COMMON PROBLEMS IN DERMATOLOGY
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THE 47TH ANNUAL MCGUIRE LECTURE SERIES

Common Problems in Dermatology

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INTRODUCTION

The skin is a rather large organ comprising 16% of body weight. It contains several cell types and cell products. Three separate compartments are present and a disease may involve one or all. The topmost layer, the epidermis, is a very active metabolic area and disease involving this area is generally acute with oozing, weeping, and scaling. The dermis, which is quite large, gives support to the entire skin and body. Dermal diseases produce swelling, enlargement, and rigidity in the skin. A disease in the subcutaneous section of the skin, the third major portion, is usually nodular and edematous.

The 47th Annual McGuire Lecture Series entitled, Common Problems in Dermatology, presented for the first time lectures in the morning with case presentations in the afternoon to illustrate the problems discussed.

There is great emphasis today on the management of common dermatosis by the primary care physician. This is really not new since Osler himself described many skin clues to systemic diseases. The problems presented in this lecture series were those which usually are diagnosed and frequently treated by the first physician who sees the patient. We hope you enjoy this series of papers as much as we enjoyed the presentations.

W. KENNETH BLAYLOCK, M.D.
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The term atopic, which means "strange disease," was first used in 1925 to describe a group of diseases which include allergic rhinitis, bronchial asthma, urticarial reactions to drugs as well as food allergies or idiosyncrasies. These conditions have in common the presence of skin sensitizing homocytotropic antibodies (IgE) in the serum of the person at some point in the natural history of the disease. There is little evidence that the dermatitis found in the atopic individual is produced by IgE which is present in the serum and skin of the person with atopic dermatitis.

Atopic dermatitis is by definition, then, an inflammatory flexural dermatosis of the skin found in the patient who has other manifestations of atopy or a family history of these disorders. It is probably the number one cause of hand eczema in adults. This particular disorder causes many persons to be rejected for military service, and the man hours lost in daily work due to this disorder are significant.

Etiology. The specific etiology of this particular type of eczema is unknown. It is multifactoral dermatosis. These factors include:

1. A genetic susceptibility.
2. A defective barrier layer in the normal skin which is accompanied by increased transepidermal water loss from the epidermis with an associated increase in absorption of antigens into the skin. The normal skin of the atopic person may be more easily damaged by irritants which include soaps and detergents, wool, and other factors.
3. Sudden temperature changes and sweat retention.
4. Topical allergens such as nickel and neomycin may induce sensitization contact dermatitis in these patients.
5. Inhaled allergens probably play little role in producing the dermatitis in adults.
6. Emotional feelings may lead to scratching and this trauma may induce the dermatitis. Frustration and anger seem to enhance itching.
7. A factor that has not been given proper attention in the past is bacterial infection and bacterial colonization in the skin.

Immunology. A specific immunologic defect has not been proven to exist in patients with dermatitis. In general, patients with localized atopic dermatitis confined to the hands and feet have a normal serum IgE level. Patients with generalized atopic dermatitis have elevated serum IgE levels, particularly when there is exudation and infection in the skin.

Patients with an elevated serum IgE level do not have serum fluctuations with the activity of the disease whether the disease is minimal or severe. The reason for this serum elevation in generalized atopic dermatitis is not clear. One possibility is bacterial infection while another is autoimmunity to an antigen such as human dander.

Clinical Manifestations. The clinical manifestations of patients having atopic dermatitis are many. The most common are listed below:

1. The infant usually presents with a dermatitis on the face, and the extensor surfaces of arms, legs, and hips are involved.
2. The child who has atopic dermatitis may manifest the eruption first on the dorsal surface of the hands and feet.
3. The medial surface of the middle finger as well as the small finger of the hand is a fre-
quent site. Accumulation of material around rings and other jewelry may be the initiating factor in producing this form of the disease.

4. The presence of chronic lichenified dermatitis on the flexural aspects of the arms, legs, and trunk as well as the hands and feet which may lead to exfoliation of the skin.

**Diagnosis.** An important clue in making the diagnosis of atopic dermatitis is a family history of asthma, hay fever, urticaria, or atopic dermatitis. The morphology and distribution of the lesions in flexural folds is helpful as well as the serum IgE level. A history of foot dermatitis as a child, particularly on dorsal surface, is helpful in establishing the atopic pattern in a patient suspected of having this troublesome dermatosis. This dermatitis on the dorsal surface of the foot in a child is usually atopic dermatitis, not contact dermatitis or dermatophytosis.

A careful physical examination of the skin to reveal other components of the atopic skin syndrome will aid in making the diagnosis. These include:

1. The history and physical evidence for recurrent allergic rhinitis with or without associated mucosal swelling of the sinuses.
2. Double lines on the face beneath the eyes may be present.
3. Allergic persons with atopic histories frequently have a light blue appearance to the mucous membranes of the nose with an associated high, arched palate.
4. Cutaneous papules on a dry skin are more common in the atopic patient.

