FAMILIAL POLY-ENDOCRINOPATHY

By
Harald M. M. Frey, Jørgen H. Vogt
and Jørgen Nerup

ABSTRACT

Two family histories are presented. In the first (family W.) two siblings, aged 12 and 16, had idiopathic Addison's disease. The younger patient also had a goitre, possibly representing Hashimoto's thyroiditis. In the second family Graves' disease was present in three generations in direct succession. The oldest patient in addition had Addison's disease, diabetes mellitus and total alopecia. Organ-specific antibodies were looked for quite extensively in the serum of the patients and their relatives, with several positive findings, but without a consistent pattern. A review is given of the literature on familial poly-endocrinopathies and the probable auto-immune character of these diseases. The present cases constitute strong evidence for a genetic transmission of these diseases, and for a common basic aetiology. If this common basis is an auto-immuno aberration, it seems most reasonable, in view of the polyglandular involvement, to assume that the immune-system proper is at fault, rather than a defect in the individual organs.

We intend to describe two families with endocrinopathies in the siblings and/or in more than one generation, with affections of more than one endocrine gland, and with the findings of organ-specific antibodies in serum, which were rather extensively searched for because of the striking familial pattern of endocrine disease.

LABORATORY METHODS

Antibodies against thyroid microsomal fraction were determined by means of the immunofluorescent technique as described by Holborrow et al. (1959), and for thyroglobulin antibodies by means of sensitized sheep red cells obtained from Burroughs
Wellcome & Co. Antibodies against gastric parietal cells, adrenal cortex and salivary glands were determined by means of immunofluorescent techniques, using non-fixed sections of human gastric mucosa, adrenal glands from man and monkey (Cercopithecus aetiops), and salivary glands as described by Irvine (1963); Blizzard et al. (1962) and Bertram & Halberg (1964).

Thyroid function studies were carried out according to Solberg & Norman (1969). Normal values for the 131I uptake in Oslo is 6.6 ± 3.2 (sd) % of dose/h, 20-55 %/24 h. PBI131I after 48 h less than 0.2 %. PBI was determined according to Foss et al. (1960). Normal values in Oslo: 3.5–7.5 µg/100 ml.

11-hydroxycorticosteroids in plasma was determined according to Mattingly (1962), as modified by deMoor & Steeno (1963), normal values being 12–25 µg/100 ml at 8 a.m., rising to more than 30 µg after ACTH stimulation.

17-ketosteroids and 17-ketogenic steroids in the urine were determined according to Norymberski et al. (1953) with modifications (Bongiovanni et al. 1957; Diczfalusy et al. 1955). Normal values for 17-ketosteroids are 5–15 mg/24 h, and a more than 10 mg increment after ACTH stimulation. From 1968, 3a-hydroxysteroids were determined in the urine instead of the 17-ketogenic steroids, the method being initiated by Skålegg & Norman (to be publ.).

Both methods give essentially the same normal values (5–20 mg/d) rising to more than 25 mg/d after ACTH stimulation ACTH stimulation tests were done with a carboxymethylcellulose absorbed preparation of purified ACTH (“Jaton Depot”), giving 120 IU im for three consecutive evenings (Foss Abrahamson, 1958). This ACTH preparation has been used extensively in our own and other hospitals in Oslo and has been found to give a reliable stimulating effect. It has recently been replaced by Synacthen Depot (Ciba) 1 mg, which is used in the same way, and is found to give an identical stimulating effect (Jørgensen, 1971).

Oral glucose tolerance tests were done with 1 g glucose/kg body weight, blood sugar being determined with the ortho-toluidine method (Hvärinen & Nikkilä, 1962), normal fasting values being less than 90 mg/100 ml, and peak values less than 160 mg/100 ml. Insulin in the serum was determined by radioimmunoassay with a method comparable to the one used for the determination of growth hormone in our laboratory (Norman & Turter, 1968), normal fasting values being less than 10 µU/ml with peak values during oral glucose tolerance test from 22 to 146 µU/ml (in 24 normal individuals).

Schilling tests were done with ingestion of radioactive vit. B 12. Normally more than 8 % of the dose is recovered in the urine in 24 h.

LATS activity in the serum was determined according to McKenzie (1958) by Docent Claus Rerup, Lund, Sweden. Figures in brackets indicate radioactivity in the blood after 8 hours in per cent of base line values.

Other laboratory methods are conventional in most hospitals.

