Reviews in Medicine

Dermatology

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Introduction

Over the last ten years there has been a dramatic surge in scientific research in dermatology and this specialty has benefited from advances in molecular biology, cell biology, immunology and pharmacology. The realization that the skin functions as an immunological organ and that mediators released from cells within the epidermis and dermis can act in an endocrine, autocrine and paracrine manner have had a major impact on our understanding of the pathogenesis of numerous inflammatory dermatoses, skin tumours and the wound repair processes. The use of immunohistochemical and immunoblotting techniques in the prenatal diagnosis of and the classification and diagnosis of many blistering disorders have become familiar. However, the genetic basis of many common skin diseases such as atopic dermatitis and psoriasis still remains unknown; a goal that may be realized by the accurate mapping of the human genome.

In this review of advances in dermatology some of these developments are brought out in the description of the following disease states, atopic dermatitis, acne and Raynaud's phenomenon and in the mode of action of two pharmacological agents, cyclosporin and essential fatty acids.

Atopic dermatitis

Atopic dermatitis may be defined as a specific dermatitis in the abnormally reacting skin of the atopic, resulting in itch with sequelae as well as inflammation. The incidence of this dermatosis in children aged 0–7 years has increased dramatically from approximately 3% in the period 1960–1964 to 10% from 1970–1974¹ and the incidence of atopy in the general population may now be as high as 30–40%. The cause of this is not known. Undoubtedly atopic dermatitis has a genetic component, evidenced by the high concordance rate in monozygotic twins (a risk of 0.86 compared to 0.21 in dizygotic partners) and recent work in asthma

has suggested an autosomal dominant inheritance of a defect on chromosome 11q.²

A unifying concept in the pathogenesis of atopic dermatitis has to explain the fact that the skin is abnormal in many ways.³ The skin is invariably itchy and dry which is due to a combination of increased water loss, a decreased number of sebaceous glands, reduced sebum excretion rate and reduced sweating. Patients have abnormal vascular reactivity evidenced by white dermographism during an exacerbation of atopic dermatitis and a flush reaction which may be localized or generalized and precedes the itching. Furthermore these patients have increased colonization with *Staphylococcus aureus*. There is also abundant evidence that immunological factors are contributory especially as this dermatosis has developed in recipients of bone marrow transplants⁴ and the atopic dermatitis-like eruption associated with the Wiskott-Aldrich syndrome resolves after bone marrow transplantation.

Further evidence of immunological involvement in atopic dermatitis is that the cellular infiltrate in the skin consists of predominantly 'activated' CD4⁺, HLA-DR⁺ lymphocytes and the ratio of helper/suppressor is three times more than that in the peripheral blood.⁵ Furthermore keratinocytes in lesional and clinically normal skin are HLA-DR⁺ and there may be deposition of IgG at the dermo-epidermal junction in involved and uninvolved skin.⁶ Another abnormality found in over 80% of patients is raised serum IgE levels and this is associated with Type I immediate hypersensitivity reactions to various inhalant or food allergens on skin prick testing.⁷ Serum IgE levels appear to correlate with the extent and severity of the disease but there is debate as to whether the raised IgE levels represent an epiphenomenon. This is because some patients with atopic dermatitis have normal IgE levels, that patients with X-linked agammaglobulinaemia develop atopic dermatitis in the absence of demonstrable immediate skin reactivity⁸ and that elevated IgE occurs in other dermatoses and lymphomas.⁹

Together with an abnormality of B lymphocyte

function in atopic dermatitis there is also evidence of impaired cell mediated immunity.^{10,11} Patients have an increased susceptibility to eczema herpeticum, impaired mitogenic responses of lymphocytes to several mitogens which normalizes during clinical remission, reduced incidence of allergic contact dermatitis, a reduced ability to induce sensitization to an antigen such as dinitrochlorobenzene and cutaneous anergy to microbial antigens. In contrast many authors have shown that application of patch tests, solutions or ointments containing a variety of aeroallergens (house dust mite, tree, grass and weed pollens, animal danders and molds) to the skin of patients with atopic dermatitis results in the clinical and histological features of an acute eczema.¹²⁻¹⁵ Both the time course and the cellular infiltrate have suggested that a form of delayed hypersensitivity had occurred.¹⁶⁻¹⁷

Percutaneous entry of applied aeroallergen could allow binding to the increased numbers of antigen presenting epidermal Langerhans cells in the skin of patients with atopic dermatitis.¹⁸ Recently, IgE has been identified on the surface of cutaneous dendritic cells (principally Langerhans cells and interdigitating reticulum cells) in both lesional and nonlesional skin of patients with active atopic dermatitis.^{19,20} Therefore the capacity of antigen trapping via the surface bound IgE and the ability of Langerhans cells to induce T lymphocyte activation and the generation of cytotoxic T lymphocytes could be the initiating events in the delayed hypersensitivity reaction.

