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MONILIASIS, 'AUTOIMMUNE' POLYENDOCRINOPATHY, AND IMMUNOLOGIC FAMILY STUDY

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SUMMARY

A patient with chronic mucocutaneous moniliasis of 17 years' duration developed bilateral keratitis, hepatitis and steatorrhea, conditions often found in association with coexistent adrenocortical and parathyroid insufficiency. Immunologic studies showed that the patient's serum contained organ-specific antibodies. Further clinical investigation demonstrated adrenal and thyroid insufficiency; parathyroid function was normal. Immunologic abnormalities were also detected in seventeen members of his family, indicating a possible familial predisposition to 'autoimmune' disease. A review of the literature suggested that the patient may have an incomplete form of a syndrome consisting primarily of idiopathic Addison's disease, hypoparathyroidism and moniliasis.

INTRODUCTION

Persistent local or disseminated candidiasis may accompany diabetes mellitus, malignancy of the haematopoietic or reticuloendothelial organs (Hutter & Collins, 1962; Hersh *et al.*, 1965), and idiopathic hypoparathyroidism or adrenocortical insufficiency, or both (Sutphin, Albright & McCune, 1943; Craig, Schiff & Boone, 1955). In a review of eighteen cases of hypoparathyroidism and adrenocortical insufficiency, Kunin *et al.* (1963) found seven instances of moniliasis. In all seven patients Candida infection occurred at 1–4 years of age and was the initial symptom, preceding any overt evidence of endocrine disease.

This report describes the clinical and immunologic findings in a young man with moniliasis since the age of 2 years and the results of immunologic studies on twenty-eight members of his family. The spectrum of diseases in the patient prompted a review of reported cases of combined hypoparathyroidism and adrenal insufficiency and of associated familial involvement. The data on eight kindreds in which other siblings were affected are summarized in this report.

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Case Report

A white man, aged 19 years 10 months, was admitted to the Eye Service of the University of California Medical Center in April 1965 for evaluation of severe bilateral keratitis, associated with photophobia, tearing and pain, of 8 months duration. Because of a long history of medical complaints he was transferred to the Medical Service.

He had been born of healthy parents. Birth and development were normal. At 1 year of age he had measles complicated by pneumonia. When he was 2 years old, mucocutaneous moniliasis was diagnosed from cultures of the nails and oral mucous membrane. The condition persisted, requiring his admission to a hospital at 16 years of age. His teeth, which had numerous caries and defective enamel, were extracted at that time.

In December 1963 the patient was admitted to a second hospital because of anorexia, malaise and a weight loss of 20 pounds. Jaundice developed, but urine and stools were normal in colour and pruritus was not present. He was treated with amphotericin B intravenously and corticosteroids orally for possible systemic moniliasis; after 4 weeks the mucocutaneous lesions cleared and the jaundice disappeared. In June 1964 the symptoms recurred, and he entered another hospital, where he admitted having symptoms of postural hypotension. The blood pressure levels when he was lying and standing were 90/50 and 70/50 mmHg, respectively. The liver and spleen were enlarged. Percutaneous biopsy of the liver showed changes consistent with chronic active hepatitis. Parathyroid, thyroid and adrenal function were reported to be normal. Oral administration of hydrocortisone, tetracycline and amphotericin B resulted in improved liver function and clearing of the oral moniliasis. Subsequently hydrocortisone was discontinued but was reinstituted shortly thereafter when jaundice recurred. Herpes zoster was diagnosed in January 1964, when a vesicular eruption associated with paresthesia appeared on the right side of the thorax. In September 1964 he developed bilateral keratitis of unknown origin. Despite treatment with a variety of medications, including hydrocortisone ophthalmic solution, the condition became progressively worse, necessitating a corneal debridement in December 1964. His symptoms persisted, and 7 months later he was referred to the University of California Medical Center.

At the time of admission, the patient was a short young man with severe photophobia, tearing and blepharospasm. The blood pressure was 90/50 mmHg. Scalp hair was normal; axillary and pubic hair was sparse. All teeth were missing. No evidence of cutaneous or mucous membrane moniliasis was seen. The thyroid was palpable but not tender or enlarged. The testes were small (about 3 cm in diameter); by history erection and ejaculation had occurred.

