827341</td>
<td>F</td>
<td>W</td>
<td>46</td>
<td>46</td>
<td>Idiopathic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>M.D.</td>
<td>964820</td>
<td>F</td>
<td>W</td>
<td>44</td>
<td>31</td>
<td>Sarcoid</td>
<td>0</td>
<td>A T</td>
<td>Negative</td>
<td>3+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>D.P.</td>
<td>225559</td>
<td>F</td>
<td>C</td>
<td>37</td>
<td>28</td>
<td>TBC</td>
<td>+++</td>
<td>A D D</td>
<td>Positive</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>P.M.</td>
<td>144800</td>
<td>M</td>
<td>W</td>
<td>56</td>
<td>30</td>
<td>TBC</td>
<td>+++</td>
<td>(A/T) D</td>
<td>Positive</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
</tr>
</tbody>
</table>

1. Diabetes: + = Prediabetic GTT; ++ = Hyperglycemia, 2 hr. po.; +++ = Diabetic GTT; ++++ = Diabetic Acidosis.
2. C.F. = Complement Fixation.
3. A.N.A. = Antinuclear Antibodies.
4. Penicillin.
5. Age of patient #13 is unknown.
G. Histologic Studies

There were 31 instances of chronic adrenal insufficiency found among the first 23,000 autopsies performed at the Johns Hopkins Hospital. Seven of these were excluded from this study: six (four tuberculous and two idiopathic atrophy) in which thyroid tissue had not been obtained, and one in which the adrenals had been destroyed by secondary neoplasm.

Of the 24 cases remaining, 16 were tuberculous in origin and eight were examples of idiopathic adrenal atrophy.

Histologic sections stained with hematoxylin and eosin were reviewed, and, where indicated, additional sections were prepared from the original paraffin blocks or from wet tissue stored permanently in formalin. Special stains for connective tissue, elastic tissue, tubercle bacilli or other purposes were performed whenever needed.

In addition, the adrenal glands of 28 patients found to have Hashimoto's disease at autopsy were re-examined. The cases were selected at random from among autopsies performed between 1945 and 1960 and consisted of 23 females and 5 males ranging in age from 32 to 62 years.

IV. RESULTS

A. Clinical Studies

Table II summarizes information on the 15 patients studied. All had Addison's disease and thyroid dysfunction, and in ten, the symptoms of adrenal insufficiency preceded those of thyroid disease; in one (Case 15) the symptoms appeared simultaneously. Two of the patients had tuberculosis. In the 13 instances in which old tuberculin skin tests were performed, reactions were negative in 11 and positive in two. Six of the 15 had had severe allergic reactions; one (Case 8) had Raynaud's phenomenon; another (Case 10) had erythema nodosum, arthritis and a positive LE cell test; and two others (Cases 6 and 15) had a positive Rose test. Ten of 13 patients tested had serum antibodies to thyroid; five also had antibodies against adrenal tissue. In addition one patient (Case 13) had antibodies against adrenal tissue alone.

Nine patients had frank diabetes mellitus.

Table III summarizes the results of tests of adrenal cortical and thyroid function performed on these 15 patients.

The pertinent clinical data for each patient are summarized in the following case abstracts:
<table>
<thead>
<tr>
<th>No.</th>
<th>Initial</th>
<th>J.H.H. history number</th>
<th>Control steroids</th>
<th>ACTH stimulation</th>
<th>SU 48 hr or water loading test</th>
<th>PBI or TRC*</th>
<th>TSH</th>
<th>RAUL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>W.B.</td>
<td>135796</td>
<td>0.0 mg/24 hr</td>
<td>No increase</td>
<td>No increase</td>
<td>PBI 0.8 µg%</td>
<td>No increase</td>
<td>2% at 2 hr</td>
</tr>
<tr>
<td>2</td>
<td>E.S.</td>
<td>784805</td>
<td>0.0 mg/24 hr</td>
<td>1.0 mg/24 hr</td>
<td>No increase</td>
<td>PBI 4.8 µg%</td>
<td>No increase</td>
<td>3% at 24 hr</td>
</tr>
<tr>
<td>3</td>
<td>V.W.</td>
<td>379718</td>
<td>0.7 mg/24 hr</td>
<td>0.8 mg/24 hr</td>
<td>No increase</td>
<td>TBC 3.1 µg%</td>
<td>No increase</td>
<td>14% at 24 hr</td>
</tr>
<tr>
<td>4</td>
<td>E.R.</td>
<td>930188</td>
<td>1.6 mg/24 hr</td>
<td>No increase</td>
<td>Water loading test positive</td>
<td>PBI 2.0 µg%</td>
<td>No increase</td>
<td>45% at 24 hr</td>
</tr>
<tr>
<td>5</td>
<td>I.A.</td>
<td>301514</td>
<td>Plasma F</td>
<td>No increase</td>
<td>Water loading test positive</td>
<td>TBC 2.8 µg%</td>
<td>No increase</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>J.E.</td>
<td>728057</td>
<td>0.0 mg/24 hr</td>
<td>2.4 µg%</td>
<td>No increase</td>
<td>PBI 2.2 µg%</td>
<td>No increase</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>H.S.</td>
<td>973423</td>
<td>0.44 mg/24 hr</td>
<td>0.42 mg/24 hr</td>
<td>No increase</td>
<td>TBC 2.4 µg%</td>
<td>No increase</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M.D.</td>
<td>237824</td>
<td>0.1 mg/24 hr</td>
<td>No increase</td>
<td>No increase</td>
<td>TBC 2.4 µg%</td>
<td>No increase</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>R.M.</td>
<td>177912</td>
<td>0.4 mg/24 hr</td>
<td>No increase</td>
<td>No increase</td>
<td></td>
<td></td>
<td>5% at 2 hr</td>
</tr>
<tr>
<td>10</td>
<td>M.M.</td>
<td>668072</td>
<td>2.5 mg/24 hr</td>
<td>No increase</td>
<td>Water loading test positive</td>
<td></td>
<td></td>
<td>13% at 24 hr</td>
</tr>
<tr>
<td>11</td>
<td>I.A.</td>
<td>Iraq</td>
<td></td>
<td></td>
<td></td>
<td>PBI 4.7 µg%</td>
<td></td>
<td>26% at 2 hr</td>
</tr>
<tr>
<td>12</td>
<td>C.S.</td>
<td>Wisconsin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51% at 24 hr</td>
</tr>
<tr>
<td>13</td>
<td>M.D.</td>
<td>304290</td>
<td>0.0 mg/24 hr</td>
<td>No increase</td>
<td>No increase</td>
<td>TBC 1.2 µg%</td>
<td></td>
<td>6% at 2 hr</td>
</tr>
<tr>
<td>14</td>
<td>D.F.</td>
<td>256569</td>
<td>0.1 mg/24 hr</td>
<td>No increase</td>
<td>No increase</td>
<td>TBC 1.7 µg%</td>
<td></td>
<td>26% at 24 hr</td>
</tr>
<tr>
<td>15</td>
<td>F.M.</td>
<td>144800</td>
<td>2.0 mg/24 hr</td>
<td>No increase</td>
<td>No increase</td>
<td></td>
<td></td>
<td>3% at 2 hr</td>
</tr>
</tbody>
</table>