Low affinity cell surface receptors for the Fc fragments of IgE (FcεR) have been identified on T and B lymphocytes, monocytes, platelets and eosinophils²¹⁻²³ and the FcεR on B cells is identical to the CD23 antigen earlier described as a B cell-activation marker.²⁴ Investigators have provided evidence that Langerhans cells also express CD23 in the skin of patients with atopic dermatitis.²⁵ The CD23 molecule not only acts as a receptor but a 32- to 35-kDa soluble form of the CD23 molecule (sCD23), otherwise known as IgE binding factor, is spontaneously shed from CD4⁺ T cells and activated B cells²⁶ and causes proliferation of CD23⁺ B cells²⁷. It would be interesting to know in the context of atopic dermatitis if the autocrine effect of sCD23 could upgrade the afferent arm of the immune response by allowing a greater number of CD23 molecules to be expressed on cutaneous Langerhans cells or whether there is an effect on IgE synthesis by B lymphocytes.

A consequence of the recruitment of activated T lymphocytes into the dermis during a flare of atopic dermatitis might be the release of interferon-γ (IF-γ) and interleukin 4 (IL-4). Since it has been shown that keratinocytes in lesional skin express HLA-DR⁵ and that IF-γ can induce the expression

of HLA-DR on keratinocytes,²⁸ it would seem extremely likely that release of IF-γ does occur. It has also been shown that IL-4 and IF-γ have a synergistic effect on the induction of CD23 on cultured Langerhans cells.²⁹ In addition keratinocytes may release several cytokines including interleukin 1 (IL-1), interleukin 6 (IL-6), tumour necrosis factor (TNF) and granulocyte macrophage colony stimulating factor (GM-CSF)³⁰ but a possible role for these mediators in the pathogenesis of the inflammatory response or indeed in regulating Langerhans cell CD23 expression in atopic dermatitis has so far not been published. Thus there appear to be several explanations for upgrading the immunological/inflammatory response in atopic dermatitis but so far little progress has been made on the downgrading process although it is known that topically applied corticosteroids decrease not only the number but also the antigen-presenting capacity of epidermal Langerhans cells.^{31,32}

A possible biochemical explanation for the immunological abnormalities seen in atopic dermatitis is that there is a defect of intracellular secondary messenger systems.^{33,34} In particular, elevated cyclic AMP-specific phosphodiesterase activity causing cyclic AMP hyporesponsiveness has been found in peripheral blood mononuclear leucocytes from patients with atopic dermatitis and abnormalities of protein kinase C and of inositol activation also have been described. However, it is not known whether these abnormalities allow further mediator release or whether these findings are secondary to chronic exposure to low levels of inflammatory mediators since similar findings have been found in psoriasis.

Acne

Acne is a chronic inflammatory disease which is characterized by the formation of comedones, erythematous papules, pustules, nodules and cysts. The pathogenesis is undoubtedly multifactorial with the abnormalities centred on the pilosebaceous unit. There may be increased sebum excretion, obstruction of the pilosebaceous duct due to hypercornification, altered bacterial colonization and inflammation. Whatever the importance of the individual aetiological factors an absolute prerequisite for the development of acne is active sebaceous glands.

Sebaceous glands are under the influence of sex hormones. Androgens increase gland size and sebum secretion and at puberty when the glands increase dramatically in size, the sebum output also increases.³⁵ Because there is a good correlation between severity of acne and the level of sebum excretion,³⁶ an obvious suggestion was that abnor-

mally high levels of sebum secretion resulted from high circulating androgens. A number of studies have documented raised androgen levels (elevated free testosterone and lowered sex hormone binding globulin) in women with acne but these findings have usually been limited to those over the age of 20 and in selected severe or therapy resistant cases.³⁷⁻³⁹ In general there appears to be no correlation between acne severity and plasma androgen levels or clinical markers of androgenicity (hirsuties, excessive body hair, male pattern alopecia, hidradenitis suppurativa) in women.^{40,41} This taken together with the poor correlation between acne severity at different sites suggests that in most cases the acne does not result from a systemic hyperandrogenaemia but rather from an abnormality locally with greater conversion of androgens in skin containing active sebaceous glands. Indeed the local conversion of testosterone to the more androgenic 5 α -dihydrotestosterone by the enzyme 5 α -reductase is increased in acne skin compared to normals.⁴² Furthermore the finding that 83% of females with acne vulgaris have polycystic ovaries and that these patients lacked the features usually associated with the polycystic ovary syndrome also suggests an alteration in local steroid metabolism or steroid hormone receptors rather than a systemic abnormality.^{43,44} This hypothesis is supported by increased urinary 5 α -tetrahydrocortisol in patients with the polycystic ovary syndrome indicating increased conversion of cortisol to 5 α -dihydrocortisol by 5 α -reductase in either the skin or liver.⁴⁵ Clearly, exciting work has yet to be done to elucidate the factors controlling cutaneous androgen metabolism and such research may provide the realization of topical antiandrogenic drugs in the treatment of acne.