The leucocyte count was 11,800/mm^3, with a normal differential count. The platelet count was 626,000/mm^3. Bleeding and coagulation times were normal, but clot retraction at 1 hr was impaired. A microflocculation test for syphilis (VDRL) was nonreactive. The fasting blood glucose was 85 mg/100 ml; an intravenous glucose tolerance curve was normal. Total serum protein was 8·4 g/100 ml; the serum electrophoretic pattern was normal. Serum calcium was 10 and phosphorus 4·1 mg/100 ml. The results of liver function tests were abnormal. Sulphobromphthalein retention was 44% at 45 min. Total serum bilirubin was 0·9 mg/100 ml. Serum glutamic oxalacetic transaminase and glutamic pyruvic transaminase levels were 142 and 160 units, respectively. The serum alkaline phosphatase level was 12·7 units (Shinowara–Jones–Reinhart). Intradermal tests for tuberculosis, histoplasmosis and coccidioidomycosis were negative, as were tests for febrile agglutinins and a lupus erythematosus cell preparation. Cultures of ocular exudate grew a few colonies of *Staphylococcus albus*; no fungi or viruses were identified. A conjunctival biopsy showed occasional inflammatory cells.

Treatment with prednisolone, 10 mg/day, was begun. After 3 days the serum glutamic oxalacetic and glutamic pyruvic transaminase levels had decreased to 81 and 36 units, respectively. Serum was obtained for special immunohaematologic studies, and the patient was discharged temporarily from the hospital on 23 April 1965.

He was readmitted several weeks later for further investigation. During the interval, his chief complaints were fatigue, anorexia and increasing irritability; symptoms of postural hypotension persisted despite prednisolone therapy. Without medical consultation, he discontinued

TABLE 1. Laboratory data during second hospital admission

Test	Value
Total serum bilirubin (mg/100 ml)	0·9
Alkaline phosphatase (Shinowara–Jones–Reinhart units)	7·0
Serum enzymes (units)	
Glutamic oxalacetic transaminase	52·0
Glutamic pyruvic transaminase	32·0
Lactic dehydrogenase	470·0
Gastric acid (mEq/l)	
Free	0
60 min after Histalog stimulation	0·22
Schilling test (% radioactivity in 24-hr urine specimen)	
Without intrinsic factor	4·6
With intrinsic factor	5·0
Serum carotene (μg/100 ml)	180·0
Faecal fat excretion (g/72 hr)	62·6
D-Xylose excretion (% recovered in 5-hr urine specimen)	8·0
Serum protein-bound iodine (μg/100 ml)	3·1
Butanol-extractable iodine (μg/100 ml)	1·4
^{131}I-uptake (% of test dose)	
At 24 hr	11·0
After TSH stimulation*	
For 2 days	9·8
For 3 days	10·0
3 hr after administration of $KClO_4$	9·0
^{131}I red-cell uptake (%)	17·0
Urinary 17-ketosteroids (mg/24 hr)†	
Baseline	2·2
After ACTH stimulation‡	0–0·9
Urinary 17-hydroxycorticosteroids (mg/24 hr)†	
Baseline	0
After ACTH stimulation‡	0–1·1
Tubular resorption of phosphorus (%)	75·2
Tubular resorption of calcium (%)	99·1
Urinary phosphate (g/24 hr)§	
Day 3	0·59
Day 4	1·10
Day 5	1·10

* Thyroid-stimulating hormone, 10 units/day.

† Patient was taking dexamethasone, 0·25 mg f.i.d.

‡ Eight-hour infusions of adrenocorticotropin, 25 units daily, for 4 days.

§ After oral administration of potassium acid phosphate, 3 g daily for 5 days.

prednisolone and took hydrocortisone, 10 mg three times daily, which had previously given symptomatic relief. Subsequently, he felt better but noted urticaria on the trunk and legs. Hydrocortisone was discontinued at the time of readmission and dexamethasone, 0·25 mg four times daily, was substituted.