**Confirmatory Tests.** Once a differential diagnosis has been outlined, diagnostic confirmatory tests are in order. In the patient with a chronic pustular dermatitis of the hands or a generalized dermatitis, the serum IgE level may be helpful in separating this disorder from other eczematous states. Elevated serum IgE levels alone, however, are not diagnostic.

**Patch Testing.** Appropriate patch tests should be performed in order to establish the presence or absence of sensitization contact dermatitis. All patients with generalized eczematous dermatitis should have patch tests performed to rule out specific cell mediated immunity to a variety of environmental antigens.

**Management.** Important modalities in the management of atopic dermatitis include:

1. The avoidance of a constant exposure to irritants as well as excessive water. Generalized bathing should be limited to twice weekly with intermittent sponge bathing.
2. The judicious use of systemic antibiotics for bacterial infections is most important.
3. Topical corticosteroid therapy combined with partial occlusion especially for hands and feet is the hallmark of anti-inflammatory therapy for atopic dermatitis. Complete occlusion of the dermatitis with a material such as polyethylene is to be avoided.
4. Bath oils and emollients are helpful.

Careful consideration must be given to the emotional aspects of this illness. Family members must receive proper instructions in handling children with this disorder, and the adolescent and adult patient will need counseling by the physician.
Oral Manifestations of Cutaneous Disease

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The list of diseases which manifest both oral and cutaneous pathology is extensive and consideration of them all is beyond the scope of a single brief report. Nevertheless, it may be useful to summarize the findings of those diseases in which both oral and cutaneous lesions are, or can be, significant. Recognition of the one can be a clue to the identity of the other, and evaluation of both skin and mucosa may often provide the first evidence of systemic disease.

The discussion will be divided into two parts: 1) primarily dermatologic diseases with oral manifestations; and 2) other diseases in which oral and cutaneous lesions are prominent features. It will be limited to a consideration of noninfectious disease processes.

1. Primarily Dermatologic Diseases with Oral Manifestations.

Erythema multiforme is an acute inflammatory disease of the skin of obscure etiology, although infectious and/or allergic mechanisms are suspect. A wide variety of predisposing factors has been implicated, the most prominent of which are infections (herpes simplex, primary atypical pneumonia) and drugs (sulfonamides, phenylbutazone). X-ray and carcinoma have also been associated with the disease. As the name implies, the lesions are multiform and may consist of papules, bullae, and the characteristic target lesions. Oral manifestations are seen in the so-called “major” type of erythema multiforme and consist of vesicles on the lips, tongue, buccal and gingival mucosa which rupture to produce painful erosions (Fig 1). The disease tends to be self-limited, although the major form is occasionally fatal and may warrant the institution of corticosteroids as well as supportive local care.

Lichen planus. This chronic papulosquamous disease is of unknown etiology, although viral and neurologic etiologies have been proposed, and psychic factors have frequently been found to be associated with the disorder. The eruption of flat-topped, angulated, violaceous papules beginning on the extremities and favoring flexor surfaces is quite characteristic, though a similar eruption termed lichenoid drug eruption occurs with a variety of drugs (antimalarials, alpha-methyldopa, gold, para-aminosalicylic acid (PAS), thiazides, tetracycline, and others). Mucous membrane lesions occur in 50% of cases; they may occur in the absence of skin lesions, and they have been observed in drug-induced lichen planus due to quinacrine, PAS, gold, sodium thiosulfate and phenothiazines. Lacy hyperkeratotic striae on the buccal mucosa and tongue are characteristic, though hyperkeratotic papules and ulcerated lesions may also be seen (Fig 2). The differential diagnosis of oral lesions includes leukoplakia, candidiasis, lupus erythematosus, and secondary syphilis, though the presence of the typical Wickham’s striae and of cutaneous lesions help in confirming the diagnosis. Corticosteroids in Orabase® and topical anesthetics are useful in the management of this condition.

Bullous diseases. Certain bullous diseases are characterized by mucous membrane lesions. Pemphigus vulgaris and its variant, pemphigus vegetans, are notorious for producing oral lesions. They are present, in fact, in almost every case, and in pemphigus vulgaris, over 50% of patients develop their first lesions in the oral mucosa. Large, flaccid bullae which rupture to leave denuded areas are found on the lips, buccal mucosa, floor of the mouth, and
PATTERSON: ORAL MANIFESTATIONS OF CUTANEOUS DISEASE

I. BLISTERS AND EROSIONS OF THE LIPS, CONJUNCTIVA, MUCOSA, AND SYSTEMIC TOXICITY IN THE MAJOR FORM OF ERYTHEMA MULTIFORME.

Fig 1—Blistering and erosions of lips, conjunctival involvement, and systemic toxicity in the major form of erythema multiforme.

undersurface of the tongue. On the skin, recurrent crops of flaccid bullae showing Nikolsky's sign are found in pemphigus vulgaris. Biopsy is useful in making the diagnosis, and direct and indirect immunofluorescence are characteristic, showing intercellular binding of IgG and complement in stratified epithelium. Corticosteroids and cytotoxic agents are used in treating this disease. Oral lesions are also seen in bullous pemphigoid and a similar disorder, cicatricial pemphigoid, but they are not seen in another blistering eruption, dermatitis herpetiformis.