Although there is evidence that patients with acne have an increased sebum excretion rate, the seborrhoea persists after resolution of the acne. There must therefore be other factors necessary for the development of the condition and one of these is ductal hypercornification. This involves a significant change in the formation and desquamation of the keratinized cell layer inside the infundibulum (the lower four-fifths) of the pilosebaceous orifice.⁴⁶ The granular layer becomes more prominent and the horny cells become more distinct and stick together so that instead of sloughing into a loose disorganizing mass, the horny cells pack together into lamellae of dense eosinophilic horn. Thus the accumulation of horny cells distends the pilosebaceous canal, producing first a microcomedo and then a clinically obvious lesion. As the comedone enlarges sebum continues to be produced, becoming mixed in with the corneocytes and eventually a stage is reached when there is obstruction of the pilosebaceous duct and the sebum becomes dammed up.⁴⁷

The pathogenesis of the abnormal ductal cornification in acne is not fully understood. It may result from hyperproliferation of the ductal epidermis and/or an increased cohesiveness of the corneocytes. Since not all ducts in an acne-prone individual form comedones, a local change affecting some but not all follicles must occur. Proposed factors that modulate the cornification include alterations in skin surface fatty acids^{48,49} and squalene,⁵⁰ bacterial colonization⁵¹ and the degree of hydration of the pilosebaceous duct. Squalene, in particular its oxide and peroxides, is implicated as being comedogenic and the surface lipids of patients with acne have an increased squalene content compared with controls.⁵² The theory that bacteria are in some way involved in comedogenesis appears unlikely however since a large proportion of closed and open comedones are totally free of bacteria.⁵³ The observation that acne may flare premenstrually can be explained by changes in pilosebaceous duct size and measurement of the orifice size has shown a reduction between the 15 and 20th days and a deterioration in the acne on the 22nd day of the cycle.⁵⁴ Whether this is due to hydration of the ductal corneocytes or direct hormonal influences has not yet been established.

A role for micro-organisms in the genesis of acne was initially proposed by Unna in 1896⁵⁵ but it is still not known whether the microflora are initiators of the lesions or whether their presence is dependent upon the local environment. The commensal flora of healthy or acne-affected pilosebaceous follicles consists of *Propionibacterium acnes*, *Staphylococcus epidermidis* and *Pityrosporum ovale*.^{56,57} It has been shown that *P. acnes* are distributed at skin sites with high numbers of sebaceous follicles⁵⁸ but there does not appear to be a direct relationship between the severity of acne and the bacterial population density.⁵⁹ Nevertheless the efficacy of antibiotic therapy in the treatment of acne strongly suggests that bacteria are involved in the pathogenesis of the disease although it is now known that tetracyclines have other actions such as interfering with protein synthesis and having an anti-inflammatory action.⁶⁰

Further evidence for the involvement of micro-organisms comes from the fact that nascent sebum is high in triglycerides and devoid of free fatty acids.⁶¹ Lipases produced by *P. acnes* act on the sebum to yield long chain fatty acids, glycerol and mono- and diglycerides and the free fatty acids are both irritant and comedogenic.⁶²⁻⁶⁴ A recent hypothesis suggests that the follicular anaerobic flora produce porphyrins which catalyse the oxidation of squalene.⁶⁵ This oxidation product is not only comedogenic but the reaction reduces follicular oxygen levels and encourages the colonization of further anaerobes such as *P. acnes*. The variability in the microenvironment of the individ-

ual follicles might then explain the highly local nature of acne and why some follicles become inflamed and others not.