On physical examination slight hyperpigmentation of the elbows, areolas and perianal skin was noted; the buccal mucosa and palmar flexures were not pigmented. When the patient was supine the blood pressure was 110/80 mmHg; when standing, it was 80/40 mmHg (1 min) and 60/0 mmHg (2 min). The liver edge was palpable 2 cm below the right costal margin. An electrocardiogram was normal. A roentgenogram of the chest showed a small cardiac silhouette. The bone age was significantly retarded (16 years).

The white cell count was 17,800/mm^3, with a normal differential count. The platelet count had increased to 788,000/mm^3. (The reason for the elevated platelet count was never discovered.) The haemoglobin was 15·6 g/100 ml, and the packed cell volume 49%. The erythrocytes were macrocytic in type; the mean corpuscular haemoglobin volume was 103 μ^3, mean corpuscular haemoglobin 33 pg, and mean corpuscular haemoglobin concentration 31%. A bone marrow aspirate showed erythrocyte hyperplasia. The fasting blood glucose was 63 mg/100 ml; an intravenous glucose tolerance curve was normal. In repeated determinations serum calcium levels ranged from 9·4 to 10·1 and phosphorus from 4·6 to 4·9 mg/100 ml; serum sodium ranged from 132 to 136 and potassium from 4·3 to 5·7 mEq/l. The serum chloride was 97 and bicarbonate 4·6 mEq/l. Sweat electrolytes were normal. The results of additional tests are listed in Table 1. These again demonstrated impairment of liver function, as well as gastrointestinal abnormalities, including steatorrhea and decreased gastric acidity. Radiographic studies of the upper gastrointestinal tract (barium contrast medium), however, were negative. The faeces contained no ova or parasites. As shown in Table 1 endocrine function tests showed thyroid insufficiency unresponsive to thyroid-stimulating hormone and adrenal hypofunction unresponsive to ACTH; tests of parathyroid function gave normal results. Urinary excretion of follicle-stimulating hormone was negative at 5 and 80 mouse units; plasma ACTH was not determined. Cultures of bone marrow, urine and ocular exudate grew no fungi. The response to a skin test with an extract of *Candida albicans* (Oidiomycin) was positive.

Hydrocortisone, 10 mg three times daily, and 9-alpha-fluorohydrocortisone, 0·1 mg daily, were prescribed. The patient was discharged from the hospital in May 1965, but is seen periodically. With continued therapy, fatigue and anorexia have virtually disappeared.

Family History

Insofar as could be ascertained from the parents, they and the patient's two sisters were healthy. The maternal great grandmother had diabetes mellitus. One maternal great aunt had deforming arthritis, one had goitre and diabetes mellitus and one had asthma. The paternal grandmother had both deforming arthritis and goitre, and a paternal aunt had been treated for goitre.

SPECIAL STUDIES

Methods

Sera from the patient and family members were tested for antibodies to human thyroid, adrenal and gastric parietal cells and for antinuclear antibodies by the indirect immunofluorescent antibody technique. The tests were performed simultaneously on unfixed sections of tissue mounted on slides coated with 0·5% gelatin. Each section was allowed to react with the control or unknown serum at room temperature for 30 min. After three washings (5 min each) in phosphate-buffered saline, pH 7·2, the sample was exposed for 30 min to rabbit antiserum to human IgG-globulin conjugated with fluorescein isothiocyanate and separated from the nonreacting dye by the method of McKinney, Spillane & Pearce (1964).

After three additional 5-min washes in buffer solution, the sample was mounted in 50% glycerine in buffer, pH 7·8, and examined through a Zeiss ultraviolet photomicroscope with a fixed BG 38 filter, exciter filter BG 3 and barrier filters 440 and 470 mμ.

The sera were tested for antibodies to thyroglobulin by the haemagglutination method of Fulthorpe *et al.* (1961) and for precipitating antibodies to uvea by the method of Aronson, Schnellmann & Yamamoto (1966). Tests for antibodies to colon were carried out by haemagglutination of cells coated with germ-free colon extract (Perlmann *et al.*, 1965). The presence of rheumatoid factor was determined with red blood cells sensitized by human or rabbit γG-globulin as described by Fudenberg, German & Kunkel (1962). Serologic tests for syphilis were performed by a standard (VDRL) microflocculation method and by the fluorescent treponemal antibody absorption (FTA-ABS) test (Hunter, Deacon & Meyer, 1964).

