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CHRONIC MUCOCUTANEOUS MONILIASIS WITH IMPAIRED DELAYED HYPERSENSITIVITY

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SUMMARY

Three patients, including two brothers, with chronic mucocutaneous moniliasis and endocrinopathy were evaluated from an immunological viewpoint. Each patient had defective delayed hypersensitivity to *Candida albicans* as manifested by a negative skin test and absent lymphocyte response after *in vitro* exposure to the antigen. Cutaneous responses to other antigens were intact, and there were no demonstrable abnormalities in humoral immunity. In one case, the *in vitro* lymphocyte response was restored following an injection of a leucocyte extract from a skin test positive subject, although the cutaneous lesions remained unchanged.

It is possible that cells of both the endocrine and lymphoid systems share a defect in synthesis and release of their respective humoral products. In the case of lymphoid cells, the defect would be limited to populations of cells participating in delayed hypersensitivity, and impair production of mediators such as macrophage migration inhibiting factor, lymphotoxin, etc., while sparing the processes of antibody synthesis. Alternatively, the selective failure in delayed hypersensitivity may result from defective lymphocyte differentiation or from loss of immune responsiveness through densensitization by chronic exposure to the fungal antigens.

INTRODUCTION

Mucocutaneous moniliasis is an uncommon disorder of childhood characterized by recurrent or chronic infections of the skin, nails and mucous membranes with *Candida albicans*. Invasion of deeper tissues or parenchymal organs essentially never occurs. In some patients, the condition is accompanied by diminished endocrine function and serum antibodies that react with endocrine tissues. Although a few instances of deficient antibody activity in parotid fluid have been recorded, agglutinating and precipitating antibodies

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against *C. albicans* usually are present (Chilgren *et al.*, 1967). Defects in delayed hypersensitivity also have been observed, but no consistent pattern has emerged (Chilgren *et al.*, 1967; Louria *et al.*, 1967). The precise role of immunological factors in this disease thus remains unclear.

In this report, three patients with chronic mucocutaneous moniliasis, two of whom had an endocrinopathy, are described. In each case monilia antibodies were present in the serum and saliva, but each patient had a defect of delayed hypersensitivity limited to *C. albicans*. In one case, restoration of delayed hypersensitivity by passive transfer of a leucocyte extract from a sensitive donor was attempted. While this procedure did not produce clinical improvement, *in vitro* studies indicated an altered responsiveness of his lymphocytes.

Case Reports

Case 1

A Caucasian male developed candidiasis of the mouth, fingernails and skin of the hands and fingers at 2 years of age. Otherwise, he was healthy until the age of eight when he received Asian influenza vaccine (October 1957). Eleven days thereafter he developed fever, headache, generalized myalgia and malaise, and within a few days he was vomiting, hypotensive, confused and dehydrated. The serum sodium was found to be 120 mEq/l, and the diagnosis of adrenal insufficiency was established by an ACTH stimulation test. In 1967, at age 17, he developed diarrhoea with numerous light-coloured, floating, foul-smelling stools. The physical examination was remarkable only in that the skin was generally hyperpigmented, and the lesions of chronic candidiasis were present on the mucous membranes of the buccal cavity, on the fingernails and on the skin of the hands. Radiographic studies of the gastro-intestinal tract and measurements of intestinal absorption were normal except for a 72-hr faecal fat of 87·7 g (normal value—18 g). A biopsy of the mucosa of the small intestine was normal. Extensive studies revealed no other evidence of endocrine dysfunction.

Case 2

The clinical history of this case, a younger brother of Case 1, was quite similar in that he developed candidiasis of the nails, hands and mouth at 3 years of age. Four years later he was hospitalized for evaluation of diarrhoea and weight loss. Except for the lesions of candidiasis the physical examination at that time was normal. Intestinal function studies showed steatorrhoea, but there was no evidence of endocrine dysfunction. Eight months after discharge he suddenly became weak and listless. A serum sodium value of 127 mEq/l suggested adrenal insufficiency, and this diagnosis was confirmed by an ACTH infusion test. *Candida albicans* was cultured from the mouth, skin and nails.

