

Familial Chronic Muco-cutaneous Candidiasis*

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Chronic oral candidiasis has been described in association with abnormalities of the endocrine system on many occasions, both in case reports (Sutphin, Albright, and McCune, 1943), and more general reviews (Kunin *et al*, 1963). Chronic candidiasis has also been recorded in the familial thymic aplasia described by Nezelof (Nezelof *et al*, 1964), Swiss-type agammaglobulinaemia (Hitzig, 1968) and DiGeorge's syndrome (DiGeorge, 1965). More recently deficiency of the migration inhibitory factor (MIF), where cell mediated immunity appears to be partially defective, has been shown to be a feature of some patients with chronic candidiasis (Valdimarsson *et al*, 1970). It has also been associated with defective granulocyte function, as in chronic granulomatous disease (Quie *et al*, 1967) and myeloperoxidase deficiency (Lehrer and Cline, 1969).

During the last 3 years a group of patients has been investigated (Wells, 1970) who have chronic oral candidiasis with no other significant clinical abnormality. In some of the kindreds, sibs were found to have the disorder, and there was often a family history of consanguinity. We have suggested that this new group, hitherto undescribed and which we have called familial chronic muco-cutaneous candidiasis (FCMC), has a genetically determined abnormality, inherited as an autosomal recessive trait which results in susceptibility to candida infection. It is possible that an inherited biochemical or immunological abnormality results in this picture.

Present Investigation

Ascertainment. Most of the patients were referred to one of us (R.S.W.) in the genetic clinic at St John's Hospital for Diseases of the Skin following a postal questionnaire which was sent to all the consultant

dermatologists in England and Wales. Three families have been under observation for several years. Some were referred from general practitioners and others from the Dental Department at Guy's Hospital, and the Eastman Dental Hospital. From all these sources a total of 61 people were ascertained, of whom 46 were included in this study. Very detailed information was available for 3 other affected individuals who had died, and who must have had the same condition.

Method of Investigation. Many of the propositi were seen in hospital outpatient clinics, and subsequently other family members were visited in their homes. In some instances both the propositi and their families had to be visited, and affected individuals were seen in the North of England, North Wales, the Midlands, and the West Country in addition to London.

On these visits saliva was collected, blood taken, and appropriate skin tests were carried out. The results of a few of the latter had to be recorded by their general practitioners, or by local hospital consultants, who sent us the results on a standard form.

Thirty of the 46 patients in the study had either been admitted to hospital recently for investigation and treatment, or had been admitted in the past and so fully examined that re-admission was not necessary. Some of the others are still being investigated by us, or by other consultants in their local hospitals. It was not possible to examine personally 3 individuals; 2 were resident in the Republic of Ireland, and the other refused to see any medical or dental practitioner. They were included in the pedigrees, because there was good documentary evidence of the type of disease with which they were all affected.

A preliminary clinicogenetic classification is given in Table I, and reasons for these groupings will be discussed. Two of the individuals who had died would have been included in group 2, but, from the information in his hospital records, we could not accurately place the third, who had died from a malignant thymoma. It is very likely he would have been classified in group 4.

Investigative Protocol. Chronic muco-cutaneous candidiasis has been associated with abnormalities of cell-mediated immunity in several recent reports

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TABLE I
CLASSIFICATION OF PATIENTS SEEN IN THE PRESENT STUDY

Group	Genetic Group	Type of Candidiasis	Clinical Features	Number of Affected Individuals
1	Autosomal recessive	<i>Familial chronic muco-cutaneous candidiasis (FCMC)</i>	Chronic oral candidiasis; nails, skin, and other sites sometimes affected	22 (5 sporadic)
2	Unknown	Chronic muco-cutaneous candidiasis with other features; severely affected group	Chronic oral candidiasis; extensive skin and nail involvement; skin granulomas sometimes present; eyes, larynx, pharynx may be affected; susceptible to other infections	8 (all sporadic)
3	Autosomal recessive	Chronic muco-cutaneous candidiasis with endocrinopathy, ie, the candida-endocrinopathy syndrome	Chronic oral candidiasis; hypoparathyroidism and hypoadrenocorticism, hypothyroidism, diabetes mellitus	9 (5 sporadic)
4	Probably not genetically determined	Chronic muco-cutaneous candidiasis of late onset	Chronic oral candidiasis	7 (all sporadic)
Total				46