* TBC—Thyroxine By-Column.
Case 1: W. B. (JHH #135796)

This 44 year old white male stockroom clerk was first seen at age 11 when he developed a diffuse goiter and classical signs of hyperthyroidism. At this time the BMR was +58. One year after a subtotal thyroidectomy his BMR was -3, and he was clinically euthyroid. At age 18, he returned to the outpatient clinic because of concern over "his failure to grow". He was only 57 inches tall, but was otherwise in good health. Examination revealed a small, but well-developed adolescent male with blood pressure of 90/70, definite brownish pigmentation over the face, and normally developed genitalia. Pertinent laboratory data included a BMR of -23 and roentgenograms indicative of markedly delayed bone maturation. Over the following two years, he noted progressive fatigue, and growth remained stunted, and he was found to have more marked pigmentation. The prostate was normal. There were severe hypostenemia (107 mEq/L) and hypochloremia, consistently decreased basal metabolic rates (-33, -33, -35, and -40) and a serum cholesterol of 300 mg/100 ml. The sella turcica glucose tolerance tests were normal. He was thought to have both Addison's disease and hypothyroidism and was placed on high salt diet and desiccated thyroid, 64 mg/day, with improvement. The BMR had risen to +18 by time of discharge.

At the age of 32, he was admitted in diabetic acidosis and has taken insulin regularly since that time.

A reevaluation, at age 44, showed him to be euthyroid and his diabetes and Addison's disease to be well controlled. PBI was normal, and RAIU was markedly depressed, being unaltered by TSH stimulation. No rise in 17-hydroxyxorticoids was detectable in the patient's urine after ACTH stimulation. Old tuberculin skin test was negative.

There was a family history of Graves' disease, diabetes mellitus, and non-toxic nodular goiter. The mother, father, and two siblings were all found to have anti-thyroid antibodies.

Case 2: E. S. (JHH #784805)

This 54 year old white widow developed thyrotoxicosis at age 35. She was treated by subtotal thyroidectomy. She was first admitted to the Johns Hopkins Hospital at age 48, with hypotension, generalized pigmentation, azotemia, and hyperkalemia. Subsequent studies revealed urinary 17-hydroxyxorticoids excretion to be less than 1 mg/24 hr and PBI to be 4.5 µg%. Steroid replacement therapy resulted in complete alleviation of symptoms.

During another admission at age 53, ACTH failed to stimulate 17-hydroxyxorticoid excretion, PBI was normal, the RAIU was elevated and thyroxine-by-column was decreased (3.1 µg%). On the basis of these findings and strongly positive tests for thyroid antibodies, a diagnosis of Hashimoto's disease was made. Old tuberculin skin test was negative at the 1:1000 dilution.

There was a family history of asthma, multiple food and drug allergies, hypertension and Graves' disease.

Case 3: V. W. (JHH #379718)

This 49 year old colored woman, was first admitted at age 41 with exfoliative dermatitis secondary to an allergy to phenobarbitol which she had been taking for control of idiopathic epilepsy.

Endocrine evaluation revealed a depressed PBI and low normal RAIU which rose to normal with TSH stimulation. Fasting blood sugars were elevated, but no glycosuria was noted. Cortisone therapy was given for her dermatitis but was discontinued after discharge.

Evaluation at age 49 resulted in a diagnosis of hypothyroidism with thyroid function unaltered by four days of TSH stimulation. The patient exhibited decreased adrenocortical reserve with low baseline 17-hydroxyxorticoid excretion and negative ACTH stimulation test. Old tuberculin skin test was negative at a 1:1000 dilution.