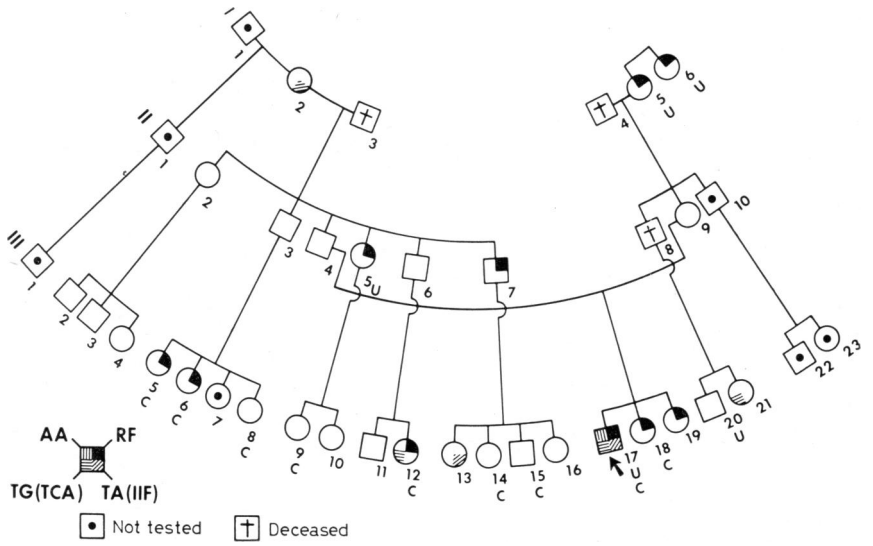

FIG. 1. Family pedigree showing immunologic abnormalities in propositus (indicated by arrow) and family members. AA = antibodies to adrenal; TA(IIF) = antibodies to thyroid cytoplasm; TG(TCA) = antibodies to thyroglobulin; RF = rheumatoid factor; U = antibodies to uvea; C = antibodies to colon.

The patient's serum was also tested for antibodies to unfixed liver, pituitary, parathyroid adenoma, jejunum and gastric smooth muscle by the indirect immunofluorescent technique described above, for antibodies to gastric intrinsic factor by the method of Ardeman & Chanarin (1963), and for a factor present in normal serum that is capable of inhibiting Candida (Louria & Brayton, 1964).

Results

Fig. 1 shows the immunologic abnormalities found in the propositus and family members. The patient's serum contained antibodies to adrenal tissue (titre 1:64), thyroid cytoplasmic constituent, thyroglobulin and colon. It also contained rheumatoid factor. The test for precipitating antibody to uvea was positive. The serum lacked the anti-Candidal factor

present in normal serum, and no inhibitor of the factor could be found when his serum was mixed with normal serum. All other tests on his serum were negative.

The sera of both parents gave negative reactions in all tests. Immunologic abnormalities were found in seventeen of the remaining twenty-six relatives. The sera of nine family members, including the patient's two sisters, contained rheumatoid factor (RF). The sera of one of the RF-positive relatives (III-2) and of a cousin (III-21) contained thyroglobulin antibodies. Thyroid antibodies were present in the sera of two other family members (I-2) and III-13). The serum of a 14-year-old cousin gave a false-positive reaction for syphilis (weakly reactive in the VDRL test and non-reactive in the FTA-ABS test). Antibodies to uvea were detected in the sera of four relatives (I-5, I-6, II-5 and III-20). In tests for antibody to colon, the sera of eight relatives (III-5, 6, 8, 9, 12, 14, 15 and 18) had titres of 1:32 or greater. None of the family members had serum antibodies to gastric parietal cells or antinuclear antibodies.

DISCUSSION

Several unusual features of the present case warrant comment: the possibility that the patient has an incomplete form of the syndrome of adrenal and parathyroid insufficiency and moniliasis, the presence of chronic moniliasis without associated hypoparathyroidism, and the detection of a number of organ-specific antibodies in his serum and of immunologic abnormalities in seventeen members of his family.