(Marmor and Barnett, 1968; Chilgren *et al*, 1969; Valdimarsson *et al*, 1970). Some of these patients have the candida-endocrinopathy syndrome. It is also possible that one of the conditions necessary to establish such an infection is a defective oral epithelium, since it has been reported that it is not possible to induce candidal infection experimentally on a healthy oral mucous membrane (Maibach and Kligman, 1962).

A comprehensive protocol was designed to investigate these 3 aspects, which included investigations of cell-mediated and humoral immunity, a search for endocrine abnormalities, and tests to exclude deficiency states which might lead to a defective epithelial formation. The latter in particular was directed to those associated with glossitis and angular cheilitis such as iron, folic acid, and vitamin deficiency.

The methods of investigation of immunological function are fully described elsewhere (Valdimarsson *et al*, 1972 b).

Skin testing using Bencard candida antigen, a somatic candida preparation* and purified protein derivative (PPD) was carried out, to assess the development of delayed hypersensitivity. Sensitization was attempted with dinitrochlorobenzene (DNCB) in some patients.

Lymphocyte function was assessed by transformation to phytohaemagglutinin, concanavalin A, and candida mitogens using tritiated thymidine incorporation as a marker. MIF and lymphocyte cytotoxicity were also measured. The laboratory protocol made it possible to differentiate between lymphocyte nonresponsiveness and inhibition of the response due to factors present in the serum.

Polymorphonuclear function was assessed by the nitroblue tetrazolium (NBT) reaction (Baehner and Nathan, 1968) and measurement of yeast cell killing, by the dye exclusion technique (Lehrer and Cline, 1969).

Serum was examined for antibodies to candida and

immunoglobulins were measured by the method of Mancini, Carbonara, and Heremans (1965). Saliva was tested for blood groups, H substance, and IgA levels.

Clinical Features

Sex. Of the 46 patients in the study, 22 were males and 24 females. If the 3 who died were included, there would be 25 males. There was no indication that the severity or any other feature was different in the 2 sexes, except that 2 females reported a premenstrual exacerbation of their symptoms.

Age of Onset. All the patients in groups 1, 2, and 3 (see Table I) developed chronic oral candidiasis in the early years of life, and many mothers were emphatic that the condition had been present in their children before the age of 2. Some older individuals could not give such exact information, but most remembered having it when they were young. At the time of this investigation the people seen were of all ages; the youngest was aged 4 and the oldest 67.

The 7 people in group 4 were easily separated from the others, because none had any lesions before they were 35 years old, and most had no disease before the age of 50. The chronic oral candidiasis had proved resistant to conventional treatment. It is possible that they have a disorder which is inherited, but it is more likely that they have an acquired abnormality, the cause of which has not been determined. The age of onset was so strikingly different from the others, that it seemed reasonable to separate them on these grounds alone.

* Prepared by Professor J. Pepys (The Institute of Diseases of the Chest).

Chronic Oral Candidiasis. Every patient (Table I) had one clinical feature in common, namely chronic oral candidiasis. This remained in spite of intensive treatment, and was uninfluenced by changes of dentures, climate, or environment. In almost every instance it was the reason why they were attending hospital clinics, and many had been out patients for most of their lives.

The tongue was usually enlarged, fissured, and indented by the teeth. The white candidal areas could be scraped off, with difficulty in some patients, leaving a smooth, red, raw, shiny surface.

The buccal mucous membranes were coated with a thick, white membrane, which could be removed, leaving a raw, red surface. In some instances there was chronic hyperkeratosis, producing an irregularly raised surface.

Most of the patients had an angular cheilitis often causing great discomfort, always bilateral, and usually symmetrical.