Case 4: E. R. (JHH #930168)

This 22 year old white man was first admitted at age 14 for evaluation of generalized hyperpigmentation, weight loss, and weakness.

He was found to be hypotensive, hypostreumic, and hyperkalemic. A glucose tolerance test revealed a diabetic curve, but no glycosuria was noted. During a standard intravenous ACTH stimulation test he developed an anaphylactoid response, and plasma corticoid levels failed to rise significantly. Adrenocortical replacement therapy was begun. Old tuberculin and histoplasmin skin tests were negative.

During subsequent visits, an ACTH stimulation test revealed no rise in 17-hydroxyxorticoid output. At age 17, a firm, symmetrical thyroid gland 1½ times normal size was noted, but the patient was considered clinically to be euthyroid, and no thyroid function studies were obtained.

Family history was positive for diabetes, tuberculosis, and epilepsy.

Case 5: I. A. (JHH #391514)

This 61 year old white housewife, first noted gradual weight loss, postural syncope, and generalized hyperpigmentation at age 43. She was admitted to another hospital with chest pain, nausea and vomiting, and a diagnosis of Addison's dis-
ease was made. A single fasting blood sugar was elevated.

At age 44, she was admitted to Johns Hopkins Hospital with acute adrenal insufficiency and was noted to have a visibly enlarged thyroid. Her BMR was -20, DOCA pellet implantation therapy was begun.

At age 48, she was re-admitted in shock, and steroid replacement therapy was begun. During the following decade she was admitted on several occasions for DOCA pellet implantation.

At age 60, reevaluation revealed an inability to stimulate the adrenals with ACTH, a normal PBI, but a low thyroxine-by-column (2.8 μg%), a diabetic glucose tolerance test, and a negative old tuberculin skin test.

Case 8: J. E. (JHH #728067)

This 53 year old white woman was diagnosed at age 67 as having Addison's disease on the basis of hypotension, hyponatremia, hyperkalemia, generalized hyperpigmentation, and weight loss. She was begun on steroid replacement therapy. One month later she was referred to the Johns Hopkins Clinic where the diagnosis was confirmed. 

At age 50, she was admitted to the Johns Hopkins Hospital and treated for an Addisonian crisis. Her thyroid was noted to be approximately twice normal size, but she was considered clinically to be euthyroid. Roentgenograms of the chest and abdomen were normal; old tuberculin skin test was negative.

Case 7: H. S. (JHH #973460)

This 13 year old white girl was referred to the Johns Hopkins Hospital at age 10 for evaluation of Addison's disease diagnosed a few months earlier when she had had an episode of peripheral vascular collapse during an attack of gastroenteritis. Because she had been noted at that time to be hyperpigmented, hyponatremic, and hyperkalemic, she was begun on steroid replacement therapy.

On admission, steroids were discontinued, and she developed hyponatremia and hypokalemia. A water excretion test was positive, and ACTH failed to bring urinary 17-hydroxycorticoids to normal levels. PPD, histoplasmin, and coccidiodin skin tests were negative. Her glucose tolerance curve was diabetic. Steroid replacement therapy was instituted. At age 11, she was found to have a firm goiter. An LE cell test was negative.

Case 8: M. D. (JHH #237824)

This 50 year old white salesman was found to have Addison's disease at the age of 25 when he was admitted to Presbyterian Hospital in New York in mild crisis with hypotension, generalized hyperpigmentation, weakness and weight loss. DOCA pellet implantation therapy was instituted at that time, and cortisone was added to his regimen three years later.

Shortly after the diagnosis of Addison's disease was made, he developed recurrent episodes of classical Raynaud's phenomenon each winter. At age 35 he was found to have a diffuse non-tender goiter, which persisted for at least four years. He has consistently demonstrated a positive STS with negative tests for specific treponemal antigens since the age of 39.

During admission to the Johns Hopkins Hospital for DOCA pellet implantation at age 49, reevaluation revealed the failure of ACTH stimulation to raise urinary 17-hydroxycorticoids, a PBI of 4.7 μg%, and a depressed RAIU. Calcification of the pines and Paget's disease of the skull were noted. A glucose tolerance test showed an abnormal curve of diabetic type. The patient was clinically euthyroid; old tuberculin skin test was negative.

Family history was positive for Graves' disease and Raynaud's phenomenon.

Case 9: R. M. (#177912)

This 57 year old white housewife was first admitted to the Johns Hopkins Hospital at age 33 with generalized hyperpigmentation, weight loss, weakness, nausea, and vomiting. A glucose tolerance test at that time was normal. DOCA pellet implantation therapy was begun.

The patient was readmitted on more than 20 occasions for treatment of adrenal crises or for pellet implantation prior to being placed on cortisone at age 46. She had a severe urticarial rash of undetermined origin at age 34, and she was noted, at age 44, to have diffuse thyromegaly with a low normal RAIU. At age 49, the RAIU was elevated and the PBI was normal. Her glucose tolerance test was typical of diabetes mellitus. Old tuberculin skin test was negative.

At age 55, a normal PBI, a low concentration of serum thyroxine (thyroxine-by-column), and a markedly elevated RAIU were observed. The patient was clinically euthyroid, and exhibited a firm thyroid gland about twice normal size.

Case 10: M. S. (JHH #68072)

This 36 year old white woman was first admitted to the Johns Hopkins Hospital at age 27 with acute arthritis of the metacarpophalangeal joints, erythema nodosum, myalgia, and a history of pleurisy and urticarial reactions to penicillin, sulfonamides, and barbiturates.
She was admitted at age 33 with hyperpigmentation, vitiligo, weakness, and hypotension and was subsequently found to have markedly depressed urinary 17-hydroxycorticoids. Old tuberculin skin test was negative. PBI and glucose tolerance test were normal.