At the present time, both brothers continue to have infections with *C. albicans* resistant to systemic and topical treatment, but the lesions have become less severe each year. They receive replacement steroid therapy, and their growth and development has been otherwise normal. Neither the parents nor three younger brothers have clinical evidence of candidiasis or endocrinopathy, and no other relatives are known to be affected.

Case 3

A Caucasian male was adopted at 7 months of age. Little is known of the family history except that the mother had asthma. The pregnancy and neonatal periods were normal. At 8 months of age *Candida albicans* infections appeared in the mouth, over the skin of the hands, neck and perianal region, and in the nails. The patient was first seen at the University of Kansas Medical Center in 1964 at the age of 2 years for evaluation of episodic fever and failure to gain weight. No cause for these problems was found. In particular, there was no evidence of endocrine abnormality or immunological disease although his serum did contain rheumatoid factor activity. When he was recently restudied there was still no clinical evidence of abnormal endocrine function, although his serum contained adrenal antibodies in addition to rheumatoid factor, and there was no delayed hypersensitivity to antigenic extracts of *C. albicans*.

Pertinent clinical and laboratory data for all three patients are summarized in Table 1.

TABLE 1. Clinical and laboratory features of patients with chronic mucocutaneous moniliasis

	1	2	3
Age of onset (years)			
Moniliasis	2	3	8/12
Adrenal insufficiency	8	8	—
Steatorrhea	17	7	—
Blood lymphocytes (mm^3)	3000	2700	2500
Urinary steroids (mg/24 hr)			
Baseline 17-KS	0·64	1·5	1·3
Baseline 17-OHS	0·67	1·4	4·0
Post-ACTH 17-KS	1·67	2·3	15·1*
Post-ACTH 17-OHS	0·56	1·9	—
PBI (μg/100 ml)	7·6	7·0	8·1
Serum calcium (mEq/l)	4·5	4·8	4·9
Serum phosphorus (mEq/l)	2·7	2·0	2·7

17-KS, 17-Ketogenic steroids; 17-OHS, 17-hydroxysteroids. PBI, protein bound iodine.

* Ketogenic steroids after metapyrone.

METHODS

Subjects

In addition to the three patients with chronic moniliasis, five healthy people with positive delayed hypersensitivity reactions to *C. albicans* and nine subjects in whom this test was negative were evaluated. The skin-test negative group included four patients with isolated deficiencies of IgA and five healthy volunteers.

Skin tests

Cutaneous hypersensitivity was assessed by intradermal administration of 0·1 ml of fresh antigenic extracts of histoplasmin (Parke-Davis), second strength purified protein derivative of tubercle bacilli (PPD) (Parke-Davis), mumps virus (Lilly), Trichophytin, 1000 protein nitrogen units (pnu)/ml (Hollister-Stier) and *Candida albicans*, 1000 pnu/ml (Hollister-Stier). Wheal and flare responses were read at 15 min. Induration of 0·5 cm or greater at 24 or 48 hr constituted a positive delayed reaction.

Preliminary experiments demonstrated that commercial aqueous extracts were cytotoxic because of the phenol preservative and glycero-saline preparations apparently lacked specificity. Therefore an additional extract of *Candida albicans* was prepared for use as a skin test antigen and for studies of *in vitro* lymphocyte transformation. A stock culture of the organism was grown in liquid Saboraud's medium at 37°C for 72 hr. The cells were collected by centrifugation, washed and suspended in normal saline, and killed by making the suspension 1:10,000 with merthiolate. They were then washed twice, resuspended in a small volume of saline and lysed by sonication for 20 min at maximum probe intensity in a Biosonic Model II instrument (Bronwill Scientific Co., Rochester, New York). The cellular debris was separated from the fluid phase by centrifugation, and the supernatant was dialysed against phosphate-buffered saline, pH 7·4, to remove residual merthiolate.