The inflammatory component of acne is almost certainly of greatest concern to the patient and may be the precursor of persistent scars. Inflammatory lesions consist of macules, papules, pustules, nodules and cysts. Through careful mapping of developing lesions it was found that the earliest inflammatory cells consisted of a predominantly T helper lymphocytic periductal and perivascular lymphocytic infiltrate.⁶⁶ Polymorphonuclear leucocytes were present at later stages (72 hours) and were more evident when there was disruption of the duct wall. Interestingly, these authors refuted the currently held dogma that disruption of the follicular wall is a necessary requirement for the inflammatory process since this was only found in 14% of inflamed lesions at 6 hours and in 18% at 72 hours. Immunofluorescent studies have shown that activation of complement accompanies the cellular infiltrate since there is deposition of C3 in the walls of small dermal blood vessels and at the dermo-epidermal junction in early inflamed lesions.⁶⁷

There has been great interest in unravelling the pathogenesis of the inflammatory process and to understand how drugs such as antibiotics and the synthetic retinoids are so successful in reversing these changes. The main focus has been on mediators released by the micro-organisms within the pilosebaceous duct and the effect of these mediators on polymorphonuclear leucocytes rather than the lymphocyte. It has been shown that *P. acnes* produce cytotoxins⁶⁸ (compounds which stimulate chemotactic activity and do not require the presence of serum factors) some of which have been identified as lipases,⁶⁹ a prostaglandin-like substance and a low molecular weight substance.⁷⁰ The cell wall of *P. acnes* stimulates *in vitro* the classical and alternate complement pathways⁷¹ and other comedonal contents of non-bacteriological origin may be important in acting as cytotoxins and activating complement.

There is also evidence of a host response in acne with some patients having antibodies to *P. acnes* and others demonstrating delayed skin test reactivity to *P. acnes*, both of which correlate with acne severity.^{72,73} Furthermore investigators have demonstrated lymphocyte transformation to *P. acnes* and increased cellular immunity using the leucocyte migration inhibition test.

The precise pathogenesis of acne remains unclear and the reason why the disease is usually self limiting also is not known at present. Fortunately the disease responds satisfactorily to available treatment.

Cyclosporin

Cyclosporin is a lipophilic cyclic undecapeptide composed of 11 aminoacids produced by a strain of *Fungi Imperfecti*, *Tolypocladium inflatum* Gams and was first isolated from samples of soil in Wisconsin and the Hardanger Vidda in Norway in 1969. The antilymphocytic action of cyclosporin was first described by Borel in 1976⁷⁵ and the drug was first used in human organ transplantation in 1978. Its possible role as a dermatological treatment was first appreciated in 1979 when 4 patients with psoriatic arthritis noticed a rapid clearing of their psoriasis and an improvement of their arthritis following treatment with cyclosporin.⁷⁶ In 1984 administration of cyclosporin to a patient with crippling psoriatic arthritis resulted in mobilization together with clearing of the psoriasis.⁷⁷ Subsequent studies have established that low-dose cyclosporin induces remission in severe psoriasis and that this is maintained with continued therapy.^{78,79} Tachyphylaxis does not occur and after stopping the drug the skin condition gradually deteriorates to its pre-treatment state with 2 to 8 weeks. Rebound worsening does not usually occur although there have been a few reports of such a phenomenon including rebound pustular psoriasis in the literature.⁸⁰

Cyclosporin in open, and in a few double-blind, studies has also been shown to be of benefit in the treatment of many other diseases including atopic dermatitis,^{81,82} lichen planus,⁸³ alopecia areata,⁸⁴ pemphigoid,^{85,86} pemphigus,⁸⁷ polymyositis,⁸⁸ dermatomyositis,⁸⁹ pyoderma gangrenosum⁹⁰ and Behçet's disease^{91,92} but at present its use should be reserved for severe conditions in which standard treatments have been unsuccessful. An initially encouraging report of cyclosporin improving ichthyosis vulgaris⁹³ was not substantiated by its further use in the treatment of lamellar ichthyosis.⁹⁴ Cyclosporin has also been shown to improve the cutaneous sclerosis, heal persistent digital ulcers and to lower levels of serum aminoterminal propeptide of type III procollagen in patients with systemic sclerosis.⁹⁵ However, in an earlier report in the treatment of patients with systemic sclerosis, one of four patients treated with cyclosporin died of acute renal failure⁹⁶ and in the most recent study 2 of 10 patients had abnormal post-treatment renal biopsies.

From experience obtained in the treatment of psoriasis, cyclosporin should be started at an initial daily oral dose of 3.0 mg/kg/day taken in two equally divided doses. If there has been no improvement after 2 weeks the dose should be increased by 0.5 mg/kg/day every 2 weeks to a maximum dose of 5 mg/kg/day. Doses above this carry increased risks of side effects. It is advised that topical treatment of the psoriasis be continued

so that the dose of cyclosporin may be reduced to the lowest necessary to maintain remission.