Hypoadrenocorticism–hypoparathyroidism

Whitaker *et al.* (1956) first called attention to a syndrome of 'familial juvenile hypoadrenocorticism, hypoparathyroidism and superficial moniliasis'. Kunin *et al.* (1963), in their review of eighteen reported cases of hypoparathyroidism and adrenal insufficiency, noted the frequent occurrence of moniliasis, steatorrhea, macrocytic anaemia and posthepatitic cirrhosis. Other associated conditions such as lymphocytic thyroiditis (Whitaker *et al.*, 1956; Perlmutter *et al.*, 1956; Carter *et al.*, 1959) and pernicious anaemia (Morse, Cochrane & Landrigan, 1961; Hung, Migeon & Parrott, 1963), as well as conjunctivitis, dystrophic changes in nails, hair and skin, and poor dentition, also have been reported. In their review Kunin *et al.* (1963) noted the high incidence of either parathyroid or adrenocortical hypofunction in one or more siblings. Whitaker *et al.* (1956), in commenting on familial aspects, suggested that cases in which one or another of the characteristic features are lacking may be incomplete forms of the syndrome.

In an attempt to evaluate the occurrence of partial expressions of the syndrome, we reviewed the reported cases of combined hypoadrenocorticism and hypoparathyroidism, with special attention to families in which other siblings were affected. A total of ten cases in eight kindreds were found in the literature (Table 2); in the family described by Hiekkala (1965) two siblings as well as the propositus had combined hypoparathyroidism and Addison's disease. Moniliasis was present in six of the ten patients, pernicious anaemia in two, poor dentition in two and Hashimoto's thyroiditis in one. The fourteen affected siblings had either hypoparathyroidism (ten patients) or Addison's disease (four patients); of these, six had moniliasis. Other associated findings were hepatitis, poor dentition, and steatorrhea.

TABLE 2. Data on propositi and affected siblings in eight kindreds

Source	Hypopara-thyroidism	Addison's disease	Candida infection	Pernicious anaemia	Hepa-titis	Lymphocytic thyroiditis	Steat-orrhea	Poor dentition	Other findings
Sutphin *et al.* (1943)									
Propositus	+	+	+	.	.	.	.	.	Consanguinity; one sib had
Sibling	+	.	+	.	.	.	.	.	alopecia of brows and
Sibling	+	.	+	.	.	.	.	.	sparse scalp hair
Talbot *et al.* (1943)									
Propositus	+	+	+	.	.	.	.	.	
Sibling*	.	+	+	.	+	.	.	+	Corneal opacities
DiGeorge & Paschkis (1957)									
Propositus	+	+	.	.	.	.	.	.	
Sibling	.	+	.	.	.	.	.	.	
Sibling	+	.	+	.	.	.	+	.	
Morse *et al.* (1961)									
Propositus	+	+	.	+	.	.	.	+	All had elevated sweat
Sibling	+	.	.	.	.	.	+	+	electrolytes; four were
Sibling	+	.	.	.	.	.	.	+	mentally retarded.
Sibling	+	.	.	.	.	.	.	.	Adrenal antibodies in sera of
Sibling	+	.	.	.	.	.	.	.	propositus and two sibs†
Hung *et al.* (1963)									
Propositus	+	+	+	+	.	.	.	.	Adrenal antibodies in sera of
Sibling	.	+	.	.	.	.	.	.	two living sibs
Sibling	.	+	.	.	.	.	.	.	
Kenny & Holliday (1964)									
Propositus	+	+	+	.	.	+	.	+	Alopecia. Adrenal and
Sibling	+	.	+	.	.	.	.	.	thyroid antibodies in sera of
Hiekkala (1965)									propositus
Propositus	+	+	+	.	.	.	.	.	
Sibling	+	+	+	.	.	.	.	.	
Sibling	+	+	.	.	.	.	.	.	
Sibling	+	.	+	.	.	.	.	.	
Sweetnam (1966)									
Propositus	+	+	.	.	.	.	.	.	No adrenal antibodies
Sibling	+	.	.	.	.	.	.	.	demonstrable. Paternal uncle has pernicious anaemia

* Case 1 of Craig *et al.* (1955). † In studies by Blizzard *et al.* (1962).

