RECENT ADVANCES IN DERMATOLOGY

EDITED BY

ARTHUR ROOK

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CHURCHILL LIVINGSTONE
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PREFACE

In this fourth edition of *Recent Advances in Dermatology* I have continued the policy on which the third edition was based. Reviewers of that edition have in general endorsed my conviction that, despite the multiplicity of monographs, reports of symposia and review articles covering most specialised aspects of dermatology, there is a need for practical reviews on the laboratory and clinical aspects of common diseases. With one exception the topics selected are different from those included in the third edition, so that the two volumes may be regarded as complementary. Topical therapy has been covered again because in our patients' interests the voluminous literature requires frequent expert and critical reassessment. The chapters on Opportunism and Skin Infections and on Sexually Transmitted Diseases survey increasingly important aspects of the relationship between host and potential pathogens. The third edition considered bacterial, fungal and viral infections from a different viewpoint.

Authors have been asked to review the literature of the past ten years—in the case of topical therapy, only the last four—but to do so selectively, to provide a critical, useful and readable chapter rather than a comprehensive but dreary catalogue of all the relevant publications of the decade. Some authors have very properly chosen to include some references to older work, when by doing so the new work can be better seen in context, and more clearly understood.

Cambridge, 1976 ARTHUR ROOK

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J. A. Savin W. C. Noble

INTRODUCTION

Traditional distinctions tend to become blurred when dealing with skin infections, and to separate pathogenic from non-pathogenic organisms becomes very difficult. The skin is unique in its galaxy of clinical conditions due to the overgrowth of organisms which are normally resident there—such as trichomycosis axillaris, pityriasis versicolor, and erythrasma. Presumably changes in local resistance are needed for these conditions to occur. Even the word infection is open to debate here. Technically these conditions may not be infections in the usual sense of the word, but as they illustrate so well the response to purely local factors, they will not be excluded from this review.

The term 'opportunistic' should be easy to define precisely. Whether any infection takes place or not, depends on a balance between the attacking qualities of the organism concerned (its virulence), and the resistance to infection of the host. At one end of the scale are those infections in which a highly virulent organism succeeds in breaking the defences of a normally resistant host—a good example of this would be smallpox of the non-vaccinated. At the other end lie those infections with organisms which are usually harmless, but which are able to damage a host whose resistance has been grossly lessened, perhaps by disease or by deliberate immunosuppression. The latter type of situation is easy to accept as opportunistic.

The problem, as with any spectrum, is where to draw the line. Do skin infections with *Staphylococcus aureus*, for example, fall into the opportunistic class? Staphylococcal infections are common enough among those with good general resistance; but many carry the organism on their skin with no clinical sign of infection; some loss of local defence mechanisms is presumably needed for a clinical infection to establish itself. To some extent all infections may be in this sense opportunistic. The skin is again unique in that local alterations, for example in humidity, temperature, sebum content or mechanical integrity, can easily be recognised as playing a major part in allowing some of the common skin diseases to develop. Much of the work on the role of local factors has been with organisms, such as *Staphylococcus aureus*, which some will regard as opportunistic while others do not.

Definitions of opportunism also feel the strain when it comes to patients

with common, relatively harmless infections, such as with the wart virus, which may proliferate in conditions of low resistance. Studies, such as those of Morison (1974), showing the high incidence of warts in patients with lack of cellular rather than of humoral immunity, have been of great value in increasing our understanding of the way in which these infections are limited in the normal person.

One further problem in terminology comes with the contrast between an infection, clinically recognisable as such, and colonisation of an area of skin with pathogens, recognisable by in vitro culture but not by the usual physical signs of infection. One important example of this is the regular colonisation of some common dermatoses, such as psoriasis and atopic eczema, with *Staphylococcus aureus*. These dermatoses seem to provide a more favourable environment for growth than normal skin. In this sense this proliferation of organisms is opportunistic.

We have preferred to widen rather than to restrict the opportunistic concept, believing that to allow the discussion to embrace some common skin conditions will be of more value than simply dealing with unusual organisms, admittedly important, but seldom seen in skin clinics. However, widening the definition of opportunism, and hence the scope of the chapter, carries its own disadvantages: the subject matter becomes so great that all areas cannot be discussed in depth, nor can the references quoted be a complete list. Patchiness and omissions must inevitably follow this plan, and only a limited number of selected topics can be dealt with here.