Psoriasis. Mucous membrane lesions in psoriasis are rarities, but a small number of cases have been reported. Rather rigid criteria must be met in order for a lesion to qualify as oral psoriasis. Lesions must be clearly located on mucosa and not contiguous with skin lesions; they should be found coincidentally with cutaneous lesions and their course should parallel that of skin lesions. Histologic features are suggestive, but only suggestive, of the disease.

II. DISEASES IN WHICH ORAL-CUTANEOUS LESIONS ARE A PROMINENT FEATURE.

CONNECTIVE TISSUE DISEASES.

Behçet's syndrome is an uncommon condition of unknown etiology characterized by recurrent ulcerations of the oral cavity and genitalia and by iritis. Thrombophlebitis, arthralgia, neurologic lesions, and erythema nodosum may also occur. It is seen most often in males in the third decade and presents as discreet, punched-out ulcers with erythematous borders and gray-yellow bases in the oral mucosa. A helpful diagnostic test is the occurrence of a pustule with surrounding erythema at the site of needle prick injury. This occurs 24 hours after injury and is most prominent at the height of an attack. It may be difficult to distinguish oral lesions from those of aphthous stomatitis, pemphigus or pemphigoid, and erythema multiforme. Treatments have included antibiotics, gamma globulin, and corticosteroids with or without azathioprine, all with varying results. The course is usually long and benign, although recurrent uveitis can result in severe eye damage, and neurologic involvement is indicative of a poor prognosis.

Fig 2—White hyperkeratotic lesion of the tongue in lichen planus. Dark spot above gauze is biopsy site.
Reiter's syndrome is the familiar triad of urethritis, arthritis, and conjunctivitis. Perhaps it should be considered a tetrad, since mucocutaneous lesions occur in 80% of patients. Skin findings include hyperkeratotic lesions of the palms and soles (keratoderma blenorrhagicum) and psoriasiform plaques on the skin and scalp. Oral involvement is seen in up to 40% of cases and presents as painless superficial erosions of the palate, buccal mucosa, tongue, or gingiva. Treatments have included anti-inflammatory agents, methotrexate, antimalarials, and indomethacin. The disease may abate after two to six months or persist as recurrent attacks at varying intervals.

Scleroderma also features oral pathology. Fibrosis and atrophy of circumoral skin and widening of the periodontal space are relatively well-known findings. Less often appreciated are deformation of gingival papillae with the formation of granulation tissue in gingival pockets, atrophy of the mucosa with prominent venous pattern, and papillary atrophy of the tongue, producing the so-called “chicken tongue” appearance.

Occasionally (in 10% to 20% of cases) systemic lupus erythematosus is accompanied by oral lesions, and it should be noted that mucosal ulcers are one of the fourteen diagnostic criteria established by the American Rheumatism Association (ARA). Lesions may appear as pinpoint atrophic areas with keratotic margins and surrounding hyperemia. Petechiae on the palate, buccal mucosa, gingiva, or tongue develop into shallow, painful ulcers with gray, necrotic bases.

DRUGS.

A number of drugs may be responsible for oral as well as cutaneous lesions. Antibiotics may induce toxic responses in the mouth as a result of disturbance of the ecologic balance of microflora. Black hairy tongue is an example, in which elongated, stained filiform papillae are noted. Frequent use of oxidizing agents or excessive smoking have also been associated with this condition.

Gingival hyperplasia develops in 10% to 35% of patients treated with sodium diphenylhydantoin. This reaction occurs independently of dose or duration of drug, and results from fibrosis beginning in the interdental papillae. Diphenylhydantoin has also been associated with a number of cutaneous eruptions, including an acneiform variety, bullae, and exfoliative dermatitis. Hypertrichosis is also observed.

Gold toxicity can produce hemorrhagic, ulcerative, and exfoliative stomatitis. Skin manifestations include exfoliative dermatitis and lichenoid eruptions.

Methotrexate is a chemotherapeutic agent used in the treatment of lymphomas, leukemias, and (of importance to dermatologists) severe, recalcitrant psoriasis. Toxicity may develop as shallow whitish patches on the oral mucosa, surrounded by erythematous borders. Large areas of epithelium may then necrose and slough. Many chemotherapeutic protocols include the use of folinic acid (citrovorum factor) to counteract methotrexate toxicity.

GENETIC DISORDERS.

Of the many genetic disorders with oral-cutaneous manifestations, two have been selected. Peutz-Jeghers syndrome consists of mucocutaneous pigmentation and gastrointestinal polyposis. It is inherited as an autosomal dominant trait. Flat brown, black, or blue pigmented spots are seen on the vermilion borders of the lips, oral mucosa, perioral, nasal, and orbital skin, dorsa of fingers and toes (especially over joints), palms, and soles. Though skin pigmentation tends to fade after puberty, oral pigmentation remains for life. Melena and intussusception are the chief complications. It is important to note that, although malignant change of small bowel polyps is rare, there is an increase in incidence of cancer above the ligament of Treitz and in the colon.