The variable combinations of disorders in the siblings in the eight kindreds support the hypothesis that the syndrome may occur in partial or incomplete form. The presence of moniliasis, thyroid insufficiency, chronic hepatitis, steatorrhea and poor dentition in association with Addison's disease appears to warrant inclusion of our case in this category.

Other possible variants of the syndrome may exist. For example, Collins-Williams (1950) described moniliasis and celiac 'syndrome' in a patient with hypoparathyroidism. The older sibling of Collins-Williams' patient (Case 2 of Craig *et al.*, 1955) had Addison's disease, moniliasis, celiac syndrome, alopecia, dental caries and nail lesions. The concurrent presence of idiopathic Addison's disease and thyroid disease, sometimes in association with diabetes mellitus, is well recognized (Carpenter *et al.*, 1964). Pernicious anaemia has been reported in familial Addison's disease (Berlin, 1952), as well as in hypoparathyroidism (Hurwitz, 1956; Ikkala, Siurala & Viranko, 1964).

Moniliasis

Mucocutaneous infection with Candida was included in the triad of conditions comprising the syndrome emphasized by Whitaker *et al.* (1956). Moniliasis in association with idiopathic hypoparathyroidism is well known, but its occurrence in patients with Addison's disease without coexistent hypoparathyroidism is rare. Whitaker *et al.* (1956), in reviewing a series of reports on the familial occurrence of Addison's disease, found no mention of moniliasis. The only reports of Candida infection in patients with Addison's disease appear to be the three cases described by Craig *et al.* (1955). Clinical and post-mortem findings consistent with hypoparathyroidism were reported present in at least two of these three cases, leading Kunin *et al.* (1963) to include them in their tabulation of cases of coexistent hypoparathyroidism and adrenocortical insufficiency. Of the twelve instances of moniliasis listed in Table 2, all, with one possible exception—the sibling (Case 1 of Craig *et al.*, 1955) of the propositus described by Talbot, Butler & MacLachlan (1943)—were in patients with hypoparathyroidism or hypoparathyroidism and adrenal insufficiency. Recently, however, we were sent serum specimens from two siblings (15 and 17 years old) for antibody tests. Both have Addison's disease (since age 8), which was preceded by chronic moniliasis, and one has steatorrhea; neither has shown any evidence of hypoparathyroidism during the respective 7- and 9-year periods of observation.

The role of the Candida infection is obscure. Several investigators have suggested that the moniliasis is secondary to abnormal parathyroid function (Craig *et al.*, 1955; Whitaker *et al.*, 1956). This explanation, however, does not account for the persistent moniliasis in the present case. Hypothetically, our patient's lymphocytes might be immunologically defective or pre-committed to respond to antigens other than monilia, i.e. functionally analogous to the situation in patients with hereditary alymphocytosis and impaired delayed hypersensitivity who invariably develop moniliasis (Gitlin & Craig, 1963). However, delayed hypersensitivity to intradermally injected *C. albicans* extract was demonstrated in our patient and others (Craig *et al.*, 1955; Kenny & Holliday, 1964). Perhaps more relevant to the moniliasis was the absence from our patient's serum of the anti-Candidal factor described by Louria & Brayton (1964). Alternatively, an ectodermal defect might account for the susceptibility to chronic moniliasis in our patient as well as in patients with coexistent hypoparathyroidism and adrenal insufficiency.

Immunologic findings

Organ-specific antibodies have been found in Addison's disease (Anderson *et al.*, 1957) and in hypoparathyroidism (Blizzard, Chee & Davis, 1966). To date there have been few immunologic studies of the relatives of patients with the hypoadrenocorticism–hypoparathyroidism syndrome; those cases in which organ-specific antibodies have been reported are given in Table 2. Blizzard *et al.* (1962), in studies on the family first described by Morse *et al.* (1961), demonstrated adrenal antibodies in the sera of the propositus and two siblings with hypoparathyroidism. No antibodies were detected in two other siblings with hypoparathyroidism, two healthy siblings or the parents. These workers also found adrenal antibodies in the sera of two of three other patients with hypoparathyroidism and adrenal insufficiency. Adrenal antibodies were present in the sera of two living siblings in the family studied by Hung *et al.* (1963); neither adrenal nor thyroid antibodies were present in two healthy siblings or the parents. Kenny & Holliday (1964) reported adrenal and thyroid antibodies in their propositus; no antibodies were detected in a sibling with idiopathic hypoparathyroidism and moniliasis, two normal siblings or the mother. The father's serum, however, contained antibodies to thyroid. Adrenal antibodies were not demonstrable in the serum of either the propositus or sibling studied by Sweetnam (1966).