Group 1: Familial Chronic Muco-cutaneous Candidiasis. Twelve of the individuals in this group had a chronic candidal paronychia with an associated onychomycosis affecting one or more fingers, but in no instances were more than 6 finger nails abnormal. The distribution was asymmetrical, and one particular digit was not affected more than any others. However, the infection tended to remain confined to the same nails in any one patient. The more severely affected usually said they were chronic nail biters. Only one patient had a candida infection of some toe nails.

In 5 individuals there was a history of chronic blepharitis, presumed to be due to candida, but this generally improved with advancing years. Four had some evidence of mild skin involvement, one on the scalp, one on the face, one on the hands, and another in the groins. Two were chronically hoarse due to candida laryngitis, and 3 of the females had a proven chronic candida vaginitis. Two of the older males had had an operation on their tongue for suspected neoplastic change. Apart from the mouth lesions, none of the people in this group were severely affected, their general health was good, and none had any evidence of hypoparathyroidism, hypoadrenocorticism, or diabetes mellitus.

Group 2: Severely Affected Patients. The outstanding feature of all the patients in this group was the severity of the candida infection. In addition to the chronic infection in the mouth, all had skin involvement at many different sites. The scalp, face, neck, and upper chest were the areas

most usually involved, sometimes giving rise to a candida granuloma. The limbs and groins often showed evidence of chronic candidal infection as well. In all these patients, several finger nails were involved, 5 had infected toe nails in addition to the finger nails, and in 2 every finger and toe nail was abnormal. All these patients reported eye symptoms, probably due to a candida blepharitis. Five had a chronic candidal laryngitis, and one a proven candidal pharyngitis.

Chronic skin infection with organisms other than candida, usually bacterial, was a feature in several patients, and in one there was an infection with *Microsporum canis* which could not be eradicated.

All the affected individuals gave a history of increased susceptibility to intercurrent infection, and all had had chronic chest infections, with bronchiectasis in at least 4 persons. The 2 deaths were due to chest infections; in one instance necropsy examination showed multiple lung abscesses.

The severity of the infection in the patients in this group suggested a more severe disorder of their immune mechanism compared with those in group 1. However, as they were all sporadic cases, it is possible that some of them may be more accurately classified in one of the other groups.

Group 3: Candida-endocrinopathy Patients. In addition to the mouth infection, 3 out of the 9 patients had skin infection of the scalp, face, and hands respectively; some finger nails were abnormal in 6, 4 had blepharitis, and one female a proven candidal vaginitis. Laryngeal involvement was noted in one patient. In 4 of them there was an increased susceptibility to infection other than candida, one had a very chronic infection with epidermophyton floccosum, and 2 had had infectious hepatitis.

Three of the 9 patients had hypoadrenocorticism and hypoparathyroidism, 3 had hypoparathyroidism without hypoadrenocorticism, and one the reverse situation. One patient was included in this group because he had diabetes mellitus, and another because he had hypothyroidism.

In addition to other endocrine abnormalities, one female patient had primary amenorrhoea, another secondary amenorrhoea, and one male had low ketosteroid excretion.

Group 4: Late Onset. The only clinical abnormality in 6 of these patients was chronic oral candidiasis. In one patient a malignant thymoma was found. Other reports of this association have been published (Montes *et al*, 1968).

Genetic Findings

Group 1. For pedigrees see Fig. 1.

Pedigree A. III.3. A.H. Male aged 55. The propositus had 2 sisters (III.10 and III.11) who were also affected. Two sibs (III.1 and III.8) died at or shortly after birth, the latter following a convulsion, but the others were all alive and well. The parents and the children of affected individuals were normal. Consanguinity was easily established, because both parents had the same name before marriage.

Pedigree B. III.3. H.Y. Female aged 16. The proposita's older brother (III.1) was affected, and the parents knew they were first cousins.