Cyclosporin is absorbed in the small intestine and peak blood concentrations are reached within 1 and 8 hours after oral administration.⁹⁷ The drug is metabolized in the liver by the cytochrome P450 system and is excreted predominantly into the biliary system. Several drugs are known to interfere with cyclosporin metabolism. Those that induce the cytochrome P450 dependent liver enzymes (rifampicin, phenytoin, phenobarbitone, carbamazepine) lower cyclosporin blood levels and those that inhibit the P450 enzyme system (ketoconazole, corticosteroids, oral contraceptives, calcium channel blocking drugs, erythromycin) increase cyclosporin blood levels.⁹² These may be rapidly measured by radioimmunoassay.

The most frequent side effects of cyclosporin are hypertension and nephrotoxicity, both of which are dose-related. It is essential therefore that monthly trough blood cyclosporin levels be performed, that blood pressure should be regularly monitored and that glomerular filtration rate be measured at least every 3–4 months since a rise in serum creatinine may be a late manifestation of impaired renal function. Nephrotoxic drugs potentiate the renal toxicity of cyclosporin and therefore these should be avoided. Hypertension occurs in as many as 25% of patients though the blood pressure normalizes after the drug is stopped and if continued therapy with cyclosporin is required then a calcium channel blocking drug may be an appropriate antihypertensive agent. Other side effects include hypertrichosis, gum hyperplasia, paraesthesiae, elevated potassium and uric acid levels and decreased serum magnesium.⁹⁸ A worry about the long term immunosuppressant effect of cyclosporin is the possible increased risk of malignancies and because of this it would be unwise to start this drug in any patient who has had a past or present malignancy.

To minimize systemic side effects the use of topical cyclosporin in the treatment of psoriasis has been explored. Unfortunately this has been unsuccessful but a recent report of intralesional cyclosporin showed a beneficial effect which suggests that the drug may be acting by a local mechanism.⁹⁹ Interestingly, application of a 10% gel did significantly improve the severity of atopic dermatitis in a double-blind placebo-controlled study¹⁰⁰ and there are reports of topical cyclosporin under occlusion flattening hypertrophic lichen planus and of a cyclosporin wash improving oral lichen planus.¹⁰¹

The mode of action of cyclosporin has mostly been studied in psoriasis and can be divided into its immunological/anti-inflammatory and anti-proliferative actions.¹⁰² The predominant immunological effects are the reversible inhibition of T

lymphocyte activation probably as a result of a reduced responsiveness of helper T cells to interleukin 1 and a reduction in the subsequent release of many of its cytokines and lymphokines, interleukin 2 and gamma interferon. Other effects include an inhibition of MHC II expression, inhibition of antigen presenting capacity, interference with cell surface receptors, inhibition of calmodulin-dependent binding processes and inhibition of phospholipase A₂. Cyclosporin may also have a direct effect on the epidermis through inhibition of proliferation and epidermal enzymes. In psoriasis the earliest effects of cyclosporin, before any clinical improvement has been observed, are those involving loss of gamma interferon inducible surface molecules on keratinocytes, such as HLA-DR and intercellular adhesion molecule-1. This suggests that interference with lesional T cell lymphokine release is an important early event in the resolution of psoriatic plaques.

Cyclosporin is therefore a potent therapy of many dermatological disorders but as yet it is not licensed for the treatment of any these diseases and because of its nephrotoxic capacity, long term treatment must be carefully supervised. The development of appropriate epicutaneous preparations may overcome these concerns and they are eagerly awaited.

Raynaud's phenomenon

Raynaud's phenomenon is defined as episodic discolouration and ischaemia of the digits of the hands and feet in response to cold or emotional stress, often accompanied by feelings of numbness, tingling and pain. It is manifested by pallor followed by cyanosis and then redness; these changes reflect respectively the underlying ischaemia, venostasis and reactive hyperaemia. The symptom complex is relatively common with a prevalence in the general population reported as being between 3–22%.^{103–105}

Raynaud's phenomenon can be subdivided into an isolated or primary disorder or it may be secondary, when it precedes or accompanies a systemic disorder, or be caused by drugs. The majority of cases of primary Raynaud's phenomenon can be diagnosed by a modification of Allen and Brown's criteria.¹⁰⁶ Such patients have episodes of bilateral vasospastic colour change provoked by cold or emotional stress, normal peripheral artery pulsations, absence of gangrene or digital pulp loss, absence of any obvious causal disease on history or examination, a minimum duration of symptoms of 2 years, age of onset under 25 and negative investigations for secondary Raynaud's phenomenon. These would include

negative anti-nuclear antibodies, anti-DNA antibodies, cryoglobulins and cold agglutinins, normal ESR, immunoglobulin and creatine phosphokinase levels and normal lung function tests, nail-fold capillaroscopy, chest and hand radiographs. The causes of secondary Raynaud's phenomenon are listed in Table I.