Neurofibromatosis is also inherited as an autosomal dominant trait. The occurrence of multiple cafe au lait spots in neurofibromatosis is well known. Four to 7% of cases have oral involvement with single or multiple tumors, usually on the tongue. Malignant degeneration of neurofibromas is uncommon but does occur in 2% of patients and presents as a variant of fibrosarcoma.

METABOLIC DISORDERS.

Cutaneous pathology in Addison's disease consists of diffuse pigmentation accentuated on exposed surfaces, sites of friction, palmar creases, and scars which have developed during adrenal insufficiency. The oral pigmentation is spotty in appearance and may occur in advance of other characteristics of the disease (Fig 3). The pigmentation results from increased output of beta-MSH from the pituitary, unchecked by the normal adrenal-pituitary feedback.
Addisonian buccal pigmentation may be difficult to distinguish from that of normal dark-skinned individuals and from Peutz-Jeghers syndrome, but other clinical features should aid in making this diagnosis.

NUTRITIONAL DISORDERS.

A discussion of oral-cutaneous disease would not be complete without a consideration of nutritional deficiency diseases.

Ariboflavinosis manifests as glossitis and cheilosis. Glossitis results from atrophy of the papillae of the tongue, along with dilatation and proliferation of the capillaries and concomitantly slowed circulation. The latter accounts for the tongue's characteristic magenta color. Cheilosis describes the denuded, reddened appearance of the lips at the line of closure and maceration at the angles of the mouth. Seborrheic accumulations around the nose are also seen.

The cutaneous features of pellagra are familiar, consisting of photosensitivity manifested by erythema of exposed areas. This burning, itching eruption desquamates to leave deep pigmentation and eventual atrophy. A necklace of dermatitis (Casal's necklace) and seborrhea-like dermatitis of the nose (dysebacea) are other characteristic findings. Oral disease includes an intense stomatitis, involving the tongue, gingiva, and palate, and reddening and ulceration of the lips. Pellagra today is often seen as part of a multiple nutritional deficiency state in alcoholics and chronically ill individuals.

In conclusion, this brief discussion includes only a few of many disorders in which oral and cutaneous manifestations play a prominent role. It emphasizes the importance of a thorough oral-mucosal examination in the evaluation of any perplexing cutaneous disease.

REFERENCES


Pyodermas: Diagnosis and Treatment

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The diagnosis and treatment of cutaneous infections appear to be rather straightforward at first glance. Major texts of pediatrics and dermatology indicate that the vast majority of pyodermas are due to either *Staphylococcus aureus* (*S. aureus*) or *Streptococcus pyogenes* and that antibiotics are curative. On closer scrutiny, however, one quickly becomes aware that there is a great deal of nomenclatural confusion with a corresponding lack of clarity regarding therapy—particularly on the point of whether or not topical antibiotics have any place in therapy.

Pyodermas can be divided into two main classes: primary and secondary. In a primary pyoderma, the skin is normal or at most has suffered a minor cut, abrasion, or insect bite. In such a situation, the invading organism is entirely responsible for the clinical picture. The situation is entirely different in a secondary infection. Here the underlying process is a chronic inflammatory process. for example, atopic dermatitis which first becomes colonized, usually by *S. aureus*, and secondary infection is present only when *S. aureus* has proliferated to rather high levels (see below).

**Primary Cutaneous Infections.**

Two distinct forms of primary pyodermas have been described: 1) Bullous impetigo caused by Group II *S. aureus* usually phage type 71, and 2) Streptococcal pyoderma or ecthyma due to Group A beta hemolytic streptococci. Both have distinctive clinical characteristics which can allow confident diagnosis.

Bullous impetigo presents as multiple, often coalescing superficial bullae which rupture easily and leave behind a thin varnish-like crust. This eruption is usually seen in children, most commonly on the face, although any part of the body may be involved. Fever and other systemic signs are infrequent. Therapy consists of oral antibiotics, either penicillin G 400,000 units q.i.d. for ten days or oxacillin 500 mg q.i.d. if a penicillinase producing organism is involved. Local care of compresses and topical antibiotic or steroid-antibiotic creams are useful. This form of pyoderma is rather contagious, but does not carry with it the potential for post-infection glomerulonephritis.

A severe and fortunately rare form of *S. aureus* infection is the toxic epidermal necrolysis syndrome. A toxin mediated by phage type 71 *S. aureus* causes widespread necrosis of the epidermis and results in a sloughing off skin, producing the so-called "scaled skin syndrome." The infecting organism is usually in the nasopharynx, ear, or conjunctiva and not in the skin. Treatment consists of intravenous penicillin (Nafcillin 50 mg/kg) until the lesion ceases to appear and then oral Nafcillin for seven to ten more days.