Pedigree C. IV.7. M.C. Male aged 35. The propositus and his affected sister (IV.6) were both resident in this country, but the family derives from south west Ireland. Consanguinity was strongly denied at first, but was eventually established by the propositus when he visited his relations in Ireland. His parents lived in such a small community that it

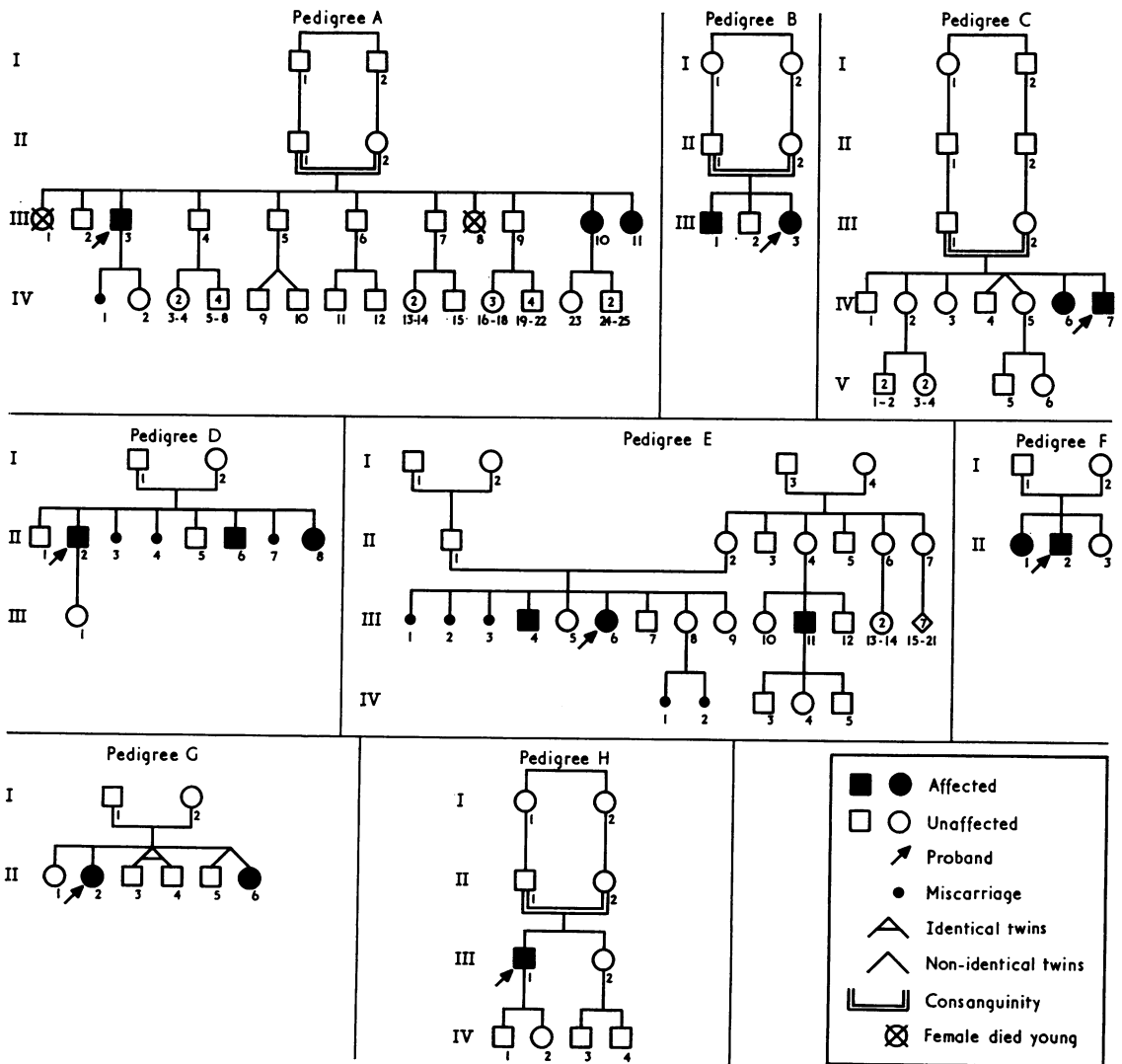


Fig. 1.

would be almost impossible to avoid marriage to a relation if both came from the same village.

Pedigree D. II.2. J.B. Male aged 21. The propositus had a brother (II.6) and a sister (II.8) who were similarly affected. The propositus's mother (I.2) had a difficult obstetric history with 3 miscarriages. The parents came from the same area in an English county town, and although they could not establish consanguinity, it is very probable that they were distantly related.