After millipore filtration and examination for sterility the antigen was diluted 1:10, 1:100 and 1:1000, and the potency compared to the commercial aqueous extract by intradermal testing. A similar process has been used by Taschdjian *et al.* (1964) to prepare 'S' or cytoplasmic antigen. The nitrogen content, determined by the Kjeldahl method, was 34 μg/ml.

Lymphocyte cultures

The technique for separation of lymphocytes from peripheral blood has been detailed elsewhere (Newberry *et al.*, 1968). Briefly, the cells were diluted with Eagle's minimal essential medium containing 15% autologous plasma and antibiotics to a final concentration of 1×10^6 lymphocytes/ml in a total volume of 3 ml. Each assay was done in triplicate with cultures containing no stimulating agent, cultures with 0·10 ml of phytohaemagglutinin-M (Difco Laboratories, Detroit, Michigan), and cultures with 0·1 ml of the locally prepared extract of *C. albicans*. Dose–response curves with healthy skin test-positive subjects demonstrated that the peak responses occurred at 5 days. The cells in all cultures were labelled with tritiated thymidine (specific activity 6·7 Ci/mM), 1 μCi/ml, at 96 hr and harvested 24 hr later. The DNA was precipitated and the radioactivity was counted in a liquid scintillation spectrometer. The results were corrected to disintegrations/min (dpm) and expressed as the ratio E/C; the mean dpm per million lymphocytes in stimulated cultures/mean dpm 10^6 lymphocytes in unstimulated cultures. An E/C ratio of 1·0 indicated no response.

Immunoglobulins

Serum or saliva specimens not assayed promptly were stored at −20°C. The concentrations of IgM, IgA and IgG in serum were measured by the single radial diffusion method (Mancini, Carbonara & Heremans, 1965), using commercial antibody containing agar gel plates and standards (Hyland Laboratories, Los Angeles, California). The saliva was collected with a Curby cap placed over the stoma of a parotid duct or by collecting secretions produced while the subject chewed paraffin. The specimens were clarified by centrifugation and filtration through gauze, and the concentration of IgA was determined by electroimmunodiffusion (Merrill, Hartley & Claman, 1967) using a secretory IgA standard prepared from colostrum, and provided by Dr Richard Newcomb. Commercial antiserum (Hyland Laboratories) from a single lot was used after it had been shown to be free from antibody activity against other immunoglobulins or light chains.

Serological studies

The titre of *Candida* agglutinins in serum and saliva was measured essentially as described by Winner (1953), although the concentration of the yeast suspension was adjusted to 3×10^6 cells/ml to facilitate microscopic reading of the end points. Antibody activity was expressed as the reciprocal of the greatest dilution producing agglutination of approximately 50% of the cells (2+). Preliminary comparative studies with unheated and heat-inactivated (56°C for 30 min) sera disclosed no differences in agglutination titres, and the results recorded here were obtained with unheated sera.

Candida precipitins were studied qualitatively by double diffusion in agar gel (Taschdjian *et al.*, 1967). The unconcentrated serum or saliva samples were diffused against a commercial aqueous extract of *C. albicans* (Hollister-Stier) and the locally prepared extract

described above. The plates were incubated at room temperature and observed daily for 7 days.

Isohaemagglutinins, antinuclear antibodies and rheumatoid factors were assayed in the clinical laboratory of the University Hospital. The antibodies against thyroglobulin, gastric parietal cells and thyroid and adrenal tissues in the serum of the moniliasis patients were determined in the laboratory of Dr H. H. Fudenberg (Wuepper, Wegienka & Fudenberg, 1969).