Reevaluation at age 36 showed that the PBI was normal but was unaltered by prolonged TSH stimulation. Her thyroxine-by-column was low (2.4 μg%) and a glucose tolerance test was typical of diabetes. LE preparations have shown homogeneous extracellular material on several occasions.

Case 11: A. I. (Baghdad, Iraq)

This 34 year old white housewife was seen at age 33 with a history of longstanding asymptomatic goiter. Two weeks prior to her visit she started to complain of enlargement, pain, and tenderness of the goiter, general weakness, lassitude, and easy fatigueability. She had had amenorrhea for the two months just prior to her visit. She had a blood pressure of 108/70, a pulse of 88, and a hard, tender, diffuse goiter. Her chest film was normal; her 48 hr plasma T3 was 0.07% of the administered dose per liter. Three weeks later, she complained of severe weakness, and her blood pressure was 80/60. At this time the association of Addison’s disease with thyroiditis was strongly suspected. Her fasting blood glucose was 90 mg%. A water loading test was positive. On thyroid and adrenal replacement therapy, she improved steadily and remains asymptomatic.

Case 12: C. S.

This white male was first seen in September 1952, because of several dental abscesses. In 1947, while in military service, he had developed gradual onset of weakness, weight loss, and increased skin pigmentation. He was hospitalized in November 1947 with nausea, vomiting, extreme weakness, and prostration. Abnormal findings included a blood pressure of 80/40 and increased pigmentation of the skin and oral mucosa. Serum chloride ranged from 82 to 94 mEq/L. A BMR was −5%. A diagnosis of Addison’s disease was made, and treatment was begun with desoxy corticosterone acetate (DOCA) with improvement.

He was rehospitalized about four years later, in July 1956, with vomiting and stupor. His last DOCA implant had been in November 1954. Physical examination revealed pigmentation, mental sluggishness, puffiness of the face and eyelids, and blood pressure of 92/66. The thyroid gland was not palpable. The impression was that he was in Addisonian crisis and had, in addition, hypothyroidism. Laboratory studies revealed: normal hemogram, normal urinalysis, blood glucose—68 mg/100 ml, Na 122 mEq/L, K 56 mEq/L, and PBI 1.8 μg%. After two days of 10 units of TSH intramuscularly, the PBI remained low, 1.2 and 1.7 μg%. Serum thyroid antibody was negative by precipitin test (gel diffusion).

Maintenance therapy of 25 mg of oral cortisol and 2 mg of DOCA linguate daily was begun, but he remained sluggish and complained of feeling cold. The addition of 120 mg of desiccated thyroid daily was followed by dramatic improvement. The patient was discharged in late August of 1956, returned to work, and has remained well.

Case 13: M. D. (JHH 830429)

This 44 year old white housewife was first seen at age 31 when she developed hyperpigmentation, progressive weakness, salt craving, and loss of axillary hair. At this time her 17-hydroxycorticosteroid excretion was 1.4 mg/day, and her O.T. was negative at 1 to 100.

She was treated with cortisone and DOCA pellet implantation, which brought about only moderate improvement. Over the next five years she complained constantly of feeling sluggish, and at age 36 her PBI was 3.9 μg/100 ml. The following year, because of persistent menorrhagia, she had a total abdominal hysterectomy and salpingoo-variectomy. At surgery, she was found to have small implants on the serosal surface of the uterus which, on pathological examination, showed “scattered groups of epithelioid-like cells surrounded by thin layers of chronic inflammatory reaction.” The myometrium showed “clusters of tubercles beneath the serosal surface” consisting of small groups of epithelioid cells and giant cells surrounded by slight chronic inflammatory reaction. Acid fast and fungal stains were negative. Repeated tuberculin skin tests were negative at a 1 to 100 dilution. The patient received eleven months of antituberculous therapy at the Mt. Wilson sanitarium after a presumptive diagnosis of “pelvic tuberculosis”. In 1957 she was readmitted with a mild adrenal crisis and treated with replacement therapy. She has been clinically stable since that time. In 1962, the patient was admitted for study and was shown to have primary adrenal and thyroid insufficiency. Her thyroid was described as being twice normal size and firm, but not nodular. Twice in childhood the patient had acute rheumatic fever accompanied by chorea. In her teens she had several subsequent episodes of swelling of the joints and extremities at nearly yearly intervals until therapy for Addison’s disease was begun at age 34. In addition, she received gold therapy at age 26 for a diagnosis of rheumatoid arthritis. She is allergic to penicillin which produces an urticaria.

The patient’s mother was begun on therapy.
for hypothyroidism at age 54. One brother underwent partial thyroidectomy for goiter at age 23. Her maternal grandmother and one of the maternal grandmother's children had Addison's disease.

Case 14: D. F. (JHH #256569)

This 28 year old colored housewife was first seen at the Johns Hopkins Hospital at age three when a diagnosis of pulmonary tuberculosis and phlyctenular keratitis was made. At age 28 she developed progressive hyperpigmentation, lethargy, nausea, and vomiting. Over the ensuing year she lost 40 lbs. She was hospitalized and had unequivocal laboratory evidence of Addison's disease, increased gamma globulin, and a positive O.T. at 1 to 100,000 dilution. She was put on steroid replacement therapy and has remained asymptomatic. At age 31 she was found to have a diffusely enlarged thyroid. However, her thyroid function tests were normal. At age 37 she was found to be stable except for the development of a diabetic glucose tolerance test. The family history was positive for pulmonary tuberculosis and arthritis.