Pedigree E. III.6. N.M. Female aged 30. The proposita and one sister lived in England, but all the others were resident in southern Ireland. The other 2 affected individuals (III.4 and III.11) were reported to have identical clinical features, and again all the family members lived in a very small rural community. Although it has not yet been possible to visit them, it would seem to be very likely that consanguinity could be established, and that an autosomal recessive hypothesis is the most satisfactory explanation for the distribution of cases in this pedigree.

Pedigree F. II.2. G.H. Male aged 5. Consanguinity was unlikely in this family.

Pedigree G. II.2. C.S. Female aged 9. Consanguinity was unlikely in this family.

Pedigree H. III.1. A.C. Male aged 42. Only one of the pedigrees of the 5 sporadic cases in this group will be given, because it is the only one in which consanguinity was established. However, consanguinity was probable in the other 4 kindreds, because one patient was born in a very small village in the Midlands, where his family had lived for many generations, one was of Jewish Ashkenazi descent, one was illegitimate and was born in a small community in North Wales, and the last had parents who both derived from the same district of a town in the north of England.

Comment

Group 1. In all the pedigrees that have been described the parents and children of affected individuals were normal. Both sexes may manifest the disorder, and it occurs in sibships. Therefore the pedigrees are all compatible with an autosomal recessive mode of inheritance, and this hypothesis is very strongly supported by the exceptionally high incidence of consanguinity, which was established beyond doubt in 4 pedigrees, was probable in 6, and unlikely in 2, but even in the latter more than one individual was affected. The condition is rare,

because a very extensive ascertainment has only revealed a small number of cases. If the probands are excluded in the sibships with more than one affected individual, then there are 10 affected persons and 27 unaffected in the 7 pedigrees. This corresponds very closely indeed to the expected ratio of 1:3. For all these reasons it is suggested that an abnormality, at present undetermined, is inherited as an autosomal recessive trait, and that it gives rise to a susceptibility to candida infection.

Group 2. All the 8 patients provisionally included in this group were sporadic cases, as were the 2 who had died. The parents of all of them, including those who were deceased, were interviewed, so that full details of the pedigrees were obtained. The 10 individuals had a total of 28 sibs, 14 male and 14 female. Consanguinity was not established in any of the kindreds, although possible in 2, but very unlikely in all the others. None of the probands had any children.

For these reasons it was not possible to draw any conclusions on the genetic aspects in this group. The early onset of the abnormality, and its severity, suggest autosomal recessive inheritance, if the disorder is genetically determined. However, it is also possible that they may have been the recipient of a new autosomal dominant mutation.

Group 3. In the sibships with more than one affected individual, 2 brothers, and a brother and sister, had the disorder. Consanguinity was likely in one family, but not the other. Of the 5 sporadic cases, consanguinity was probable in three families. However, there are many published reports of this condition which include family studies (Sutphin *et al*, 1943) and there is little doubt that it is inherited as an autosomal recessive trait.

Group 4. The genetic aspects of these 7 individuals were entirely unremarkable.

Immunological Findings

No abnormality of polymorph function was found. Antibodies to candida, of all 3 immunoglobulin classes, were not significantly different from those found in the normal population. Several abnormalities of lymphocyte function were found, in particular, an inability to produce lymphokines (MIF). This appeared to correspond with absent delayed hypersensitivity to candida in the skin, and was found in some cases even when blast transformation in response to candida occurred. This implied a specific inability of the lymphocyte to produce MIF. In other patients unresponsiveness of

the lymphocyte to candida antigen was found. This appeared to be due to the presence of a blocking antibody in the serum, which could be demonstrated by the use of lymphocytes known to respond to candida. However the responsiveness could be partially restored by washing the lymphocytes. The defective delayed hypersensitivity response to candida was sometimes associated with an inability to sensitize the patients to DNCB. Where it has been possible to test sibs of affected individuals, the same defect has generally been found in the affected relatives in each sibship, but differed between families. One other finding of interest is the almost universal occurrence of blood group O in affected individuals, associated with the presence of H substance. A detailed report of these findings is given elsewhere (Valdimarsson *et al*, 1972 b).