The pathogenesis of Raynaud's phenomenon is still unknown but several theories exist. Maurice Raynaud thought that the abnormality was central or, in his own words, due to 'increased irritability of the central parts of the cord presiding over vascular innervation'.¹⁰⁷ However, direct microneurographic recordings of median nerve sympathetic activity in normals and patients with Raynaud's phenomenon before and after a cold challenge showed no increased sympathetic outflow to the hand nor more profound or more prolonged vasoconstriction elicited by single, strong sympathetic bursts.¹⁰⁸ Further evidence that increased sympathetic tone does not entirely provide the basis of the attacks of Raynaud's phenomenon comes from the disappointing results of sympathetic denervation.¹⁰⁹

Angiographic studies have shown that the digital arteries are the major vessels affected in Raynaud's phenomenon with severe narrowing and eventual absence of filling.¹¹⁰ In contrast there is only attenuation of the palmar arches and occasional spasm of the forearm arteries. Lewis believed that there was a local fault of the vessels rather than inappropriate vasomotor impulses causing spasm of the digital arteries. This was based upon studies in which the sympathetic nerve supply to the digits was interrupted by injection of local anaesthetic around the ulnar nerve at the elbow. This invariably caused an initial rise in digital temperature but did not prevent local cold-induced vasospasm in the anaesthetized ulnar innervated area of the hand.¹¹¹ Recent advances in knowledge about the role of the endothelium in modulating vascular smooth muscle tone may define the abnormalities that may be the cause of Lewis's local fault.¹¹² There may be defective release of endothelial vasodilator mediators such as prostaglandin I₂ (PGI₂), E₂ or endothelium-derived relaxing fac-

tors (EDRF). Alternatively there may be increased release of vasoconstrictor mediators such as endothelin or altered neurovascular control mediated by the serotonergic, cholinergic, peptidergic or adenosinergic nerves.

There is evidence to suggest that altered prostaglandin release occurs in patients with Raynaud's phenomenon and there might be an imbalance between the release of the vasoconstrictor thromboxane A₂ and the vasodilator PGI₂.^{113,114} Indeed a factor, present in the serum of patients with primary and secondary Raynaud's phenomenon, has been found which inhibits the release of PGI₂ from cultured human endothelial cells.¹¹⁵ It is not known whether there is a similar mechanism affecting the release of EDRF which is also an inhibitor of platelet aggregation.

Endothelin is a 21 amino acid peptide (mol.wt. 2,492) that has recently been isolated and sequenced.¹¹⁶ It is synthesized and released by endothelial cells and has been shown to have potent vasoconstricting properties.¹¹⁷ Moreover, intravenous administration of endothelin causes a long lasting pressor response in rats and such a response may account for the long lasting vasospasm observed during an attack of Raynaud's phenomenon.

Cutaneous arterioles and arterio-venous anastomoses are supplied by adrenergic vasoconstrictor neurones and there may be increased sensitivity or density of the peripheral alpha-adrenoceptors. There is already evidence to suggest alpha-adrenergic hyper-responsiveness in primary Raynaud's phenomenon¹¹⁸ and other investigators have shown increased platelet alpha₂-adrenergic receptors in patients with primary and secondary Raynaud's phenomenon.¹¹⁹ There also may be an abnormality of neurally mediated vasodilatation in Raynaud's phenomenon, a nociceptive reflex induced by contact with cold and carried proximally by thin (A δ) afferent fibres and centrifugally in contralateral (?afferent) non-myelinated fibres.¹²⁰ In addition, in normal people there is evidence of a local vasodilatation induced by an axon reflex on stimulation of cutaneous polymodal nociceptor fibres.^{121,122} It is thought that the

Table I Causes of secondary Raynaud's phenomenon

<i>Connective tissue diseases</i>	<i>Drugs</i>	<i>Others</i>
Systemic sclerosis	β -blockers	Thoracic outlet syndrome
Systemic lupus erythematosus	Ergotamine	Vibration
Dermatomyositis	Bleomycin	Atherosclerosis
Rheumatoid arthritis	Cisplatin	Thromboangiitis obliterans
Mixed connective tissue disease	Nicotine	Direct arterial trauma
Sjögren's syndrome	Bromocriptine	Cold agglutinins
		Cryoglobulinaemia

dilatation is due to antidromic impulses releasing histamine, substance P or calcitonin gene-related peptide (CGRP). Recently one group of investigators has showed a suprasensitivity to intravenous CGRP with a greater increase in blood flow in the hands of patients with Raynaud's phenomenon than normal controls.¹²³ This suggested a deficiency of endogenous CGRP release in the patients. However, another group of investigators has shown no difference in the response to intradermal injections of histamine and CGRP in patients with Raynaud's phenomenon compared to the controls at room temperature¹²⁴ and a somewhat attenuated response to CGRP in the patients at 5°C.¹²⁵