**Family I (W.)**

A survey of the pedigree of this family is given in Fig. 1. It will be seen that there are 4 cases of diabetes and one case of Graves’ disease on the side of the mother of the two probands. No such disease was known in the family of the father. A survey of the diagnosis and the results of the serological test are given in Table 1.

The father and the youngest daughter have no positive serological test and no endocrine disease. The mother (K.W.) likewise has no endocrine disease, but LATS and antinuclear factor are present.

**Patient No. 1.** — (O. W.), a son born in 1951 was 16 years old when Addison’s disease was diagnosed in 1967.

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Patient No. 2. – (T. W.), a daughter born in 1955, was 12 years old when Addison's disease was diagnosed in 1968.

The diagnosis in both cases was based on increasing fatigue, loss of concentration, salt craving, loss of weight. The diagnosis was confirmed by the laboratory tests given in Table 2. Blood pressure was in the normal and subnormal range. Pigmentation was discrete. Both patients were considered to be euthyroid, but patient No. 2 (T. W.) has a slight goitre, rather firm, but not tender, the right lobe being greater than the left. Radioiodine uptake was higher than normal (Table 2). LATS was present in the serum of this patient. A tentative diagnosis of Hashimoto's thyroiditis at an early stage was made, based on the high NEBI fraction and the finding of thyroid antibodies. She was not given thyroxine, and in March 1970 she was still clinically euthyroid with PBI 7.4 μg/100 ml. BEI 5.4 μg/100 ml. The thyroid gland is now hardly enlarged and not so firm. Both patients improved rapidly and satisfactorily when given adequate corticosteroid substitution therapy.

Neurological examination in both patients including EEG revealed no abnormality, nor did the supplementary laboratory tests, including fasting blood sugar, oral glucose tolerance tests, Schilling tests, catecholamine excretion, serum sodium, potassium, chloride calcium, inorganic phosphorus and alkaline phosphatase activity.

Family II (A.)

A survey of this family is given in Fig. 2, in Table 3 (diagnoses and results of serological tests) and Table 4 (endocrine tests other than for thyroid disease).

The grandmother (M. A.) patient No. 3. – Born in 1896, did not know of any endocrine disease in her paternal and maternal family. From 1958 she developed symptoms of Graves' disease, and subtotal thyroidectomy was performed in 1960, 35 g of thyroid gland.
Table 1.
Diagnoses and serological findings. Family I (W.) (1968).

<table>
<thead>
<tr>
<th></th>
<th>Antibodies</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Microsomal fraction</td>
<td>Thyroglobulin</td>
<td>LATS</td>
<td>Adrenal</td>
<td>Salivary gland</td>
</tr>
<tr>
<td>Father H. W. No diagnosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mother K. W. No diagnosis</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient No. 1, son, 16 years old</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>O. W. Addison’s disease</td>
<td>(1968:320)</td>
<td>(165)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient No. 2, daughter, 12 years old</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T. W. Addison’s disease, goitre</td>
<td>March-68:45</td>
<td>(820)</td>
<td>(152)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Apr.-68:135</td>
<td>(680)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1970:trace</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daughter, born 1959 No diagnosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2.  
Survey of endocrine tests. Family I (W.).

<table>
<thead>
<tr>
<th>Patient</th>
<th>131I studies of thyroid function</th>
<th>125 diiodothyrosine test</th>
<th>Oral glucose tol. test</th>
<th>Schilling test&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uptake</td>
<td>Plasma 24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PBI&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Scanning</td>
<td>One hour</td>
<td>24 h</td>
</tr>
<tr>
<td>Patient No. 1</td>
<td>4.3</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>O. W.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient No. 2</td>
<td>6.3</td>
<td>normal</td>
<td>normal (23.5 %)</td>
<td>normal</td>
</tr>
<tr>
<td>T. W.</td>
<td>BEI 4.3</td>
<td>Enlarged</td>
<td>22 %</td>
<td>62 %</td>
</tr>
<tr>
<td>(Euthyroid slight goitre)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> μg/100 ml plasma.  <sup>2</sup> per cent of tracer dose of radioactive vit. B<sub>12</sub> in urine first 24 hours.