Endocrine Findings

The candida-endocrinopathy syndrome (group 3) is usually evident by the second decade of life. Patients previously diagnosed and receiving treatment at the time of this study, were not further investigated. Specific tests of endocrine function were performed on the other patients under 25 years of age and included tests of thyroid, pancreatic, and gonadal function, synacthen stimulation of the adrenals, and ethylene diamine tetra acetic (EDTA) infusion as a test of parathyroid function. As there is a high incidence of auto-allergic phenomena described with the candida-endocrinopathy syndrome, screening for auto-antibodies to a profile of tissues was carried out, and the results were negative. It was not possible to test all patients by identical methods, since children and adults were admitted to different hospitals, and some tests were not applicable to children under 10 years of age. All the other patients were screened for an endocrinopathy by routine biochemical testing.

No new patients with endocrinopathy were identified. However, 3 patients had some evidence of an endocrine abnormality, which, although not typical of those with the candida-endocrinopathy syndrome, might be regarded as a partial manifestation of this disorder.

One patient who was difficult to evaluate was a 19-year-old male who had long standing muco-cutaneous candidiasis, as well as a chronic skin infection with epidermophyton floccosum and recurrent chest infections. He also had iron-deficiency anaemia, which was refractory to treatment, and an absence of iron stores. Myxoedema had been diagnosed and treated 2 years before the present investigation and tests of adrenal function

were within normal limits. Serum calcium and phosphate were normal on 3 occasions, but infusion of EDTA as a test of parathyroid function gave an atypical response, because there was no fall in serum calcium during the next 24 hours. He died 4 months later of a fulminating pneumonia followed by cardiac arrest. A serum calcium at the time of his cardiac arrest was low, ie, 5.3 mg/100 ml, and remained so following initial resuscitation, suggesting the onset of hypoparathyroidism. At necropsy many endocrine glands were found to be atrophied, including the thyroid, the adrenal glands and the testes. The parathyroid glands were present and appeared hypertrophied. There was a decrease in the amount of lymphoid tissue present in the tonsils and lymph nodes, and no thymic tissue was identified. As a result of the necropsy findings this patient was classified in group 3. A patient with some similar clinical features was described by Kugelmann, Cripps, and Harrell (1963).

Two patients classified in group 1 had some evidence of ovarian dysfunction, but ovarian auto-antibodies were not detected. It is not certain whether these findings should be regarded as purely incidental or whether isolated ovarian dysfunction can be regarded as part of the candida-endocrinopathy syndrome, since primary and secondary ovarian failure have been described in conjunction with other endocrinopathies (Kenny and Holliday, 1964).

Biochemical Findings

Defective Epithelial Formation. The parameters measured in this group of investigations included serum iron and folate, vitamin A, carotene, ascorbic acid, and vitamin B 12. Pyridoxine was also measured in a small number of patients.

Iron Deficiency. It was found that of the 31 patients investigated so far, 23 showed evidence of overt or latent iron deficiency, in that serum iron estimations were persistently low, iron binding capacity was normal or raised, and bone marrow biopsies in 15 patients showed reduced or absent iron stores. Fifteen of these 23 patients had no clinical evidence of anaemia, but as their serum iron levels were low, and iron stores were absent in most cases, we have subsequently referred to them as having latent iron deficiency.

Ten out of the 14 patients investigated in group 1 had latent iron deficiency, including all the affected sibs in 3 of the families. Two patients had previous investigations to show that their latent iron deficiency had existed for more than 5 years.

All the patients so far investigated in group 2 showed evidence of marked iron-deficiency anaemia, as did one patient in group 3 and one in group 4. Latent iron deficiency was present in one patient in group 3 with an atypical endocrinopathy, and was present in 4 of the 7 patients in group 4.

Vitamin A. Eleven patients had low serum levels of vitamin A. Five of these patients were from group 1, 3 from group 2, and 3 from group 4.

Pyridoxine. Five of the 6 patients tested showed low fasting levels of pyridoxine. Four of these were from group 2 and one from group 4.