Passive transfer of delayed hypersensitivity

An extract was prepared by lysing 600×10^6 peripheral blood leucocytes from a person with strongly reactive *Candida* skin test. The cells were separated from plasma by centrifugation and sedimentation, washed twice with Eagle's MEM, re-suspended in MEM and subjected to three cycles of freezing at $-70°C$ and thawing at 37°C. The insoluble material was removed by centrifugation and the soluble fraction was sterilized by millipore filtration and injected intramuscularly into Case 3. The donor and recipient had compatible erythrocyte antigens but typing for HL-A antigens was not done. The skin tests and lymphocyte cultures were repeated 72 hr, 10 days and 30 days after the transfer.

RESULTS

A striking observation in each of the patients with chronic moniliasis was the absence of delayed cutaneous hypersensitivity to the extracts of *Candida albicans*, although delayed responses to other antigens such as mumps, PPD or trichophytin were intact. In contrast, the members of the skin test positive group developed indurations with mean diameter of 1·6 cm (range 0·5–4·0 cm). None of the people with IgA deficiency responded to the *Candida* extract, and only one member of this group developed significant induration to any antigen (Table 2). Two of the patients with moniliasis (Cases 1 and 2) developed immediate wheal and flare reactions to the extract, but responses of this type were not observed in any other subjects.

Both phytohaemagglutinin and the extract of *C. albicans* stimulated DNA synthesis by lymphocytes from skin test positive subjects. The mean E/C ratio was 90 for phytohaemagglutinin and 6·3 for the antigen stimulated tubes. Phytohaemagglutinin produced a similar increase in DNA synthesis in cells from skin test negative subjects, but there was essentially no response to stimulation with *Candida* (mean E/C = 1·1).

Lymphocytes from patients with chronic mucocutaneous moniliasis also responded poorly to the *Candida* extract. Although the results summarized in Table 2 only show the responses to a single concentration of antigen, in each case several doses were studied and similar results were obtained. Furthermore, the responses were not restored by culturing the cells in compatible homologous plasma regardless of its *Candida* agglutinating activity. The responses to phytohaemagglutinin were also lower in the moniliasis patients, and this response was not increased by culturing the cells in compatible plasma from healthy individuals.

Agglutinating antibodies against *C. albicans* were found in the serum and saliva of subjects in all groups. The patients with IgA deficiency tended to have lower titres, but there was no clear relationship of the antibody activity to the IgA concentration of the fluid. The agar gel diffusion experiments revealed two precipitin bands in serum from each of the moniliasis patients (Fig. 1).

TABLE 2. Immunologic studies

Patient group	Delayed cutaneous hypersensitivity (cm induration)					Lymphocyte cultures (E/C)		Immunoglobulins (mg/100 ml)			Saliva IgA	*Candida* agglutinins (reciprocal of titre)	
	C. albicans	PPD	Histo.	Mumps	Trichoph.	PHA	*C. albicans*	Serum IgM	Serum IgA	Serum IgG		Serum	Saliva
Moniliasis													
1	0	0	0	0·6	0·5	46	1·0	115	330	1750	11·5	256	16
2	0	1·5	0	2·1	0	25	1·8	100	260	1100	9·5	256	4
3	0	0	0	0·5	0	38	2·1	150	400	2500	11·5	128	16
Skin test positive													
1	0·5	0	1·5	0·5	1·0	105	6·6	66	172	770	7·2	128	< 2
2	2·0	0	4·0	2·5	—	55	7·4	72	220	1040	8·0	256	64
3	1·0	0	0	1·4	—	60	4·9	130	130	1200	—	256	8
4	0·6	0	0	1·4	—	119	4·2	177	330	1050	10·6	64	16
5	4·0	0	2·0	1·7	—	110	8·3	100	170	1150	7·8	128	< 2
Skin test negative													
1	0	3·5	0	2·0	—	343	0·8	26	170	1100	11·0	128	8
2	0	2·0	0	2·0	1·0	82	1·2	250	525	1300	—	64	—
3	0	0	0	0	0	—	—	130	210	740	8·0	32	8
4	0	0	0	0	0	126	1·1	260	170	1140	7·2	128	2
5	0	0	0	0·5	0·5	115	2·2	225	42	1110	9·6	256	8
IgA deficiency													
1	0	0·4	0	1·0	0	25	1·1	75	ND*	1400	ND	64	4
2	0	0	0	0	0	115	1·4	55	ND	2500	ND	64	8
3	0	0	0	0·5	0	—	—	190	ND	2200	ND	16	4
4	0	0	0	0	0	227	1·5	55	ND	1220	ND	64	32
Normal values								50–150	60–200	700–1500	Not established		