<table>
<thead>
<tr>
<th>Patient</th>
<th>11-OH-corticosteroids in plasma at 8 a.m.&lt;sup&gt;1&lt;/sup&gt;</th>
<th>17-ketosteroids in urine mg/24 h</th>
<th>3-α-OH steroids in urine mg/24 h</th>
<th>Eosinophil cells No./mm&lt;sup&gt;3&lt;/sup&gt; blood</th>
<th>Testosterone in plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After ACTH</td>
<td>Before</td>
<td>After ACTH</td>
<td>Before</td>
</tr>
<tr>
<td>Patient No. 1</td>
<td>2.6 and</td>
<td>5.3</td>
<td>1.8</td>
<td>1.6</td>
<td>11.0</td>
</tr>
<tr>
<td>O. W.</td>
<td>2.7</td>
<td>5.3</td>
<td>1.8</td>
<td>1.6</td>
<td>11.0</td>
</tr>
<tr>
<td>Patient No. 2</td>
<td>3.8</td>
<td>3.8</td>
<td>1.0</td>
<td>1.1</td>
<td>3.7</td>
</tr>
<tr>
<td>T. W.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> μg/100 ml.
tissue being removed; histological examination of this showed scattered lymphocytic infiltration and some lymph follicles, though not to the extent seen in Hashimoto's thyroiditis.

Addison's disease was diagnosed in 1962 when she was first admitted to our hospital. She was then found to have almost total alopecia of the scalp, pubes and axillae. The symptoms of Addison's disease were increasing lassitude, depression, and a weight loss of 15 kg. Blood pressure was low. The diagnosis was confirmed by laboratory tests shown in Table 4.

The serum Ca was 12.2 and 13.4 mg/100 ml and fell to 10.1 and 9.9 mg/100 ml after cortisone treatment was started. The serum P was 4.9 and 5.2 mg/100 ml before therapy, but was not checked later.

In 1963 thyrotoxicosis reappeared, PBI being 11 μg/100 ml and 131I uptake 94%/24 h. She was given radioiodine therapy, 4 mCi. Six months afterwards she was found to be hypothyroid and since then thyroxine has been given.

In 1956 diabetes was diagnosed, ketosis was present and the fasting blood sugar was above 200 mg/100 ml. She was first treated with insulin, later with chlorpropamide. In 1968 chlorpropamide was stopped for three days, after which insulin assay in blood were performed (Table 4).

The father (A. A.), patient No. 4. – Born in 1919, was the only child of pat. No. 3. Graves' disease was diagnosed in 1956, in which year thyroidectomy was performed, 45 g of thyroid tissue being removed. The histological picture was the same as in the case of his mother. Thyrotoxicosis recurred in 1963, PBI being 11.8 μg/100 ml, and thyroid uptake of 131I 65%/24 h. He was given 131I 4 mCi, and after few months the PBI fell and the cholesterol rose to hypothyroid values. Since then he has been on thyroxine treatment, myxoedema reappearing when this medication was occasionally neglected.

This patient has three children, patients No. 5 and 6, and one son born in 1959 without any evidence of endocrine disease.

Patient No. 5, Ulf A. – A son, born in 1953, developed Graves' disease with slight
### Table 3.
Diagnoses and serological findings. Family II (A.) (1966).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Thyroid</th>
<th>Antibodies</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Microsomal fraction</td>
<td>Thyroglobulin</td>
<td>LATS</td>
</tr>
<tr>
<td>Grandmother M. A.</td>
<td>Graves' disease</td>
<td>Post. rad. iodine</td>
<td>Myxoedema</td>
</tr>
<tr>
<td>Patient No. 3.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born 1896</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father A. A.</td>
<td>Graves' disease</td>
<td>Post. rad. iodine</td>
<td>Myxoedema</td>
</tr>
<tr>
<td>Patient No. 4.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born 1919</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Son, Ulf. A.</td>
<td>Graves' disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient No. 5.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born 1953</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daughter Un. A.</td>
<td>Graves' disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient No. 6.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born 1951</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 4.
Survey of endocrine tests. Family II (A.) (all of them thyrotoxic, evidence given in text).