Resistance to infection is a complicated process depending on both non-specific and specific factors. In the non-specific group are included the mechanical integrity of the skin and mucous membranes; contain non-specific bactericidal secretions, for example lysozyme; and finally phagocytosis and the inflammatory response to infection. These mechanisms are reinforced by specific immune responses both humoral and cellular.

Recent advances in this field, therefore, can be split into two major parts. First, there are gains in our knowledge of the qualities of the organisms themselves which allow them to be pathogenic: their attack mechanisms, how they spread, how the different species interact, and the way in which improved identification and classification have helped our understanding of their epidemiology. Secondly, and here the gain has been immense, there is new knowledge about defence mechanisms. Immunology has gone ahead faster than any other branch of medicine over the last few years. We have chosen not to expand this chapter by including a detailed exposition of immunological principles: these can be found elsewhere. However, some knowledge of this is required for an understanding of opportunism. There can be no more beautiful demonstration of immunological principles than the range of defects seen in candidosis.

CANDIDOSIS

Candida albicans is a classic opportunistic pathogen. Candidosis ranges from a brief, trivial, surface infection of the otherwise fit, to an overwhelming and often fatal systemic infection. The seriousness of the infection is roughly proportional to the degree to which the host's defences are compromised. The organism has two growth phases: yeast cells (blastospores) and mycelium. It is a fair working rule that the organism exists as a commensal in the yeast phase only, but that the mycelial phase, with its very clearly defined ultrastructural organelles (Cawson and Rajasingham, 1972), is always to be found in clinical candidal infections. Antigenically the two phases are now known to be both qualitatively and quantitatively different (Evans et al, 1973). So far routine tests for serum antibodies have used only cytoplasmic antigen extracted from the blastospore phase, and this may have given rise to false positive reactions in patients carrying the organism as a commensal. The use of a specific mycelial antigen might help here but the main defence against candida is not through circulating antibodies; indeed it is a deficiency of cellular immunity which is commonly found in chronic mucocutaneous candidosis.

Candidosis is best viewed as an extremely sensitive biological detector of weakness in the body defence system; and, while it is convenient to divide immunological defences into humoral and cellular events, they really form an interlocking series of reactions reinforced by non-specific defence mechanisms such as phagocytosis.

Transient Infections

Even in the common transient local infections, predisposing factors can often be found; for example, candidosis of the groin of healthy male soldiers (Lynch, Minkin and Smith, 1969) was associated with a higher bodyweight than controls, and also a higher incidence of diabetes in the family, and a more frequent intake of systemic steroids in the preceding three months. The birth control pill may also have an effect: in one study women taking the pill were found to harbour *Candida* in the vulva twice as often as controls (Oriel et al, 1972), though this has not been a universal finding (Spellacy et al, 1971). In a separate study (Oriel and Waterworth, 1975), both tetracycline and minocycline rapidly increased the isolation of vaginal yeast even though minocycline has an anticandidal action as well as an antibacterial one. The clinical picture of erosio interdigitale blastomycetica can only be produced experimentally with local occlusion and high humidity (Rebora, Marples and Kligman, 1973).

Candidal vulvo-vaginitis is common in pregnancy. The emphasis has swung away from a purely local cause for this, such as an alteration of pH due to high glycogen content of the vaginal epithelium leading to an increased

fermentation by lactobacilli, towards those immunological changes in pregnancy which may act to prevent rejection of the fetus with its range of foreign antigens. Cellular immunity in pregnancy is reduced (Finn et al, 1972), perhaps by an inhibitory serum factor (St Hill, Finn and Denye, 1973).

Newborn infants with candidosis tend to have lower levels of leucocyte myeloperoxidase than uninfected children (Renz et al, 1974), and these workers feel that at least some of the activity of clotrimazole in their study may have been due to stimulating myeloperoxidase activity. Reports of the way in which topical steroids can predispose to candidosis, for example in lichen planus (Cawson, 1968), paved the way for the obvious side effect of oropharyngeal candidosis affecting asthmatics using beclomethasone dipropionate inhalations (Milne and Crompton, 1974).