Streptococcal pyoderma begins as superficial vesicles, but quickly erodes and develops a central ulceration with a thick crust and an areola of erythema surrounding the ulceration. These lesions occur primarily on the lower extremities of children during the hot, humid summer months and are frequently associated with lymphadenopathy and fever. Streptococcal skin infections do not result from the strains responsible for throat infections and anti-streptolysin-0 (ASO) titers are feeble, although antibody response to other streptococcal antigens (DAN-use B and hyaluronidase) can be vigorous. Cultures reveal Group A streptococci under the crust and under the edges of the advancing ulceration while...
the crust itself may reveal only *S. aureus*. Treatment studies in both humans and in hamsters support the view that streptococci are the important agents since the presence of penicillin-resistant staphylococci in mixed lesions does not interfere with effective treatment with penicillin G.\(^3\)\(^4\) It is this streptococcal variety of pyoderma which carries the risk of post-infection glomerulonephritis. There are no studies demonstrating the prevention of glomerulonephritis by penicillin treatment and in fact there is considerable clinical evidence to suggest that renal complications may occur despite penicillin treatment.\(^5\)

Treatment consists of benzathine penicillin 2.4 million units intramuscularly for extensive deep-seated lesions.\(^6\) The role of topical antibiotics is unsettled. Several studies comparing topical to systemic therapy concluded that systemic therapy was superior. However, no attempt was made to separate deep, extensive lesions from the early more superficial variety. Our own view is that in early lesions, compresses and topical antibiotics are quite effective.\(^7\)

**Secondary Infections: Impetiginization.**

Inflamed skin provides fertile soil for bacterial overgrowth, and it is not surprising that dermatic skin can become colonized and then infected with various pathogens. In most cases, the organism involved is a *S. aureus*. A variety of phage types are found, but rarely are the highly virulent strains such as type 71 isolated. Beta hemolytic streptococci are rarely recovered from dermatoes; in several hundred studied cases we have found five examples of Group A beta hemolytic streptococci complicating an underlying disorder—two were in epidermolitic hyperkeratosis and the other three occurred as severe "athlete's foot" infections.\(^8\) Candida albicans and gram-negatives are found in two situations, namely in dermatoes occurring in wet body regions and in patients on long-term antibiotic therapy.

The question arises of when does the recovery of an organism from a dermatosis indicate infection is present and that antibiotic therapy is indicated. Through our quantitative studies we have to date evolved to an understanding of the following guidelines for interpretation of routine non-quantitative culture reports.

   *Staphylococcus epidermidis (S. epidermidis)*, lipophilic diptheroids.
2. Gram-negatives.
   The relative virulence of these organisms has not been fully established as yet. *Pseudomonas* certainly appears to be relatively virulent, but the density required to aggregate an underlying dermatosis and the density of *Escherichia coli* (*E. coli*), *Proteus*, and others have not been elucidated. These organisms can be found in low numbers in wet body areas such as the groin, axilla, and toe space, and at low numbers these organisms do not damage intact human skin. Present evidence would suggest that a useful guideline would be that if a culture reveals the predominant organism to be a gram-negative, then it most likely is contributing to the clinical picture. The choice of an antibiotic would be one that would include activity against the gram-negative isolated.
3. *Candida albicans*.

Our experience with this organism in experimental infection situations has taught us that it is extremely toxic to human skin. A far lower inoculum is needed to induce an infection than with any other organism we have studied to date. For example, as low as ten *Candida* cells will result in a severe reaction after three to four days of growth under saran wrap while thousands of cells and prior suppression of the resident flora are required for experimental *S. aureus* infections.\(^9\)\(^10\) The isolation of *C. albicans* from a dermatitis such as diaper dermatitis is therefore a very significant finding, and anti-yeast measures are indicated.

4. *Propionibacterium*.

Two main groups have been identified: *P. acnes* which is susceptible to *P. acnes* bacteriophage is more prevalent and found in greater densities in the sebaceous areas than is the phage-resistant *P. granulosum*. Recovery of this organism from a skin culture does not indicate an infection, rather it is a member of the resident flora. This organism does, however, appear to play a central role in acne vulgaris. Acne patients carry a much greater density of this organism than do aged-matched controls.\(^11\) The current hypothesis is that this organism influences the acne process by virtue of production of free fatty acids through hydrolysis of sebaceous gland triglycerides. Those antibiotics which lower *P. acnes* in vivo such as tetracycline, erythromycin, and clindamycin are also judged to be useful in the management of acne, while penicillin and sulfonamides neither lower *P. acnes* nor help in the treatment of this disorder. To date, we have not encountered *P. acnes* resistant to antibiotics, and clinical failure during antibiotic therapy does not indicate that another factor is involved, for example, hormonal disturbance, emotional dis-
tress, or other factors. To date, only systemic antibiotics have been found to lower *P. acnes* levels. Recently, however, there is some evidence suggesting that topical benzoyl peroxide may be an effective agent for suppressing *P. acnes*.

5. *S. aureus*.