<table>
<thead>
<tr>
<th>17-ketosteroids mg/24 h</th>
<th>17-ketogen. steroids mg/24 h</th>
<th>Eosinophil. cells No./mm³</th>
<th>Schilling test¹</th>
<th>Blood sugar mg/100 ml Insulin μU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Patient No. 3</td>
<td>0.7</td>
<td>0.6</td>
<td>2.7</td>
<td>1.7</td>
</tr>
<tr>
<td>M. A.</td>
<td>0.9</td>
<td>0.3</td>
<td>2.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1 mg Synacthen depot im at 10 p.m. 11-OH-corticosteroids in plasma μg/100 ml at 8 a.m.</th>
<th>(Na)/(K) in morning urine</th>
<th>Schilling test¹</th>
<th>Oral glucose tolerance test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Patient No. 4</td>
<td>12.5</td>
<td>65.8</td>
<td>3.9</td>
</tr>
<tr>
<td>A. A.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient No. 5</td>
<td>18.3</td>
<td>42.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Ulf. A.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient No. 6</td>
<td>13.4</td>
<td>57.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Un. A.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹) Per cent radioactive B₁₂ recovered in urine/24 h.
eye symptoms (as his father and grandmother) in 1965 when 12 years old. He had a slight goitre, PBI was 13.8 μg/100 ml, and ¹³¹I uptake 90%/24 h. Since 1965 he has been on Neo-Mercazole treatment. Thyrotoxicosis reappeared when the drug was tentatively stopped after 18 months.

Patient No. 6 (Un. A.). – A daughter, born 1951. A goitre developed in 1967, but PBI was then 5.5 μg/100 ml and she was considered to be euthyroid. In 1968 Graves' disease was evident with PBI 13.9 and 12.8 μg/100 ml and ¹³¹I uptake of 78%/24 h. After initial therapy with 400 mg of perchlorate and 200 mg of propylthiouracil, she has been given propylthiouracil 50 mg twice daily.

She menstruated with some irregularity from the age of 13 years.

Because of the poly-endocrinopathy of M. A. and the finding of antibodies to gastric parietal cell in A. A. further tests were done as shown in Table 3. Except for M. A. the adrenocortical function was found to be normal. Subnormal absorption of B₁₂ was not found.

In the three younger members of the family an oral glucose tolerance test was performed. The finding in A. A. showed a reduced glucose tolerance with adequate insulin response. His two children showed normal glucose tolerance and peak values of insulin at 60 minutes.

COMMENTS

Familial occurrence of Graves' disease

The frequent familial occurrence of Graves' disease in particular, and of thyroid disorders in general, is well documented. Bartels (1941) in an extensive monograph concluded that Graves' disease is probably always hereditary and calculated the risk of developing the disease among sisters of affected patients to be 8.2%. Martin (1945) and Heimann (1966) also stress the familial aspects of Graves' disease in contradistinction to toxic nodular goitre. Studies of twins by Lehman (1939), Harvald & Hauge (1956) and Hassan et al. (1966) strongly support this view. There is however no agreement concerning the mode of inheritance, and even greater confusion as to the nature of the genetic effect.

Family A. reported here is remarkable in several respects. The occurrence of Graves' disease in three generations strongly argues for a genetic transmission, possibly of a dominant trend. It is also noteworthy that the age of onset of the disease becomes lower in successive generations, indicating potentiation of the inherited defect. There has never to our knowledge been a family reported in which the hereditary aspects of Graves' disease have been so clearly demonstrated.

Familial occurrence of Addison's disease

The familial aspect of Addison's disease is less pronounced than that of Graves' disease. This may be due to the fact that Addison's disease is more rare, or to a weaker hereditary tendency. Thus families with Addison's disease in two generations are almost unknown (Brochner Mortensen 1956). There have however, been several reports of this occurrence in siblings (Bamatter et al.
The combination of Addison’s disease and thyroid disease

Among our patients, M. A. had Graves’ disease, Addison’s disease, diabetes mellitus and total alopecia, while T. W. had Addison’s disease and goitre.

The combination of Addison’s disease and Graves’ disease is a rare occurrence. Isolated case reports have appeared, among them one by one of us (Frey 1959). Recent reports by Stewart et al. (1962) and Burke & Feldman (1965) bring the total number of the combination up to 27 cases by 1965. According to Frederickson (1951) and Gastineau et al. (1964) the incidence of Graves’ disease in Addison’s disease is greater than would be expected by chance. The over-representation of thyroid diseases other than hyperthyroidism in Addison’s disease is even more convincing. Gastineau & Arnold (1963) found among their 538 Addisonian patients 7 % with goitre and 2 % with myxoeedema, a significant increase above chance occurrence. Even far higher figures have been presented in selected materials. (Blizzard & Kyle 1963; Carpenter et al. 1964; Goudie et al. 1966; Irvine 1962–63). According to Carpenter et al. (1964) lymphocyte infiltration in the thyroid gland is present in 82 % of cases of “idiopathic” Addison’s disease.

The combination of Addison’s disease and diabetes mellitus

The combination of Addison’s disease and diabetes mellitus is not particularly rare. According to recent reports (Pappas 1967; Tzagournis & Hamwi 1967) 120 examples of this combination have been described by 1967.