* ND, Not detectable.

With the exception of the patients with IgA deficiency, the immunoglobulin concentrations were rather unremarkable. There were no patterns that characterized the moniliasis patients.

A survey for antibodies against tissue antigens revealed adrenal antibodies in Case 3 and anti-thyroglobulin in Case 2. Rheumatoid factor was also present in the serum of Case 3. The siblings and parents of Cases 1 and 2 were also studied and no abnormal serological factors were found. The parents of Case 3 were not available for study.

Skin tests performed on Case 3 24 hr, 10 days and 30 days after administration of the extract of allogeneic cells were negative. However, when the patient's lymphocytes were restudied at 30 days by *in vitro* stimulation with the *Candida* antigens, a normal response with an E/C of 5·6 was found. The phytohaemagglutinin response was 38.

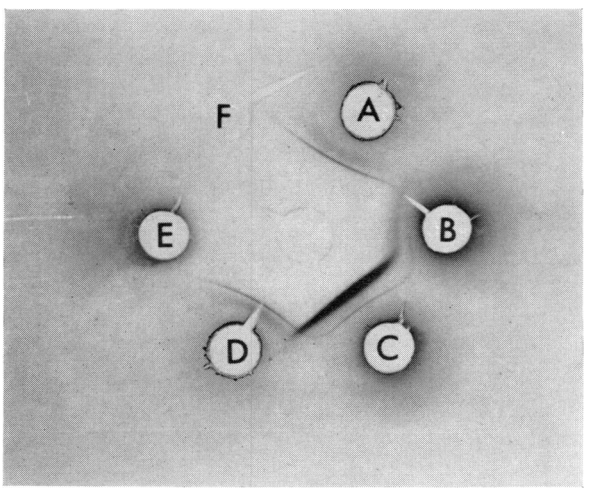

FIG. 1. Double diffusion in agar gel. The *Candida* extract was placed in the centre well. Wells A and D, serum from case 3; well B, serum from case 2; well C, serum from case 1; well E, serum from healthy skin test positive subject; well F, saline. A thin line of precipitation extends clockwise from A to D. The heavier band at well C has identity with a band at well B and possibly with the second band at well D.

DISCUSSION

Although *Candida albicans* is ubiquitous and frequently may be cultured from the gastrointestinal tract or skin of healthy individuals (Winner & Hurley, 1964; Clayton & Noble, 1966), systemic candidiasis is rare and usually occurs in patients with malignancies (Hutter & Collins, 1962) or recipients of immunosuppressive drugs (Rifkind *et al.*, 1967). For example, in an evaluation of patients dying after renal homotransplantation, nearly half had evidence of systemic fungal infections and *Candida* species were most frequently found (Rifkind *et al.*, 1967).