*Staphylococcus aureus* is the usual organism recovered from inflamed skin. A variety of phage types are recovered; virulent strains such as type 7I are not frequent. In a series of studies, we have established that a density of one million *S. aureus* organisms per sq cm is the level at which antibiotic therapy will produce clinical improvement.12 Our definition of a *S. aureus* secondarily infected dermatosis is therefore expressed in quantitative terms. Certain eruptions far more commonly harbor levels of *S. aureus* exceeding our established quantitative criteria for presence of a secondary infection. In atopic dermatitis, as many as 45% of even the chronic lichenified variety and 100% of the acute exudative form will harbor more than a million *S. aureus* per sq cm. In such cases, even though overt clinical signs of infection are lacking, topical or systemic therapy will produce a rapid suppression of this organism in one week’s time and result in clinical improvement. Other conditions frequently harboring more than a million *S. aureus* per sq cm include numular eczema, neurodermatitis, exfoliative erythroderma, and chronic familial benign pemphigus, and again antibiotic therapy will often be useful in these conditions. In psoriasis and seborrheic dermatitis, *S. aureus* very rarely achieves a high enough density to be clinically significant, and antibiotic therapy is rarely useful except when *S. aureus* growth has been stimulated, which can happen, for example, during occlusive therapy with impermeable plastic film. An important corollary of this principle of the quantitative aspect of *S. aureus* secondary infections is the role of steroids in such conditions. One might predict that topical steroids could lead to an aggravation of a condition heavily colonized with *S. aureus*. Clinical experience does not support the theory, however. The explanations for this apparent paradox is that topical steroids are effective in suppressing the inflammation which promotes *S. aureus* colonization and proliferation. By removing the conditions favoring *S. aureus* growth, the return of the normal protective flora is promoted rather than *S. aureus* overgrowth.

Therapeutic Approaches.

In primary infections such as bullous impetigo, ecthyma, and cellulitis, systemic antibiotic therapy is curative because invading pathogenic bacteria are responsible for the entire clinical picture. Local compresses to remove crusts and topical steroids to suppress cutaneous inflammation are useful adjuncts, but the main thrust of therapy is to remove the offending pathogen.

In secondarily infected dermatoses, a variety of therapeutic approaches are available and often several modalities must be simultaneously utilized. Both topical and systemic antibiotics are effective, and choice is determined principally by the extent and severity of involvement. Steroids are indicated for suppression of the underlying inflammatory condition, which promotes a more normal skin and the return of the normal flora. The combination of steroids and antibiotics appears to offer a rational approach.

In excessively wet areas such as the axilla, groin, and toe web space, and in severely exudative lesions anywhere, therapy must also include “drying” agents. Excessive moisture promotes bacterial growth and must be controlled in order to obtain satisfactory results. The use of compresses is often indicated. Dyes such as gentian violet and Castellani’s paint which have both astringent and antimicrobial activity provide a double-pronged approach.

The object of therapy should be to restore the skin to a noninflamed status and to promote return of the normal protective resident microflora. Antibiotics are used to remove pathogens, steroids suppress inflammation, and compresses remove excessive moisture. Successful therapy involves attacking all aspects of a disorder.

REFERENCES


Acne Vulgaris

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Acne vulgaris displays all the characteristics of a polygenic disorder in that hereditary factors are apparent with strong family tendencies for the disorder while the phenotypic expression of the disease varies over a wide spectrum. All that is known for certain concerning the genetics of acne is that concordance is extremely high in identical twins. In the past decade, various investigations have resulted in much clearer concepts of pathogenesis and have brought us to the point of effective therapy for the majority of cases. In this report, I will summarize recent concepts in the pathogenesis of acne vulgaris.

I. Acne Histopathogenesis.

The histopathogenesis of acne involves two main pathways: 1) impaction and distension of sebaceous follicles by tightly packed horny cells and 2) disruption of the follicular epithelium allowing discharge of the follicular contents into the dermis which then induces an inflammatory reaction.

The clinical counterparts of this process range from the non-inflammatory comedo to inflammatory papules, pustules, and nodules.

The sine qua non of acne is the formation of comedones. Ordinarily the epithelium lining the canal of sebaceous follicles produces keratinized cells which are sloughed and carried to the surface in a stream of sebum. Comedo formation begins when follicular horny cells begin to stick together. As horny cells fail to dehisce, an expanding solid mass accumulates and dilates the follicle. Recent electron microscopic study of the dynamics of comedo formation confirmed these observations and also demonstrated a decrease in lamellar granules (membrane coating granules, Odland bodies). A decrease in membrane coating granules with comedo formation suggests that these structures may act as lysozymes and promote cell separation and not function to keep cells together as “cementsomes” as proposed by Hashimoto. Further studies on the dynamics of comedo formation and the ultrastructural changes which result in failure of separation of horny cells are needed. The developing comedo surfaces clinically first as a “whitehead” in which the surface opening is microscopic and then bulges above the skin surface as a “blackhead.” The color is due to melanin pigment produced by melanocytes which are found in the upper 20% of sebaceous follicle epithelium.