In addition to the above proposed pathogenetic mechanisms for Raynaud's phenomenon there are also a number of other well documented abnormalities which may account for the reduced digital blood flow,^{126,127} and reactive hyperaemia¹²⁸ in such patients but probably are not so important in the dynamic sequence of events that lead to an attack of Raynaud's phenomenon. Viscosity of blood from patients with primary Raynaud's phenomenon is normal at 37°C but at 27°C it is increased compared to normal controls.¹²⁹ In most patients with secondary Raynaud's phenomenon, especially those with an underlying connective tissue disease, blood viscosity is increased probably as a result of increased levels of fibrinogen and gammaglobulins.^{130,131} However, since blood viscosity represents a sum of many interacting factors the measurement of red blood cell deformability has been performed. This was found to be normal in patients with primary Raynaud's phenomenon but reduced in patients with Raynaud's phenomenon associated with systemic sclerosis.¹³² Moreover, these investigators showed that red blood cells from the latter patients had a reduced negative surface charge which, through increased adhesiveness to the blood vessel wall, might be a further factor in reducing digital blood flow.

The earlier suggestion that endothelial cell dysfunction may be one of the fundamental abnormalities in Raynaud's phenomenon is supported by measurement of von Willebrand Factor (vWF) antigen levels. The circulating protein Factor VIII is a complex of two factors, Factor VIIIc which is linked by non-covalent bonds to a high molecular weight polymeric glycoprotein vWF which is mainly synthesized by endothelial cells and to a lesser extent by platelets and megakaryocytes. It is known that disturbances of endothelial cell integrity *in vitro* can stimulate the release of vWFAg and it has been on the basis of this fact that measurement of circulating vWFAg has been measured in several diseases in which microvascular injury occurs. Raised levels have been found in patients with primary Raynaud's phenomenon¹³³ and in

patients with Raynaud's phenomenon associated with systemic sclerosis.¹³⁴ Furthermore, a cold challenge increased these levels still further. It would have been interesting to compare this data with an histological assessment of the digital arteries in primary Raynaud's phenomenon but unfortunately the only ultrastructural study that has been performed on such patients examined salivary gland blood vessels and these were normal.¹³⁵ Although much has been learnt about the pathogenesis of Raynaud's phenomenon it is still not known why the attacks of digital ischaemia are more common in women and even less is known about the role of environmental temperature versus the rate of heat loss from the skin in triggering attacks.

Essential fatty acids and dermatology

There is increasing awareness that there may be a link between the diet and skin disease,¹³⁶ and now several studies have shown that increasing the oral intake of essential fatty acids has a beneficial effect on a variety of dermatoses.¹³⁷ In order to understand the rationale for using these agents, it is first necessary to outline the biochemistry of essential fatty acids.¹³⁸

There are two types of essential fatty acids known as the $\omega 6$ and $\omega 3$ series and this nomenclature is based upon the position of the first double bond relative to the methyl end of the molecule; thus the $\omega 6$ series have their first double bond at 6 carbon atoms along the carbon chain. Mammals are incapable of introducing double bonds at these positions and rely upon marine sources (α -linolenic acid) for the $\omega 3$ series of fatty acids and plant sources for the $\omega 6$ fatty acids (linoleic acid). Both types of fatty acids appear to be metabolized by the same or a closely related enzyme sequence and an outline of the products is shown in Figure 1.

The metabolism of essential fatty acids in the skin is different from that in most other tissues since the epidermis lacks both the $\delta 5$ - and $\delta 6$ -desaturase enzymes.^{139,140} Thus linoleic acid cannot be converted to γ -linolenic acid nor dihomo- γ -linolenic acid to arachidonic acid and because the epidermis turns over rapidly it is likely that storage of these metabolites is minimal. Therefore the epidermis is dependent upon the continual formation of these metabolites in other organs, principally the liver,¹⁴¹ and on their transport to the skin by the blood.