An apparently unique variant of superficial moniliasis is characterized by chronicity, resistance to therapy and frequent association with abnormalities of endocrine function. In these patients, the infection usually begins during early childhood and remains localized to the mucous membranes, nails and skin. The endocrinopathy may not appear until many

years later, and the adrenals and parathyroids are most commonly affected. The pattern of associated abnormalities is quite broad and includes thyroiditis, pernicious anaemia, steatorrhoea, hepatic cirrhosis and hypoplasia of the dental enamel (Kunin *et al*, 1963; Hung, Migeon & Parrott, 1963; Kenny & Holliday, 1964; Wuepper & Fudenberg, 1967; Blizzard & Gibbs, 1968). There is no evidence of direct invasion of the endocrine organs by the fungus, and autoimmune mechanisms have been suggested in the pathogenesis of the syndrome (Hung *et al.*, 1963). The evidence for immunological factors is indirect, and derives much of its support from the frequent occurrence of antibodies against parathyroid, thyroid, adrenal and gastric mucosal cells in the sera of these patients (Hung *et al.*, 1963; Kenny & Holliday, 1964; Wuepper & Fudenberg, 1967; Blizzard & Gibbs, 1968; Wuepper *et al.*, 1969).

Some observations have suggested a genetic predisposition to development of the syndrome. Cases have occurred in siblings and asymptomatic relatives of affected persons occasionally have tissue antibodies in their sera (Wuepper & Fudenberg, 1967). The presence of this disease in the two male sibs (Cases 1 and 2) both of whom had a remarkably similar course would tend to support a genetic etiology. Autosomal recessive inheritance has been suggested for this entity, but neither the mode of inheritance nor the relationship of the antibodies to the pathogenesis of glandular dysfunction has been established definitely (McKusick, 1968). Wuepper & Fudenberg (1967) recently suggested that the antibodies should be tentatively considered as 'markers' indicative of a genetic predisposition to the development of immunological disease.

The cases described in this report are representative of the clinical features of the syndrome. In each patient mucocutaneous moniliasis developed before the 3rd year and remained resistant to therapy. The siblings (Cases 1 and 2) were apparently free from other disorders until age 8 when each had an acute illness prompting the diagnosis of adrenal insufficiency. Case 2 had been extensively studied only 8 months earlier and no evidence of endocrine dysfunction was found, although organ specific antibody studies were not done. Both siblings subsequently developed steatorrhoea, but the function of other endocrine organs has remained normal. Adrenal antibodies were not detected in their serum, but these assays were not done until several years after the appearance of adrenal failure and the antibody activity is known to decrease with time (Wuepper *et al.*, 1969). Case 3 currently has adrenal antibodies but a recent metapyrone test was normal, and there were no clinical or laboratory indications of endocrine hypofunction.

Because the moniliasis is less dramatic in onset than the endocrine failure, relatively less attention has been devoted to the possible immunological factors important in host resistance. Louria & Brayton (1964) reported that normal serum contained a factor that was apparently lethal for *C. albicans*. Subsequently it was shown that the reduction in colony counts resulted from aggregation of the pseudo-germ tubes without an actual decrease in the number of metabolically active yeast cells (Chilgren, Hong & Quie, 1968). Some patients with chronic mucocutaneous moniliasis have another serum factor that inhibits this aggregation even in high dilutions (Louria *et al.*, 1967; Chilgren *et al.*, 1968). The inhibitor is contained in the IgG fraction of serum and can be removed by absorption of the serum with *C. albicans*. No relationship has been established between the inhibiting IgG and autoantibodies in the patients with the moniliasis-endocrinopathy syndrome.

Antibodies to *C. albicans* occur in the sera of healthy people as well as patients with moniliasis, and it has not been possible to define their role in immunity to this fungus.

Active immunization with attenuated or killed yeast cells has enhanced survival of animals to subsequent lethal challenge (Dobias, 1964). Moreover, a case of pulmonary candidiasis has been successfully treated with immune serum (Hiatt & Martin, 1946). Chilgren *et al.* (1967) recently reported two patients with mucocutaneous moniliasis and deficient *Candida* antibodies in the IgA of the parotid fluid. This finding may be significant in view of the hypothesis that IgA provides local immunologic protection to mucous surfaces (Tomasi, 1968). However, their patients also had defective delayed hypersensitivity, so the significance of the local antibody defect remains uncertain.