Case 15: F. M. (JHH #144890)

This 57 year old storeroom clerk was first admitted to Johns Hopkins Hospital at age 32 with a history of weakness and orthostatic syncope of two years duration, and progressive darkening of the skin of three months duration. Pertinent physical findings included lethargy, blood pressure of 84/59, and hyperpigmentation. His BMR was -18 and -23. Old tuberculin skin test was positive at 1 to 1000 dilution. Administration of purified adrenal cortical extract over a three day period resulted in a positive sodium balance. The patient was thought to have both Addison's disease and hypothyroidism and was discharged on a high salt diet.

The patient was readmitted in October 1938, and in January 1939, because of continued weakness with periodic exacerbations. On both admissions marked subjective and objective improvement resulted from injection of desoxycorticosterone acetate in oil. During the period 1939-1952, the patient had five emergency hospital admissions. He arrived the first time in an unresponsive state with hyperactive deep tendon reflexes, was found to have a blood sugar of 28 mg/100 ml and responded dramatically to intravenous glucose. The next four emergency admissions were due to moderate to severe Addisonian crisis. Calcification of the pineal was first noted in 1950.

Cortisone replacement therapy was begun in June 1952, with immediate and marked subjective improvement. Hyperpigmentation diminished gradually on cortisone therapy, and pigmentation is no longer remarkable. Since 1952, the patient has had three fasting blood sugar determinations of 120 mg/100 ml or higher in addition to a diabetic glucose tolerance test.

Because of persistently low BMR determinations, the patient has been intermittently on desiccated thyroid, in doses ranging from 35 to 125 mg/day. This therapy has not been attended by any real subjective or objective improvement. In 1967, he was found to have PBI levels of 2.7 and 2.9 µg%, cholesterol of 335 mg/100 ml; his radioactive iodine uptake was at the lower limits of normal (slope = 0.35) and not altered by TSH.

On the most recent admission (February 1962), PBI and RAI uptake were extremely low and again were not altered by TSH. At this time a Rose test was positive (1:10 for washed cells, 1:160 for sensitised cells).

It is noteworthy that throughout the patient's course, repeated evaluation has revealed no evidence of pituitary dysfunction. Libido has been good, prostate and testes have always been described as normal, and his target glands have shown no response either to TSH or to ACTH.

At most recent follow-up visit in December 1963, he was entirely asymptomatic.

B. Histologic Observations

Table IV summarizes the results of a reexamination of the histologic findings in 24 autopsies of patients with Addison's disease.

1. Adrenal lesions. In the 16 cases of tuberculosis, the adrenals were enlarged; massive caseation, fibrosis, and chronic inflammation were constant findings. Calcification was frequent, and, in addition to extensive loss of cortical cells, medullary tissue was regularly involved. This nonspecific destruction of both cortex and medulla in adrenal tuberculosis has been noted frequently in the past (36, 58, 133).

In the eight cases of idiopathic atrophy, the adrenals were invariably tiny. Indeed, in several instances grossly identifiable glandular tissue was absent, and only by making serial histologic sections of suprarenal fat and connective tissue were cortical remnants found. Medullary tissue was generally spared. As has been pointed out in the past (36, 58, 133), the changes in the adrenal cortex referred to as "atrophy" represent far more than a gradual "passive" shrinkage of the gland. The histologic picture is one of necrosis of individual cells and groups of cells with apparent attempts at regeneration with formation of tiny cortical...
<table>
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<th>Age</th>
<th>Type of disease</th>
<th>Duration of symptoms</th>
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<th>Thymic atrophy</th>
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nODULES. There is subacute and chronic inflammation with infiltration by lymphocytes, macrophages, and plasma cells, and of nonspecific repair with fibrosis. Overall, the process appears to be a slowly progressive necrosis of cortical cells with resultant cycles of inflammation, attempted regeneration, and repair by fibrosis. In occasional glands, one or more lymphoid follicles with active germinal centers were noted, but these were never plentiful and could not be looked upon as an essential feature of the lesion at this late stage. It is conceivable, of course, that lymphoid follicles may have been more numerous at an earlier time in the course of the lesion.

2. THYROID LESIONS. In the past, the thyroid lesions have been referred to as being “similar” to those in the atrophic adrenal. However, frank necrosis of thyroid epithelium was never seen. There was an extensive infiltration of lymphocytes and moderate numbers of plasma cells which, while variable in intensity, involved all of the gland. Numerous germinal centers were present and occasional mild fibrosis was noted.

Characteristic changes of the type described by many observers in the past were noted in the thyroids of three of the 16 patients with tuberculosis Addison’s disease and in all eight of those with idiopathic adrenal atrophy. This greater incidence of thyroid changes in the idiopathic Addisonian group has been noted and commented upon by others (14, 17, 141) and is clearly evident in the summary in Table I.

While the lymphoid tissue gave the appearance of compressing or displacing thyroid follicles, no evidence of direct epithelial injury was seen. Although Hurlthle or Hashkensky cell changes were demonstrable in every gland, these were relatively infrequent. The thyroid epithelium tended to be normal or low in all follicles. Desquamation was not seen or was trivial in amount.