Mycology

Nothing has emerged from mycological investigation of these patients to suggest that the actual organisms with which they were infected were in any way different from those found in the environment and in normal individuals. In 2 patients species of candida were isolated which had characteristics different from *Candida albicans*. In these cases *Candida parapsilosis* and *Candida guilliermondii* were isolated together with *Candida albicans* from various sites on a very heavily infected skin. A remarkable feature in some cases was the paucity of colonies grown from material taken from lesions which clinically seemed to be heavily infected. This was true even in cases in which numerous hyphae could be demonstrated in biopsy material.

Treatment

5-Fluorocytosine (Roche). Five patients were treated with systemic 5-fluorocytosine (200 mg/kg). Substantial initial improvement was observed in all of them, but this was not maintained in 4 of the 5 patients. One developed neutropaenia and a generalized macular eruption on the 10th day of treatment, which therefore had to be discontinued. One patient who had the candida-endocrinopathy syndrome, developed a severe relapse of his oral candidiasis, during the 4th week of therapy. At this time there was no alteration in his blood picture or liver function tests.

Although the numbers were small, it was concluded that 5-fluorocytosine did not effect any lasting improvement in this group of patients with chronic muco-cutaneous candidiasis.

Clotrimazole (Bayer 5097). Two patients, both with extensive skin involvement, have been treated with systemic Clotrimazole (100 mg/kg) for 3 months. Both have shown substantial improvement in the appearance of the skin lesions and of the oral candidiasis.

After 2 months, one patient developed an acute gingivitis, which was not characteristic of oral candida infection, and he was found to have a marked neutropaenia. The drug was stopped and antibiotics were given orally. There was no relapse of the oral lesion while taking antibiotic therapy, and the skin remained clear of lesions. The white cell count returned to normal within 2 weeks. Other patients have been treated with some improvement in the clinical condition, but the incidence of side effects has been high.

Iron Therapy. Eleven patients have been treated with oral iron, parenteral iron, or a combination of both for several months, and 9 have shown significant clinical improvement. This observation has been supported by a small clinical trial and more detailed studies of iron metabolism are in progress (Higgs and Wells, 1972).

Vitamin A Therapy. One patient has been treated with large doses of vitamin A, but the treatment had to be discontinued because of headaches and other signs of toxicity. There was some clinical evidence of improvement.

Immune Therapy. Two patients in this series have been treated. Initial delimitation of the immune defect has led to the use of transfer factor in one patient unable to respond to candida antigen by lymphocyte transformation, although MIF was produced. In this patient a good clinical improvement was noted, accompanied by improved responsiveness *in vitro*. The effect was temporary, but could be repeated by further administration of transfer factor.

In the other patient, although lymphocyte DNA synthesis occurred following candida antigen challenge, there was no production of MIF. This patient was given HL-A identical lymphocytes from his brother with marked clinical improvement, which has been maintained for 18 months (Valdimarsson *et al*, 1972 a).

Discussion

Clinical Aspects. The clinical features of familial chronic muco-cutaneous candidiasis (group 1) were consistent and well defined. The patients had chronic oral candidiasis, often from early childhood, and the nails, skin, and other sites were sometimes affected. They did not have any endocrinopathy, but many showed variable immunological abnormalities. It is a very rare condition.

Some of the severely affected individuals in group 2, may be more correctly classified in group 1, but it

seems likely that different causes may be determined for these patients. The individuals in group 3 were diagnosed by the additional features of an endocrinopathy, and group 4 patients by the late onset of their chronic oral candidiasis.

Genetic Aspects. Although not absolutely conclusive, the pedigrees studied strongly suggested autosomal recessive inheritance in group 1. Sibs of either sex were affected, and there was a very high incidence of consanguinity compared with the general population. Parents and children of affected individuals were unaffected. There is no way at the present time of diagnosing those who are heterozygotes. If the candida-endocrinopathy syndrome is regarded as an inborn error of metabolism, then it is likely that familial chronic muco-cutaneous candidiasis may be classified in a similar way.

Although we have described only four groups, there may be others, for instance, if a susceptibility to chronic candidiasis can be shown to be inherited as an autosomal dominant trait.