In 63 % of the cases diabetes appears first (Solomon et al. 1965). More interesting, however, is the very high incidence of diabetes mellitus in pre-existing Addison’s disease.

Thus Blizzard et al. (1967) found 10 diabetics among their 118 patients with
idiopathic Addison’s disease, and Turkington & Lebovitz (1967) presented 32 Addisonian patients among whom 6 had diabetes. This is far above the regular incidence of diabetes (1–3% in the USA (Tzagournis & Hamwi 1967)). Similar figures have been reported by others (Carpenter et al. 1964; Irvine 1962–63).

We are not aware of any report commenting on plasma insulin in these patients. In our patient M. A. insulin response to meals was adequate. Her son A. A. showed reduced glucose tolerance with unimpaired insulin response.

In addition to the high incidence of diabetes mellitus, it is being increasingly realized that Addison’s disease is also frequently accompanied by disorders of other endocrine glands and various other diseases, especially pernicious anaemia. The incidence of thyroid abnormalities has already been commented on. Turkington & Lebovitz (1967) found evidence of polyglandular failure in 41% of their Addisonian patients. Among 118 patients with idiopathic Addison’s disease, Blizzard et al. (1967) found thyroid disorders in 30, hypoparathyroidism in 18, diabetes mellitus in 10, pernicious anaemia in 7, moniliasis in 7, cirrhosis of the liver in 2, total alopecia in 3 (cf. our patients M. A.).

The presence of hypercalcaemia in Addison’s disease in our patient M. A. is a rarely reported and unexplained finding only few instances being known (Pedersen 1967; Walser et al. 1963). The phenomenon is apparently unrelated to any concomitant parathyroid disease, the mechanism being unexplained.

As for the theoretical implications of poly-endocrinopathies, the possibility of common aetiological factors lies near at hand. The study of organ-specific antibodies in the serum lends further support to this possibility:

Adrenal antibodies

The first report of antibodies against adrenal tissue in cases of Addison’s disease was that of Anderson et al. (1957). Blizzard & Kyle (1963) found circulating antibodies (Coon’s technique) in 36 of 81 Addisonian patients. Isolated reports of antibodies have also been presented by Hung et al. (1963), and Mead (1962). It is noteworthy that the presence of antibodies is almost totally restricted to cases of idiopathic in contradistinction to tuberculous Addison’s disease. This has been borne out by several reports (Andrada et al. 1968; Goudie et al. 1966; Irvine et al. 1967; Nerup et al. 1966), unanimously indicating that antibodies are present in over 50% in idiopathic and practically never in tuberculous Addison’s disease.

The finding of adrenal antibodies has very rarely been reported in children. A total of 10 children have been examined, and antibodies were found in 4 of them (d’Albora & Martin 1966; Bamatter et al. 1966; Hung et al. 1963; Irvine et al. 1967). The present report increased this figure to 6.

One other remarkable feature of patients with idiopathic – in contradistinction to tuberculous Addison’s disease is the high incidence of antibodies against
other organs, particularly the thyroid and stomach. The presence of over-
disease in these and other organs has already been commented upon, and has
been reviewed by Eisenstein (1968). But also when there is no clinical or
biochemical evidence of disease, Addisonian patients in a surprisingly high
percentage of cases have antibodies in their serum. In the 48 patients of Nerup
et al. (1966) 11 had goitre while as many as 23 had antibodies against thyro-
globulin or microsomal fraction. Both Irvine et al. (1967) and Goudie et al.
(1966) point out the high incidence of thyroid and also of anti-gastric antibodies
in patients with idiopathic Addison’s disease.

According to recent opinion, gonadal failure may also be over-represented
in idiopathic Addison’s disease. In the experience of Turkington & Lebovitz
(1967), 23% had gonadal failure. Irvine et al. (1968) found antibodies against
theca interna cells of the ovary in 5 of 77 Addisonian cases, and all of these
had amenorrhoea or premature menopause. Moreover, Anderson et al. (1968)
found antibodies against gonadal steroid-producing cells. Some indication of
gonadal involvement is present in our patients Un. A. and T. W., but their
young age makes the interpretation of this finding difficult.