Autoantibodies have also been reported in the various diseases found in association with coexistent hypoadrenocorticism and hypoparathyroidism. For example, antibodies to gastric parietal cells are found frequently in pernicious anaemia and atrophic gastritis (Taylor *et al.*, 1962; Irvine *et al.*, 1965), antibodies to unfixed thyroid tissue and to thyroglobulin in lymphocytic thyroiditis (Holborow *et al.*, 1959; Fulthorpe *et al.*, 1961), antibodies to jejunal epithelial cells in steatorrhea (Malik *et al.*, 1964), and antibodies to smooth muscle in liver disease (Johnson, Holborow & Glynn, 1965).

On the basis of these reports, the detection of antibodies to adrenal and thyroid tissue in our patient was not surprising. The presence of antibodies to colon and to uvea, however, was unexpected. Antibodies to colon have been reported in ulcerative colitis (Perlmann *et al.*, 1965), but no evidence of this disease was found in our patient or in the eight family members whose sera also contained antibodies to colon. Malabsorption of vitamin B_{12} was demonstrated in our patient, but was attributed to the presence of steatorrhea, since addition of intrinsic factor did not improve vitamin B_{12} absorption as determined by the Schilling test. Although our patient had steatorrhea and impaired liver function, no antibodies to gastric smooth muscle or jejunum were detected in his serum. The significance of the uveal antibodies in the propositus and several family members is not known. Aronson *et al.* (1966) noted that precipitating antibodies to uvea are found more often when ocular disease is present than when it is absent. Whether a relationship exists between the antibodies to uvea and the severe bilateral keratitis in our patient is uncertain at this time. Rheumatoid factor was also present in our patient's serum and was the most common serologic abnormality in the family members (Fig. 1).

Genetic predisposition

Both hypoadrenocorticism and hypoparathyroidism have been attributed to abnormal immunologic mechanisms. The presence of autoantibodies in such patients, however, in no way constitutes evidence that the antibodies are pathogenic. They may only be concomitants of the disease. The absence of adrenal antibodies in tuberculous Addison's disease (Irvine,

1963) suggests that such antibodies are not a result of tissue damage. Until their role in disease has been fully delineated, we prefer to regard autoantibodies as immunologic 'markers' indicative of a genetic predisposition to diseases of immunologic aberration.

The occurrence of the hypoadrenocorticism–hypoparathyroidism syndrome or one of its variable expressions in the eight kindreds reported in the literature also suggests a heritable disorder. An infectious agent might also result in a high familial incidence of disease. The finding of immunologic 'markers' in seventeen of our patient's relatives argues against an infectious aetiology and is consistent with the hypothesis of genetic predisposition to diseases of immunologic aberration (Fudenberg *et al.*, 1962; Holman, 1962; Fialkow, Fudenberg & Epstein, 1964; Fudenberg & Franklin, 1965; Fong, Nuckton & Fudenberg, 1966). It is likely that the syndrome of hypoadrenocorticism–hypoparathyroidism, together with the diseases that frequently accompany the syndrome, represents an immunologic aberration that is probably genetically determined. An 'autoimmune' polyendocrinopathy is only one aspect of the syndrome. Furthermore, the syndrome may occur in partial or incomplete form with only one or two endocrine deficiencies.

Since chronic moniliasis may accompany or precede evidence of endocrine dysfunction in such cases, evaluation of the endocrine and immunologic statuses of patients with persistent Candida infection seems warranted. The detection of adrenal and thyroid antibodies in our patient's serum led to further evaluation and to the additional clinical diagnoses of Addison's disease and hypothyroidism.

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