All glands were described grossly as small in contrast to the usual enlargement of the thyroid in Hashimoto’s disease. Again, this may reflect only the advanced stage of the process. In general, the microscopic picture seems best referred to as a lymphocytic thyroiditis although all of the individual components of Hashimoto’s disease were present to some degree. The criteria used to divide lesions into these two categories are far from clear, and, without rehearsing past arguments (7, 46, 54, 57, 94, 121), the decision in the individual case can be regarded as a quantitative judgment rather than a qualitative analysis.

3. OTHER LESIONS. Three patients with idiopathic adrenal atrophy, Case #7, reported previously by Duff and Bernstein, Case #8, and Case #20 showed tiny foci of necrosis in the anterior hypophysis with accumulation of round cells and plasma cells. While these lesions resembled closely those in the adrenal, more so than did the thyroid changes, there was nothing to suggest that the destruction of hypophysal substance had progressed to a point that would be functionally significant.

None of the sections of pancreas showed more than a trivial abnormality; diabetes had been detected in no patient during life.

4. THE ADRENAL GLAND IN HASHIMOTO’S DISEASE.

Review of the microscopic sections of the adrenal glands of 28 patients found to have typical Hashimoto’s disease at autopsy revealed no lesions resembling the changes of idiopathic adrenal atrophy. The adrenals were normal; nothing was seen which could be interpreted as an early stage of the adrenal lesion in idiopathic Addison’s disease.

V. DISCUSSION

Twelve of the 15 patients with Addison’s disease reported here were shown also to have some abnormality of thyroid function uncomplicated by pituitary disease and, therefore, can be categorized as examples of Schmidt’s Syndrome. Two of the three remaining patients (Cases #4 and #7, Table II) had goiters, but no studies of thyroid function were obtained; the remaining patient (Case #14) had a goiter but no discernible abnormality in thyroid function. The original thyroid abnormality in two cases was hyperthyroidism; however, one of these patients developed myxedema after subtotal thyroideectomy. In five other patients there were overt clinical signs of hypothyroidism. In two cases, the clinical diagnosis of Hashimoto’s thyroiditis was made, and five other patients had goiters but lacked clinical signs of impaired function.

Of further interest is the fact that eight of the 15 patients had unequivocal diabetes mellitus; another exhibited an abnormal glucose tolerance test, and another had hyperglycemia two hours postprandially. In both cases with thyrotoxicosis, the thyroid abnormality was
noted before the clinical-diagnosis of Addison's disease was made. However, in seven of the ten cases of Schmidt's syndrome concurrent with diabetes, Addison's disease preceded the onset of both the carbohydrate defect and the thyroid abnormality.

The increasing frequency with which coexistent adrenal insufficiency and diabetes mellitus have been reported has been emphasized by Beaven et al (8) and Wehrmacher (140). The results of the present study document an apparent increase in patients showing adrenal and thyroid insufficiency and diabetes mellitus. Table I (*) summarizes additional cases of this triglandular abnormality reported by others.

Thus, to Schmidt's triglandular syndrome may be added the coincidence of adrenal insufficiency and diabetes mellitus as well as the glandular triad of Addison's disease, thyroid dysfunction and diabetes mellitus.

A. Antibody Studies

Antibody studies were obtained in all 15 patients. Thirteen patients showed antibodies against thyroid and nine against adrenal. It is interesting that both patients with Addison's disease of presumably tuberulous origin failed to demonstrate antibodies against adrenal but did manifest antibodies against thyroid. Two patients had a positive Rose test, another had a biological false-positive STS (this same patient had a history of Raynaud's phenomenon), and the serum of still another patient contained antinuclear antibodies similar to those found in systemic lupus erythematosus. For the present, it can only be said that the findings are in accord with those reported by others (2, 3, 10, 11, 52, 92) in various endocrinopathies and are of special interest in view of the previous suggestion of immunologic mechanisms in etiology.

B. Histologic Considerations

Extensive studies of Hashimoto's thyroiditis have pointed out that its histologic picture resembles in some ways that seen in experimental auto-immune thyroiditis, and the studies of Miescher et al provide important evidence that a delayed type of hypersensitivity response caused the actual damage (95). On the basis of extensive study of the histopathologic changes in experimental delayed hypersensitivity such as those of Waksman (140) and of Gell (48), the characteristic morphologic phenomena in these immune reactions can be summarized as: (1) the accumulation of hematogenous cells, lymphocytes, and monocytes around vessels in close relation to the tissue which contains antigen; (2) the increase in number of these cells, either by further accumulation or proliferation; (3) invasion of parenchyma by histocytes; and (4) direct destruction of antigen-containing elements by these histocytes. Plasma cells are present in some reactions but may be absent. In some cases, the antigen-antibody reaction may be so intense that germinal centers are actually formed in the tissue concerned, and the injured tissue literally seems to become a part of the immune apparatus.

That the findings described above bear a resemblance to the histologic changes in nontuberculous adrenal atrophy, in the lymphocytic thyroiditis of Addison's disease, and in Hashimoto's disease is evident. Furthermore, as Schmidt pointed out, the lesions in the salivary gland in Mikulicz's disease or what is now commonly referred to as Sjögren's disease are also similar to those already mentioned.

However, morphologic similarity alone does not permit conclusions as to a common etiology. Indeed, as has been mentioned, several slight differences in the histologic details of these human lesions, while possibly explainable upon duration of injury or stage of disease, may actually reflect etiologic differences and hence, be of more importance than the similarities.