Thyroid antibodies

Thyroid antibodies were present in 3 generations of our family A. They
were both of the anti-thyroglobulin- and of the anti-microsomal-fraction-type.
Traditionally, the presence of thyroid antibodies is thought to be more charac-
teristics of myxoedema and Hashimoto’s thyroiditis than of thyrotoxicosis
(Godal 1967; Halberg et al. 1968; Stanbury 1967), but Buchanan et al. (1962)
note that complement-fixing antibodies (microsomal fraction) are found in
thyrotoxicosis, particularly in individuals with a family history of thyroid
disease, and when lymphocyte infiltration in the gland is severe.

Highly pertinent and interesting in this connection are the recent opinions
on the subject that all the mentioned thyroid disorders may have some common
basic and possibly genetic aetiology. The close genetic relationship between
various disorders of the thyroid gland has been discussed at length by Halberg
(1967, p. 143). Striking examples of this relationship have been published by
Doniach et al. (1967): One pair of monozygotic twins, where one sibling had
Graves’ disease and the other Hashimoto’s thyroiditis, and by Hall et al. (1964):
A father with Graves’ disease had a daughter with Hashimoto’s thyroiditis, and
a girl with Graves’ disease had a father with Hashimoto’s disease. The paternal
transmission strongly points to a true genetic connection in these cases. There
are also several reports on the finding of thyroid antibodies in the serum of
relatives of patients with various disorders (Anderson et al. 1964, Hall et al.
1960; Saxena 1965).

Anderson et al. (1964) point out that Graves’ disease often occurs in combi-
nation with other diseases in which organ specific antibodies are present

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(Addison’s disease, pernicious anaemia, myasthenia gravis). These investigators, and also Irvine et al. (1962) and Williams et al. (1966), found a positive correlation between anti-gastric and anti-thyroid antibodies in patients with thyrotoxicosis and other thyroid disorders.

One particular aspect of thyroid auto-immunity is the longacting thyroid stimulator (LATS). LATS, being an immunoglobulin, is now considered an antibody (the antigen is unknown) with the peculiar property of being able to stimulate thyroid gland function. McKenzie (1968) did not, however, find any correlation between LATS-activity and thyroid antibodies in the same sera, while Bastenie et al. (1967) and Weissbecker et al. (1967) reached the opposite conclusion: LATS activity was found most frequently in those patients with hyperthyroidism who also had thyroid antibodies. Neutralization experiments ruled out any identification of LATS with the above mentioned thyroid antibodies.

The findings of LATS has so far been considered specific for Graves’ disease, and the presence of this factor in the sera of T. W. and her mother is confusing. T. W. probably has Hashimoto’s thyroiditis. However, Jayson et al. (1967) recently reported the finding of LATS in the serum of one female with this disorder. Her monozygotic twin sister had thyrotoxicosis and also had LATS in her serum. The finding strengthens the impression of a common immunological defect of genetic origin in these thyroid disorders. LATS has never before been demonstrated in a case of Addison’s disease, nor has it ever been found in relatives of LATS-positive patients (McKenzie 1968).

**Concluding remarks**

Do both Addison’s disease and Graves’ disease belong to the auto-immune group of disorders? A majority of investigators tend to support this contention in the case of Addison’s disease of the “idiopathic” type (Burke & Feldman 1965; Doniach et al. 1967; Irvine 1962–63). The evidence has been summarized by Eisenstein (1968) and is very suggestive. The case for Graves’ disease is less convincing, although a number of investigators favour this theory (Anderson et al. 1964; Burke & Feldman 1965; Doniach et al. 1967; Hassan et al. 1966). McKenzie (1968) concluding an extensive survey, also tends to support the same view-point.

The finding of antibodies in serum has had considerable impact on the discussion. Several investigators, however, maintain that the antibodies are probably secondary to the disease, or that they function in perpetuating the pathological process without being of aetiological importance (Blizzard et al. 1967; Carpenter et al. 1964; Saxena 1965; Williams et al. 1966).

Positive proof for auto-immunity is hard to provide. We are of the opinion that the auto-immune concept at present provides the most plausible explanation for the laboratory and clinical features of these diseases. The cases pre-
sent here have not weakened this impression. The main importance of these cases, however, has been to show

1. a genetic mode of transmission, and
2. a polyglandular involvement.

If we assume that these disease are auto-immune in nature, our cases have supplied strong additional evidence that such diseases may be inherited, and that they are inter-related. We do not know the nature of the inherited defect. It may be an aberration in the immune-system proper, or it may be some defect in the individual endocrine glands, leading to immunological intolerance. The polyglandular affection makes the last alternative less probable. We consider the finding of antibodies in some of our patients to be of minor importance, since we feel uncertain about their pathogenetic role.

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REFERENCES


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