A mature comedo is thus several millimeters deep and firmly entrenched. Attempts to dislodge these lesions by vigorous, abrasive washing in humans and in experimentally induced lesions in the rabbit ear model fail dismally. The significance of this area of research to the clinician is that vigorous washing is of little use in acne therapy. Former concepts of obstruction at the follicular outlet which could be relieved by frequent washings and use of “peeling” agents were grossly incorrect. Such theories do not stand up to the overwhelming evidence that comedones represent an impaction of the follicular canal with a solid mass of horny cells. Comedones are deep structures and successful therapy can only be achieved by altering the abnormality in follicular keratinization. Retinoic acid’s mechanism of action involves its effect on keratinization. As a side effect, it can produce “peeling” and dryness, but this is unrelated to its mode of action. In the treatment of both experimentally induced comedones and naturally occurring lesions, retinoic acid induces the formation of horny cells which no longer stick together.

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the synthesis or quality of the cement substance which binds horny cells into solid impactions thus attacks the disease at the very point of origin.

Acne becomes an inflammatory process when the comedo ruptures. Disruption of the follicular wall may be partial or complete. The severity of the clinical lesion correlates directly with the extentiveness of the rupture and ranges from a segmental disorganization of follicular epithelium, resulting in a quick-healing pustule, to major breakdowns and dissolution and formation of a deep indolent nodule.

Rupture is not a consequence of simple pressure. Neutrophils first collect along the border of the follicle, usually in a circumscribed fashion, and then invade the epithelium, inducing spongiosis and cellular degeneration and finally rupture of the follicular epithelium. A dermal abscess consisting first of leukocytes and later mononuclear cells and giant cells then develops. Partial ruptures heal by resorption and the horny impacted mass remains in situ. In moderate-sized ruptures, the severed ends of epithelium send out sheets of undifferentiated cells which undermine and reincapsulate the abscess analogous to the healing processes involved in superficial wounds. A new epithelial lining is formed and redifferentiates into a keratinizing membrane and produces coherent horny cells. With repeated breaks and repair, secondary comedones develop which are recognizable clinically because they have irregular shapes and sizes and can mimic small keratinous cysts.

Massive rupture of developing comedones results in the follicular contents being literally extruded into the dermis, and a violent inflammatory reaction results which is seen clinically as a tender, erythematous papule or nodule. These lesions are deep and can persist for weeks as a foreign body granuloma replaces the initial abscess.

The significance of these insights in the pathogenesis of inflammatory lesions rests in the fact that pustules, papules, and nodules actually represent an inflammatory process and not an infectious one despite the similarity of the lesions to pustules and furuncles caused by *Staphylococcus aureus* (*S. aureus*). The fact that an acne nodule represents an inflammatory process accounts for the benefit of intralessional corticosteroid therapy. If these lesions were infections, steroid injection would surely worsen the condition. Similarly, appreciation that papules, pustules, and nodules are inflammatory reactions to extruded follicular material is important when evaluating antibiotic therapy in acne. Antibiotics do not induce pustules and papules to resolve. Rather they work in an indirect way to minimize formation of new lesions.

II. Bacteria and Acne.

It has long been recognized by clinicians that systemic antibiotics are beneficial in the therapy of inflammatory acne, but it is not until relatively recently that the role of bacteria has been studied.

Three kinds of organisms are constantly found in the sebaceous-rich areas and they constitute the normal resident microflora of all persons, regardless of the presence or absence of acne. They include: 1) the yeast Pityrosporum; 2) aerobic coagulase negative cocci; and 3) the anaerobic diphtheroid now officially classified as *Propionibacterium acnes* (*P. acnes*). The aerobic cocci and Pityrosporum are mainly located superficially near the orifices of sebaceous follicles. *Propionibacterium acnes* inhabits the depths of the follicle and there is considerable evidence implicating this organism in the pathogenesis of inflammatory acne.

1. Large numbers of *P. acnes* accumulate in follicles immediately preceding comedo formation.
2. Acne subjects have significantly greater numbers of *P. acnes* than aged-matched controls. This difference is present in those between 11 and 20 years of age, but does not exist in older individuals.
3. *P. acnes* produces substances capable of inducing comedo formation in the rabbit ear model.
4. *P. acnes* is responsible for the liberation of free fatty acids which are comedogenic and capable of inciting pronounced inflammatory reactions.
5. In the absence of *P. acnes*, inflammatory lesions are not seen. Comedones provoked in the rabbit ear never rupture because they are sterile; coal tar and chloracne are predominantly comedonal. The antimicrobial activity of those agents prevents the development of inflammatory lesions.
6. Antibiotics, such as tetracycline and erythromycin which suppress *P. acnes* are beneficial in therapy, while others such as penicillin and sulfonamides do not effect *P. acnes* population and are ineffective in acne therapy.
7. Prolonged antibiotic therapy also appears to
eventually result in a decrease in comedones.12

Studies to date thus have implied that a normal resident organism is acting somehow to promote the follicular rupture and subsequent inflammatory reaction which results in clinical papules, pustules, and nodules. The mechanisms by which P. acnes induces inflammatory lesions is still to be settled. The significance of free fatty acid production has recently been seriously challenged by the finding that a topical lipase inhibitor suppressed free fatty acid formation, yet the clinical disease was unaffected.19 However, P. acnes also possesses a variety of other enzymes including hyaluronidase which may be more significant in the disruption of the follicular epithelium that leads to an inflammatory lesion.