While the histologic changes in both adrenal and thyroid in idiopathic Addison's disease are compatible with immunologic damage, they are by no means specific enough to exclude other causes of injury.

The differences, quantitative more than qualitative, between the thyroiditis of Addison's disease and Hashimoto's disease have been commented upon, and it must be admitted that the line of distinction is not sharp, allowing for considerable overlapping in interpretation. Failure in this study to find evidence of any adrenal lesion in 28 cases of Hashimoto's disease is, perhaps, more significant in this light. Whether idiopathic adrenal atrophy or Hashimoto's disease or both eventually prove to be autoimmune disorders, it now seems unlikely that they are of common etiology or that they are manifestations of the same underlying process.
positive serologic tests for syphilis and patients with systemic lupus erythematosus (123). These latter two groups also consist predominantly of women.

While the eventual significance of reported epidemiologic studies of Hashimoto's disease, Sjögren's disease, and systemic lupus erythematosus must await the results of more inclusive investigations in which such factors as preselection of patients and use of controls among the general population are considered, it seems worthwhile to attempt a compilation from the literature of information concerning Addison's disease.

Along with the difficulties of any retrospective study, an analysis of the type undertaken here faces three special problems: (1) the failure of many authors to specify sex of patients; (2) the frequent reporting of "Addison's disease" without specifying tuberculous, idiopathic, or other etiology for the disorder; and (3) the existence of numerous clinical studies unsupported by pathologic data, and numerous histologic studies giving incomplete clinical information.

Except for occasional references, noted in Table I, family studies are lacking. As noted in Table II, familial occurrence of endocrinopathy or allergic disease was found in some patients reported here. However, it is clear that there presently exists no basis for evaluating this type of sporadic observation and we can only conclude that the systematic collection of information in the future would be desirable.

An analysis of the incidence of lymphocytic thyroiditis in Addison's disease, compiled from published reports in which a group of cases of specified etiology (tuberculous or idiopathic) were examined and the presence or absence of thyroid lesions noted appears in Table V. These data clearly support the oft-repeated observation of individual authors that thyroid changes are much more frequent in patients with idiopathic adrenal atrophy than in patients with adrenal tuberculosis.

Table VI is a summary of information on the sex distribution or thyroid lesions and/or clinical thyroid dysfunction in patients with Addison's disease, compiled from Tables I and II. The preponderance of females with thyroid dysfunction or thyroid lesions among patients with Addison's disease of idiopathic or of tuberculous origin is evident. Other than to point out this sex

### TABLE V

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of cases of lymphocytic thyroiditis in patients with Addison's disease caused by:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atrophy</td>
</tr>
<tr>
<td>1. Dubois (1919)</td>
<td>3 of 5</td>
</tr>
<tr>
<td>2. Brenner (1928-9)</td>
<td>3 of 5</td>
</tr>
<tr>
<td>3. Wells (1930)</td>
<td>8 of 8</td>
</tr>
<tr>
<td>4. Susman (1930)</td>
<td>4 of 4</td>
</tr>
<tr>
<td>5. Crooke &amp; Russell (1935)</td>
<td>5 of 5</td>
</tr>
<tr>
<td>6. Baetenie (1937)</td>
<td>3 of 7</td>
</tr>
<tr>
<td>7. Jaffe (1937)</td>
<td>3 of 4</td>
</tr>
<tr>
<td>8. Duffin (1943)</td>
<td>5 of 5</td>
</tr>
<tr>
<td>9. Sloper (1953)</td>
<td>7 of 11</td>
</tr>
<tr>
<td>10. Bloodworth et al (1954)</td>
<td>7 of 8</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>45 of 57</strong></td>
</tr>
<tr>
<td><strong>Present Study:</strong></td>
<td><strong>8 of 8</strong></td>
</tr>
<tr>
<td><strong>New Total:</strong></td>
<td><strong>53 of 65</strong></td>
</tr>
</tbody>
</table>

### TABLE VI

<table>
<thead>
<tr>
<th>No. cases</th>
<th>Adrenal disease</th>
<th>Evidence for thyroid dysf.</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Unsufficient</td>
<td>Clinical</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>21</td>
<td>Tuberculosis</td>
<td>Clinical</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>Tuberculosis</td>
<td>Histologic</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>39</td>
<td>Atrophy</td>
<td>Clinical</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>53</td>
<td>Atrophy</td>
<td>Histologic</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td><strong>139</strong></td>
<td></td>
<td></td>
<td><strong>37 (27%)</strong></td>
<td><strong>102 (73%)</strong></td>
</tr>
</tbody>
</table>

C. Incidence of Thyroid Changes in Addison's Disease

The histologic changes in the thyroids of patients with Addison's disease bear a close resemblance to those in Hashimoto's disease, and there is also a striking similarity between these thyroid lesions and those in the salivary glands of patients with Sjögren's disease or Mikulicz's disease (99).

Both Hashimoto's disease and Sjögren's disease occur predominantly in women (123); in both disorders there is highly suggestive serologic and other evidence of an immunologic origin (12, 123); and, in both, limited studies have given evidence of a familial tendency to abnormal serologic reactivity similar to that observed for individuals with chronic biologic false
distribution and to urge further studies of incidence and of familial tendencies to endocrinopathy or other disorders, with appropriate controls, little can be added to the tabulation.