The delayed or cellular hypersensitivity response to a variety of fungal, bacterial and viral antigens presumably occurs as the result of interaction between the antigen and 'sensitized' lymphocytes. A relationship between delayed hypersensitivity and immunity to infections has been suggested by several observations. Enders *et al.* (1946), reported that host resistance to the mumps virus correlated more directly with the intensity of the delayed skin responses than the complement fixing antibody titres. Marmor & Barnett (1968) described a 21-year-old girl with persistent oral and cutaneous moniliasis who was anergic to a panel of common antigens and could not be sensitized with chlorodinitrobenzene (CDNB) or with leucocytes from a donor with positive skin responses. Her humoral immune mechanisms were intact. A similar case has been studied by Buckley *et al.* (1968), whose patient also had cutaneous anergy and could not be sensitized with CDNB. The humoral responses in this individual also were normal. Restoration of delayed hypersensitivity by a graft of allogeneic bone marrow from a skin test positive donor was accompanied by clearing of the moniliasis.

Another important model that may elucidate the relationship between delayed hypersensitivity and immunity to fungus infections is the DiGeorge syndrome of congenital absence of the thymus and parathyroids (Kretschmer *et al.*, 1968). These children have intact antibody production, but cell mediated reactions such as delayed allergy and graft injection are severely impaired. Recovery from moniliasis recently was observed in such a patient following restitution of cellular immunity with an allogeneic thymus graft (Cleveland *et al.*, 1968).

The approach to reconstitution of delayed hypersensitivity employed in our case was different. Lawrence *et al.* (1963) have shown that cellular hypersensitivity could be transferred to skin test negative recipients with lysates of peripheral blood leucocytes. This technique has the theoretical advantage of conferring specific immunologic responsiveness without exposing the patient to viable lymphoid cells potentially capable of causing a graft-*versus*-host reaction. Unfortunately, this procedure did not alter our patient's cutaneous responses or produce a beneficial effect on the moniliasis. The number of cells used greatly exceeded doses known to be effective, and while the activity of the extract was not confirmed in a skin test negative control, the change in *in vitro* responsiveness of the patient's lymphocytes would indicate that the material was active. The disparity between the lymphocyte transformation experiments and the cutaneous responses may reflect the relative sensitivities of the two methods. There is evidence that delayed hypersensitivity involves a relatively small number of specifically responsive cells that interact with antigen and elaborate factors that are chemotactic (Ward, Remold & David, 1969), cytotoxic (Kolb & Granger, 1968) and inhibit migration of macrophages (David, 1968). It is possible that a genetically determined or quantitative defect in secretion of mediators or in cellular responses to such mediators could explain negative cutaneous reactivity. Furthermore,

this type of genetic defect could occur in cells of both the lymphoid and endocrine systems in patients with moniliasis and endocrinopathy, resulting in inability to synthesize and/or secrete the respective humoral products. Unfortunately, while a lesion of this type could account for the clinical features in anergic patients, it would not explain the findings in those subjects with only a partial impairment of delayed hypersensitivity. For the same reason, genetically defective failure to differentiate a population of lymphoid cells capable of recognizing and reacting to the antigens of *C. albicans* is deemed unlikely.

On the other hand, the immune response to *Candida* in our patients may have been intact during early life, then lost, possibly through desensitization by chronic exposure to the antigens. Experience with other human delayed hypersensitivity reactions such as Rhus dermatitis has demonstrated that desensitization is difficult, but possible (Kligman, 1958). Serial studies of cutaneous reactions and lymphocyte transformation particularly in the younger sibs of affected patients would permit evaluation of this hypothesis. However, the latter postulate also does not adequately explain the simultaneous endocrine failure. Patients with the moniliasis-endocrinopathy syndrome will require continual sophisticated study if the pathogenic mechanisms of this complex disorder are to be accurately identified.

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