The effects of essential fatty acid deficiency on the skin have mostly been studied in animals since such a pure deficiency in the absence of vitamin and other deficiencies is rare in humans. In the animals the skin becomes erythematous and scaly, the hair becomes thin and lost, transepidermal water loss is greatly increased and normal healing of wounds

Figure 1 Outline of metabolism of ω 3 and ω 6 essential fatty acids.

fails to occur, possibly as a result of defective collagen formation.^{142,143} On histology the epidermis becomes thickened and the thickened stratum corneum instead of being made up of the normal closely-packed layers consists of loosely packed layers of keratin. Furthermore, the hair follicles are frequently plugged with keratin, the sebaceous glands hypertrophy and there are increased numbers of phospholipid granules throughout the stratum corneum. Similar cutaneous changes have been observed in humans deficient of essential fatty acids secondary to intestinal resection, chylous ascites and prolonged parenteral feeding.¹⁴⁴⁻¹⁴⁶ The diagnosis can be established by the very low concentrations of arachidonic and linoleic acids in the dermis in the presence of appreciable amounts of eicosatrienoic acid.^{147,148}

The clinical similarity between the skin changes of essential fatty acid deficiency and atopic dermatitis led to the measurement of unsaturated fats in the blood of children suffering from this dermatosis. It was found that there was a deficiency of unsaturated fats and subsequent feeding with fat supplements produced clinical improvement.^{149,150} However subsequent studies produced inconsistent results and it was not until 1981 when administration of evening primrose oil (rich in linoleic and gamma-linolenic acid) in a controlled study produced a modest but significant improvement in atopic dermatitis that further interest in essential fatty acids was rekindled.¹⁵¹

Measurement of plasma phospholipids in patients with atopic dermatitis has shown normal levels of linoleic and linolenic acid but levels of the metabolites of the ω 3 and ω 6 essential fatty acids were low, suggesting a possible block at the level of the δ 6-desaturase enzyme.^{152,153} Other workers have shown plasma dihomogamma-linolenic acid and arachidonic acid levels are lower than normal in these patients.¹⁵⁴ If impaired δ 6-desaturation is important in atopic dermatitis, then administration

of gamma-linolenic acid should produce clinical benefit by bypassing the block.

Gamma-linolenic acid is present in human milk and in variable quantities in the seed oil of the evening primrose *Oenothera biennis*.¹⁵⁵ Epogam capsules containing 500 mg of evening primrose oil (40 mg of gamma-linolenic acid) have produced clinical improvement in atopic dermatitis and a meta-analysis of nine multi-centre trials showed a substantial and significant reduction in itch and a non-significant clinical improvement in the cross-over trials.¹⁵⁶ There also was a positive correlation between the improvement of the atopic dermatitis and changes in dihomogamma-linolenic acid and arachidonic acid levels in plasma phospholipids. Other workers do not believe that the efficacy of this preparation has been proved¹⁵⁷ but nevertheless Epogam is now licensed for the treatment of atopic dermatitis in the UK at the dose of 4-6 capsules twice daily in adults and 2-4 capsules twice daily for children.

The mechanism by which evening primrose oil produces improvement in atopic dermatitis is not known but it is possible that the elongation product of gamma-linolenic acid serves as a precursor for prostaglandin E₁ (PGE₁) synthesis and it has been reported that plasma PGE₁ levels increase twofold during administration of evening primrose oil.^{152,158} PGE₁ seems to be a crucial mediator for lymphocyte, mast cell and basophil function, the regulation of arachidonic acid metabolism and suppression of diverse effector systems of inflammation.¹⁵⁹ This prostaglandin activates adenylate cyclase, thereby increasing cAMP levels and causes a dose-dependent inhibition of histamine release from basophils and mast cells.^{160,161}

There has been considerable interest in the role of 5- and 12-lipoxygenase products in the pathogenesis of the inflammatory process in psoriasis.¹⁶² Eskimos appear to be completely clear of psoriasis¹⁶² and because their diet is high in

eicosapentaenoic acid which competes with arachidonic acid and reduces its conversion to potentially inflammatory metabolites, attempts have been made to treat psoriasis with concentrated fish oil. Several open studies showed that fish oil supplements produced some improvement in plaque psoriasis and these results were confirmed in a double blind trial.¹⁶⁴ Furthermore this treatment resulted in a substantial inhibition of leukotriene B₄ production by the peripheral blood polymorphonuclear leucocytes *in vitro*.¹⁶⁵

There has also been speculation that essential fatty acid deficiency may be involved in the pathogenesis of acne. Levels of linoleic acid in sebum decrease progressively as the severity of acne

increases¹⁶⁶ and such a deficiency in the pilosebaceous epithelium might account for the characteristic follicular hyperkeratosis of acne.¹⁶⁷ However, administration of evening primrose oil in one study did not produce clinical benefit¹⁶⁸ although in another study essential fatty acid supplements needed to be continued for 6 months before an improvement was observed.¹⁶⁹

Clearly, the role of essential fatty acids in the skin is only slowly being understood and the opportunity to modulate inflammatory eicosanoid production and the second messenger cell signalling system is an exciting challenge in the treatment of several common skin disorders.

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