Immunological Aspects. Two possibilities for the inheritance of susceptibility to candidiasis exists. Either it is the result of a specific defect leading to infection with candida alone, or candidiasis is an expression of lack of immunity which may result from many different inherited defects, only one of which may operate in each patient. The affected sibs who have been tested always had the same defect as the proband, for instance, in one family, deficiency of migration inhibitory factor production, in other words a relatively localized immune defect, which might be in keeping with an inherited abnormality. The possibility exists that the more severe immune defects would be lost to this series by early death, but there was no evidence that this occurred in the close relatives of affected patients. We can assume that the defects found in these individuals were representative of the defects found in this disease.

Iron Metabolism. The existence of latent iron deficiency without anaemia is well documented (Stafford, 1961; Heinrich and Bartels, 1968), but its clinical importance remains controversial (Beutler, Fairbanks, and Fahey, 1963; Verloop, Leim, and de Wijn, 1970). As it has not been correlated with any specific disease entity, doubt has been cast on the need to correct such a state.

Glossitis and angular cheilitis may be associated with iron deficiency in a small proportion of patients, although the reason why this should be so is not clear (Bothwell and Finch, 1962). However, the finding of latent iron deficiency may be of im-

portance in the pathology of chronic muco-cutaneous candidiasis, since chronic lack of tissue iron can result in defective epithelial formation. This would not have been treated, as most patients were not anaemic and would not therefore be considered to be iron deficient. Consequently, a superimposed candidal infection might become persistent, while the epithelium remained dystrophic, and could lead to an alteration in the immune response over a prolonged period of time, as the antigen load was gradually increased. Such a parasitic relationship may ultimately become extremely difficult to eradicate. There is also some evidence to suggest that iron deficiency may in itself have a direct effect on the development of lymphoid tissue (Schmidt, 1928).

Detailed analysis of these results are recorded elsewhere (Higgs and Wells, 1972), in which evidence is presented to show that these findings are of clinical importance. The deficiency of iron may precede the onset of the chronic oral candidiasis and suggests a specific abnormality of iron metabolism, which could be of fundamental importance in the pathology of this condition, whether immunological abnormalities are present or not.

Further Studies. In mice a link has been demonstrated between pyridoxine deficiency and depression of both antibody production and the cell-mediated response (Axelrod and Trakatellis, 1964). Since pyridoxine deficiency may predispose to angular cheilitis, glossitis, skin changes, and a microcytic anaemia of a nonspecific type (Vilter *et al*, 1953), the existence of such a link with depression of the immune response has suggested a further study to estimate pyridoxine levels in the rest of these patients.

Summary

From hospital records, referral by dermatologists, and other sources, 46 persons who had chronic oral candidiasis were ascertained. A clinicogenetic classification was formulated, with 4 groups. Twenty-two of these individuals were considered to have a newly defined syndrome, which we have called familial chronic muco-cutaneous candidiasis (FCMC; group 1). There was a high incidence of consanguinity, suggesting that the disorder has an autosomal recessive mode of inheritance. Five of these patients had no family history of the condition, but all the others had one or more affected sibs. A description of the clinical features is given.

Of the remaining 24 individuals, 8 were found to be severely affected, with a susceptibility to other infections (group 2). As they were sporadic cases

it was not possible to form any conclusions on the genetic aspects. Nine were found to have the candida-endocrinopathy syndrome, which is inherited as an autosomal recessive trait (group 3). The remaining 7 individuals developed the disorder late in life (group 4).

Tests of specific immune responsiveness were abnormal in over half of the patients investigated.

Of the 31 patients from all groups so far fully investigated, 23 showed evidence of iron deficiency. Eight persons had evidence of anaemia due to iron deficiency, including all those in the clinicogenetic group 2. The remaining 15 had evidence of latent iron deficiency, as defined by a low serum iron and reduced or absent iron stores in the presence of a normal haemoglobin. This was true of 10 out of 14 patients in group 1 who were fully investigated and included affected sibs in 3 families.

These findings appear to be of clinical importance, whether abnormal tests of immune function exist or not, and suggest the possibility that a fundamental abnormality of iron metabolism may be associated with familial chronic muco-cutaneous candidiasis.

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