Systemic Candidosis

Systemic candidosis must be separated from mucocutaneous candidosis. It is seen against a background of severe illness. A characteristic eruption has been described (Bodey and Luna, 1974) which is quite distinct from that of chronic mucocutaneous candidosis. It consists of a variable number of well-circumscribed, firm, raised, red nodules ranging from 0.5 to 1.0 cm in diameter, and was seen in 10 of their 77 patients with systemic candidosis. Biopsy of these nodules showed yeast bodies and pseudohyphae in the dermis and in the blood vessels.

The neutrophil may be a major participant in the defence against systemic candidosis which is seen mainly in those with haematological malignancies. Leukopenia seems to predispose to it. Phagocytosis of *Candida* is not always accompanied by efficient killing of the organism. In one study (Lehrer and Cline, 1969), phagocytosis of *Candida* was successfully achieved by leucocytes from a patient with myeloperoxidase deficiency, and from three patients with chronic granulomatous disease, whose neutrophils fail to generate hydrogen peroxide, but despite this the intracellular *Candida* organisms were not killed.

Chronic Mucocutaneous Candidosis

Mucocutaneous candidosis is a rare condition with many causes. An increasing accuracy in pinpointing the exact deficiency in the host is now being knit together with an improved clinical and genetic classification. This must lead to a better chance of rational treatment for an affected individual, based upon an understanding of the mechanisms operating in his particular case. The problem is a complex one, and deficiencies may not be confined to a single area. For example, a child with a lifelong history of both recurrent pyogenic infection and mucocutaneous candidosis, showed a diminished neutrophil chemotactic responsiveness to account for the former, and a defect in cell-mediated immunity for the latter (Clark et al, 1973).

Investigations of chronic mucocutaneous candidosis have shown a spectrum of immunodeficiency and current classifications may not yet be complete. The comprehensive classification by Higgs and Wells (1973), has been chosen here as the most convenient framework for discussion. The outline of this classification is, for convenience, shown in Table 1.1.

They divided their cases into two main groups. In the first, the infection was associated with one of the defined immunodeficiency syndromes which are dominated by severe infections of various types. Examples include the Swiss type of agammaglobulinaemia, hereditary thymic dysplasia, and the DiGeorge syndrome. Patients in this group thrive poorly and die in early childhood although this is usually from viral or bacterial pneumonia rather than from candidosis. The use of antifungal agents and attempts at grafting fetal tissues, such as bone marrow cells, have met with little success. Fatal graft versus host reactions tend to occur, though this risk seems to be substantially reduced if only HL-A compatible tissue is transplanted.

Table 1.1 Classification of chronic mucocutaneous candidosis (based on Higgs and Wells, 1973)

Group I	Associated with primary immunodeficiencies e.g. Swiss-type agammaglobulinaemia, or hereditary thymic dysplasia
Group II	Candidosis is the main clinical feature 1. Familial chronic mucocutaneous candidosis 2. Diffuse chronic mucocutaneous candidosis with or without granulomata 3. Candida endocrinopathy syndrome 4. Acquired, e.g. in thymoma

Their second main group, with its four subdivisions, consists of patients who may develop chronic mucocutaneous candidosis early in childhood, but who usually survive at least to early adult life, and whose candidosis of mouth, skin and nails, is responsible for the main clinical features.

Their first subdivision consisted of individuals with the recessively inherited form of mucocutaneous candidosis which they had previously defined (Wells et al, 1972). These patients tend to have responded poorly to prolonged applications of local antifungal agents. Tests of cell-mediated immunity were abnormal in many, but the pattern was variable and did not correlate precisely with the clinical state. One important finding was the high incidence of latent iron deficiency. Iron is important for mitosis and iron deficiency per se seems to associate with reduced cell-mediated immunity both in adults (Jonson et al, 1972) and in malnourished children (Bhaskaram and Reddy, 1975). Wells and Higgs noted the reversal of negative to positive delayed skin tests to *Candida* in several of their patients after iron therapy, but clinical improvement was not confined to those who showed this change. They felt that iron therapy might have improved the quality of the oral epithelium indirectly,

and that the unusual difficulty found in raising the serum iron levels could indicate a fundamental defect in iron metabolism.