D. The Significance of Schmidt’s Syndrome

Information from the published reports of others and the observations in the present study offer firm support for several statements concerning an association between adrenal disease and thyroid disease:

1. Thyroid dysfunction, particularly hypothyroidism, is more often present in patients with Addison’s disease than in the general population.

2. Even more frequent than clinically recognized thyroid dysfunction in Addison’s disease are characteristic histologic changes in the thyroid gland.

3. While overt thyroid insufficiency and/or lymphocytic thyroiditis can occur in males or in patients with tuberculous Addison’s disease, their incidence is clearly greater in females and in patients with Addison’s disease of the idiopathic type.

4. This predominance in females and in idiopathic adrenal atrophy is striking. Despite the variation in reports on differences in the sex incidence of Addison’s disease alone or in the frequency of tuberculosis of the adrenals and idiopathic atrophy of the adrenals, neither of these offers a likely explanation for the pattern of occurrence of thyroid lesions.

5. Well-documented exceptions exist but adrenal insufficiency has generally been observed to precede recognizable thyroid disease or, occasionally, the onset of the two has appeared to coincide.

6. Finally, it seems clear that involvement of the thyroid in Addison’s disease is explainable neither as an effect of deficiency in adrenal cortical secretion alone nor as a result of depression of hypophyseal function.

The failure in this study to find histologic changes in the adrenals of individuals with Hashimoto’s disease seems to support indirectly the validity of the morphologic distinction between lymphocytic thyroiditis as seen in Addison’s disease and Hashimoto’s struma lymphomatosa.

The occasional instances in which thyrotoxicosis has preceded the onset of depressed thyroid function in individuals with Addison’s disease may be explainable on much the same basis that this train of events is accounted for in Hashimoto’s disease. Presumably, an initial “overcompensation” or encroachment upon functioning parenchyma can lead to transient hyperfunction in the early stages of the thyroid lesion.

There is an apparent increase in the occurrence of diabetes mellitus as a third endocrinopathy in Addison’s disease. Whether the increase is a result of better observation or of better management with prolongation of life is really not an issue. It is proposed that Schmidt’s syndrome as a concept may be augmented by a triad of Addison’s disease, hypothyroidism, and diabetes mellitus. The histologic changes in patients with diabetes and Addison’s disease have yet to be studied systematically. Presently, there is no pathologic evidence to support a common etiology of the pancreatic and adrenal lesions. The clinical characteristics of the diabetes associated with Addison’s disease are not sufficiently distinctive to differentiate it from ordinary forms of disordered carbohydrate metabolism although further study of newly detected cases might shed light on this matter. A larger body of information must be accumulated concerning the time of onset of diabetes in relation to adrenal insufficiency, the incidence of diabetes among Addisonians as compared to a comparable control group in the general population, family surveys, and serologic tests. The recent studies of Moore and his colleagues (86, 98) indicating a higher incidence of thyroid and other tissue antibodies in diabetics than in the general population are, perhaps, a suggestion of support for the concept of a triad of endocrinopathy in Addison’s disease but, clearly, many more observations are needed. Above all, systematic, prospective, long-term investigations of the clinical evaluation of polyendocrinopathy are desirable.

The role of immunologic procedures in the further clarification of these endocrine disorders deserves comment. At the least, if autoimmune damage is offered as a hypothesis for their etiology, the finding of circulating antibodies which react specifically with components of normal tissue is encouraging and a stimulus to further investigation. The characterization of the tissue antigens, including the determination of their intracellular location is an obvious and very important step (11). Indeed, having the anti-
body and the antigen is reasonably conclusive proof or an "autoimmune system" associated with a disease. Whether the autoimmune system is the cause or the result of the disease is the important question to be answered. Experimental studies in animals have shown that autoinmune can lead to tissue damage, but it is also apparent from observations in animals and in man that tissue damage of an unrelated type can lead to autoinmune. The detection of adrenal antibody in patients with adrenal tuberculosis is an example of this problem. Of more interest, perhaps, is a disease such as sympathetic ophthalmia in which damage by trauma and infection appears to set in play autainmune mechanisms which, in turn, destroy normal tissues. The importance of the temporal sequence in interpreting serologic tests is difficult to overemphasize. Hence, the recognition of the likelihood of polyendocrinopathy in patients with Addison's disease makes it possible to study the sequence of immunologic events in a selected group while serial observations of endocrine function are being performed in a prospective study.

The fact that lymphocytic thyroiditis is observed occasionally in individuals with adrenal tuberculosis is of interest. If one speculates that some type of immune mechanism involving the thyroid is a sequel to initial "autoimmune" damage to the adrenal cortex in idiopathic atrophy of the adrenal, might it not be possible that damage to the adrenal of another sort will sometimes initiate the same sequence? Further exploration of the differences in thyroid complications of Addison's disease of varying etiologies should include the possible importance of preservation of adrenal medullary function in idiopathic atrophy in contrast to its destruction in tuberculosis and mycotic infections.

SUMMARY

The concept of Schmidt's syndrome, coexisting adrenal insufficiency and thyroid dysfunction, is discussed on the basis of past case reports, a review of 24 autopsy cases of Addison's disease, and clinical studies of 15 new cases.

Of the 15 cases studied clinically, 10 had diabetes mellitus, 13 had circulating antibodies against thyroid tissue, and 9 had antibodies against adrenal tissue.

It is suggested that Schmidt's syndrome with diabetes mellitus may be a polyendocrinopathy and that its basis may be immunological. The need for additional observations is stressed and further studies are suggested.

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BIBLIOGRAPHY