It is hard to know how to reconcile this with the known anticandidal effect of transferrin. The systemic candidosis of some patients with leukaemia has been associated with high serum iron levels and an accompanying saturation of iron-binding capacities (Caroline, Rosner and Kozinn, 1969). In vitro, iron-binding proteins such as transferrin inhibit bacterial growth by binding iron so efficiently that none is available to the microorganisms. Some organisms, in reply, also produce iron-binding substances, siderophores, and it has been suspected (*Lancet*, 1974) that the ability of an organism to compete with its host for iron is a feature of pathogenicity.

In mucocutaneous candidosis, the predominant effect may rest upon depressed cell-mediated immunity; other factors may include low levels of myeloperoxidase, and possibly upon changes in the growth of other organisms in the mouth, caused by the low iron levels, which would normally have suppressed growth of the yeast. Other mechanisms may be involved such as the decreased serum complement activity noted in one family with chronic mucocutaneous candidosis (Drew, 1973).

Their next subdivision was termed 'diffuse chronic mucocutaneous candidosis' and included some with granulomas. Though susceptible to bacterial chest and skin infections they usually survive childhood. A detailed analysis of the immunological investigations of 26 patients of this type was published by Valdimarsson et al (1973). Four main immunological patterns emerged. Five patients failed to produce macrophage migration inhibition factors (MIF) in vitro, although the lymphocytes were normally activated to DNA synthesis after challenge with *Candida* antigen. This finding supported the original suggestion of MIF deficiency made first by Chilgren et al in 1969.

If lymphocytes do not release MIF, macrophages will tend not to appear at the site of antigenic stimulus where a mutually stimulating action between lymphocytes and macrophages may be needed for a normal expression of delayed hypersensitivity, and the effective elimination of organisms. Treatment with leucocytes from an HL-A compatible sibling has been highly successful in one case (Valdimarsson et al, 1973); the grafted cells remained competent in the recipient, and the clinical benefit persisted for the 17 months of observation afterwards.

Two patients with adequate MIF, but defective macrophages, were detected; interestingly both showed granuloma formation, a feature not seen in those with defective MIF formation. Nine patients with absent delayed hypersensitivity also failed to produce MIF but their lymphocytes were not activated by *Candida* in vitro. This was thought to have been due to a factor in their serum specifically inhibiting *Candida*-induced lymphocyte transformation. In the 10 other patients no abnormalities of humoral or cellular immunity could be found.

'Immunological rehabilitation' will depend upon the exact range of defects

encountered in a particular patient. Attention must also be directed to associated immunoglobulin abnormalities in view of the report of impaired IgG precipitating antibodies to *Candida*, and lowered salivary IgA antibodies to *Candida*, in some cases (Lehner, Wilton and Ivanyi, 1972).

Transfer factor (TF) is a non-antigenic substance isolated from leucocytes which is capable of transferring immunological reactivity. Its use avoids the risk of graft versus host reactions, and sensitisation to HL-A and other antigens. Successful treatment with transfer factor has been recorded (Pabst and Swanson, 1972; Valdimarsson et al, 1972b; Mackie et al, 1975), sometimes aided by the use of amphotericin B (Feigin et al, 1974). This treatment seems likely to help only those patients with reduced lymphocyte transformation to *Candida*, rather than those with inadequate production of MIF as their primary fault. For the latter, a transfusion of HL-A compatible leucocytes is a possibility: in one patient (Valdimarsson et al, 1972a), already referred to above, a remarkable response persisted for a 17 month period of observation, implying that the grafted cells were remaining functionally competent in the recipient.

The *Candida*-endocrinopathy syndrome is inherited as an autosomal recessive trait. Its known associations have increased to include Hashimoto's disease, pernicious anaemia, chronic active hepatitis and alopecia areata (Stankler and Bewsher, 1972). The incidence of organ-specific antibodies (Blizzard, Chee and Davis, 1967), suggests an autoimmune mechanism. One recent 26-year-old patient has been reported to have developed multiple squamous cell carcinomata of the oral cavity (Richman et al, 1975). This early onset might suggest a defective immunological surveillance, but also *Candida albicans* seems able to induce epithelial hyperplasia (Cawson, 1973).

The final group of cases was of cutaneous candidosis occurring for the first time later in life, usually over the age of 50; in some ways these echo the endocrine-candidosis group, with a thymic tumour underlying a tendency to autoimmune diseases such as myasthenia gravis (Montes et al, 1968; Schoch, 1971), as well as defective cellular immunity.

DERMATOPHYTE INFECTIONS

In general, the balance between the dermatophyte and its host is less evenly poised than is the case with *Candida*. Unlike *Candida*, chronic dermatophyte skin infections are common in many apparently healthy people. This could imply that local factors such as mechanical trauma (Abdallah, 1971), blistering (Rosenthal and Baer, 1966), moisture (Allen and Taplin, 1973), and the anatomy of the toe spaces, are of more importance than are alterations in immunity.

Nevertheless there has been a steady stream of reports of extravagant fungal infections in those with abnormal immunity: for example, a *Microsporum equinum* infection of the scalp of an adult taking prednisolone for

breast carcinoma (O'Grady, English and Warin, 1972), mycetoma formation by *Trichophyton rubrum* in a patient on prednisone for asthma (Burgoon et al, 1974), subcutaneous abscesses in a patient on steroids for pemphigoid (Thorne and Fusaro, 1971), and a chronic *Epidermophyton floccosum* infection in a lymphoma patient with immune deficiency (Levene, 1973). Mixed dermatophyte and *Candida* infections have been seen in patients with thymic tumours (Baer et al, 1964; Savin, unpublished observations). Bagnall and Grünberg (1972) quote the very striking example of an epidemic of generalised *Trichophyton mentagrophytes* infections in capuchin monkeys: only those grossly debilitated by worm parasites were affected.

The whole subject of the immunocompetence of those with chronic fungal infections has recently come under review. While it is local factors which are of the greatest importance in acquiring an infection, it has been stated that 80 per cent of men chronically infected with dermatophytes have failed to reject this infection for immunological reasons (Jones, Reinhardt and Rinaldi, 1974). They suggest the mechanism may either be a relatively specific lack of cell-mediated immunity to trichophytin, or a curious response in which a brisk type I humoral immunity antagonises cell-mediated immunity. The propensity of atopics to develop immediate humoral immunity seems to be linked with their special liability to dermatophytosis (Jones, Reinhardt and Rinaldi, 1973), and supporting this is the association of asthma or hay fever, rather than atopic dermatitis itself, with chronic fungal infections.

There are of course differences between the types of fungus. Hanifin, Ray and Lobitz (1974) investigated one group of patients with *T. rubrum* infections, and another with *T. mentagrophytes* infections, for immediate and delayed cutaneous reactivity to trichophytin. The *T. rubrum* cases were likely to show either no reactivity at all, or only the immediate type; while the mentagrophytes cases usually had delayed hypersensitivity, with or without the immediate type. Curiously, Knight (1973) noted that a positive delayed reaction to trichophytin did not affect the ease with which he could infect human volunteers with *T. mentagrophytes*; in this his findings differed from those of Jones et al (1974) who found a close association between cell-mediated immunity to trichophytin and resistance to fungal infection.

Several other factors may be important in determining whether a patient develops a chronic fungal infection. For example, a significant number of elevated glucose-tolerance curves was found in one study of 29 patients with recurrent *T. rubrum* infections (Jolly and Carpenter, 1969), There may be interactions between the normal skin flora and the fungus: *T. mentagrophytes*, for instance, can, by its penicillin production, increase the proportion of penicillin resistant bacteria in the area (Bibel and Lebrun, 1975). The role of serum fungal inhibitory factors is not yet understood (Carlisle et al, 1974).

Racial differences must also be considered in assessing results. Blank, Mann and Reale (1974) have found differences between caucasoids and negroids in Philadelphia with respect to their experience of dermatophyte

infections. Of children attending the clinics, 91.5 per cent were negroid, and perhaps these differences were due to socioeconomic status. But the observations of Allen and Taplin (1973) in Vietnam, that US servicemen, both caucasoid and negroid, became infected with zoophilic *T. mentagrophytes*, whilst the Vietnamese military and civilian population were infected with *T. rubrum*, might imply genuine racial differences.

IMMUNOSUPPRESSION

By immunosuppression is meant a state in which established immunity and the response to new antigens are impaired (Bagshawe, 1972). The term covers changes in cell-mediated as well as antibody-mediated immunity. Whilst immunosuppression may occur naturally in diseases of the lymphoreticular system, it may also be induced for therapeutic reasons and the dermatologist can expect to be shown patients suffering from common infective conditions in an unusual form or from previously rare infections. The subject of immunosuppression and skin infection has been reviewed by Savin and Noble (1975) and for full references the reader is referred to this article.

Skin disease must be seen in perspective in relation to other disease. Eickhoff et al (1972) in a study of 216 patients with renal transplants found that skin infection (22 per cent) was less common than lung (42 per cent) or urinary tract (35 per cent) infection. Turcotte (1972) found six cases of herpes simplex, four of cellulitis and three of herpes zoster amongst 93 transplant patients at risk for a total of 1000 months.

Viral Infections

Perhaps the most interesting development here has been the suggestion that Hodgkin's disease itself is an infective condition, with a long incubation period, transmitted by person-to-person contact (Vianna et al, 1972). Their study of an extended 'epidemic' at a high school in New York State suggested that contacts sometimes developed other types of lymphoma also. The relationship between Hodgkin's disease, infectious mononucleosis and the EB virus, has been discussed in detail (*Lancet*, 1972). However, it would be premature to judge this difficult issue before further evidence is available. It has, of course, been long known that various forms of malignancy, including lymphomata, may be induced by immunosuppression (Allison, 1970). Transfer factor prepared from patients with Hodgkin's disease in remission may prove to be a useful line of treatment (Ng et al, 1975).

Serum copper estimations seem to be a valuable way of assessing the activity of Hodgkin's disease, the level tending to rise as the disease becomes more active. Herpes zoster infections are undoubtedly particularly common in patients with Hodgkin's disease: it has now been shown that serum copper

levels fall steadily for as long as 200 days before the episode of shingles (Thorling and Thorling, 1974).

Infections with other viruses in immunosuppression are now very well documented. Extensive herpes simplex may lead to the death of renal transplant patients (Montgomerie et al, 1969) and is also seen in patients with lymphomata (Lynfield, Farhangi and Runnels, 1969). Viral warts can be very frequent in Hodgkin's disease and Perry and Harman (1974) feel that the appearance of luxuriant warts should suggest the possibility of immune deficiency. Brodersen, Genner and Brodthagen (1974) in a study of tuberculin sensitivity, found that children with warts had a mean zone of induration of 10 mm compared with about 15 mm in controls. They point out that it is not possible to decide whether the reduced sensitivity results from the wart infection or whether the warts are a marker for defective cellular immunity. Extensive molluscum contagiosum has been recorded in two patients treated with methotrexate and prednisone (Rosenburg and Yusk, 1970). Varicella may also be associated with mortality in cancer patients (Armstrong et al, 1970) and is more common in those on active therapy than those in remission (Feldman, Hughes and Daniel, 1975). Cytomegalovirus, giant orf and severe progressive vaccinia, have all been described in immunologically compromised patients.

Fungal Infections

Infection with some unusual fungi has been reported, including *Fusarium solani* in acute leukaemia (Cho et al, 1973) and *Phoma* species in induced immunosuppression (Young, Kwon-Chung and Freeman, 1973). More common fungi such as *Pityrosporum*, *Candida* and *Histoplasma* have all been implicated in secondary disease of patients with some form of immunosuppression.

Bacterial Infections

Infections with the acid-fast bacilli have attracted some attention. *Mycobacterium tuberculosis* was troublesome in patients with neoplastic disease (Kaplan, Armstrong and Rosen, 1974): the severity of tuberculosis being directly related to the vigour of the antineoplastic therapy. *M. marinum* and *M. cheloni* have also been in evidence (Sage and Derrington, 1973; Aaronson and Park, 1974; Graybill et al, 1974). Fraser et al (1975) believe the administration of prednisone and azathioprine to have prevented the granulomatous cell-mediated response and to have resulted in a cellulitic inflammatory reaction to *M. kansasii*.

Non-staphylococcal toxic epidermal necrolysis (scalded skin syndrome) has been reported as associated with deficient cell-mediated immunity in leukaemia, during renal failure, in lymphoma patients, in a patient receiving prednisolone and azathioprine and in drug abuse. In experimental systems,