Further studies in our laboratory indicate that P. acnes appears incapable of developing resistance to tetracycline and erythromycin. This is of importance when evaluating a patient whose acne is not responding as favorably as expected to systemic antibiotics. Propionibacterium acnes resistance does not explain resistant cases. Some patients, however, can have significant impairment of intestinal absorption if they ingest antacids or large quantities of milk.

There are two useful techniques for documenting poor absorption of antibiotics. The easier technique involves the use of a Wood's light. Propionibacterium acnes makes a coproporphyrin which fluoresces coral red under Wood's light examination. During antibiotic therapy, the intensity of this fluorescence is markedly decreased and often completely eliminated. The nose and nasolabial folds are the areas of maximum fluorescence and easiest to examine. If these areas still fluoresce heavily after a month of systemic antibiotic therapy, then incomplete intestinal absorption of the antibiotic is likely. The second technique involves measurement of the degree of resistance of the surface aerobic flora to the antibiotic a patient is taking. Normally the surface aerobic cocci show little (less than 20%) resistance to tetracyclines, erythromycin, and clindamycin. After two to three weeks of therapy, approximately 80% of the surface aerobic flora will be resistant to a systemically administered antibiotic. By quantitatively culturing the surface aerobic flora on media with and without added antibiotics, one can rapidly estimate the degree of resistance. If the antibiotic has not been absorbed, the surface flora will not have developed a high degree of resistance. Quantitative cultures provide precise data, but even semi-quantitative analysis, easily done by any laboratory, gives sufficient data to document whether or not a particular patient has a problem in absorption of an antibiotic.

These two techniques can therefore be used to determine rationally whether a change in antibiotic therapy is indicated rather than blindly switching from one agent to another.

For twenty years, successful antibiotic therapy in acne has been limited to systemic agents. More recently, as basic information has accumulated on the factors involved in percutaneous penetration, the age of topical antibacterial therapy has arrived. Agents are now available which can penetrate sebaceous follicles sufficiently to suppress P. acne. Benzoyl peroxide is now available in several formulations and has been shown to effectively suppress P. acne and to be effective in the control of inflammatory acne.14 More recently, 2% erythromycin has been shown to exert a similar beneficial effect. Unquestionably, several other agents, formulated to penetrate skin, will be forthcoming. While the use of systemic antibiotics in acne has proved to be unusually free of serious side effects, the future on antibacterial therapy in acne lies in effective topical agents.

III. Sebum Production and Acne.

Acne and excessive production of sebum are inseparable. While there is some individual overlap, acne patients have a greater mean sebum production than age- and sex-matched controls.15 Furthermore, the severity of the disease parallels sebum production—an absolute characteristic of acne conglobata is excessive oiliness. Acne does not make its debut until pre-puberty when sebaceous glands start to enlarge under the influence of adrenal hormones. This pre-pubertal onset of acne coincides with enhanced supplies of cortisol and adrenal androgens accompanying adrenal gland maturation. Cortisol appears to act in a permissive fashion in two ways: 1) Corticosteroids are known to augment the action of testosterone on androgen-sensitive tissue.16,17 2) corticosteroids potentiate the follicles' ability to undergo retention hyperkeratosis and form comedones.18 With the onset of gonadal function and testosterone production, a further increase in sebum secretion occurs and acne severity increases. While adrenal and gonadal hormones are prerequisite to development of sebaceous gland size and function, all studies indicate that acne patients have normal circulating levels of androgenic hormones.15 No difference exists even when the most severely afflicted are compared with appropriate control subjects. Enlarged sebaceous
glands and overproduction of sebum seem therefore to indicate an end-organ sensitivity. In fact a recent study does suggest that the sebaceous glands of acne patients metabolize testosterone to the metabolically more active dihydrotestosterone at a much greater rate than those of non-acne subjects.18 Such a finding supports the hypothesis of end-organ sensitivity and explains why testosterone blood levels are not higher in acne patients. This study suffered, however, by not matching controls to sebum production, and until such studies are performed, the inviting concept of end-organ sensitivity to normal levels of testosterone is not yet proven. Future investigations of this end-organ hypersensitivity promise to reveal basic secrets of the acne process.

Currently, researches are being made for topically effective agents which act to produce a local suppression of sebum production. If an agent or agents can be found which are free of systemic effects, a major advance will have been made.

IV. Miscellaneous Factors.

Diet. No evidence exists to incriminate dietary factors. The few studies on this subject have all come to the conclusion that diet does not play a role.19,20 Dietary restrictions do not constitute rational measures in an anti-acne regimen.

Friction and Trauma. Once one understands the evolution of an inflammatory lesion, the adverse effect of friction is apparent. Repeated trauma to a follicle, distended by an impaction of horny cells, promotes rupture of the follicular epithelium and the formation of new inflammatory lesions. The common sources of friction include overzealous washing, particularly with abrasive soaps, habits of leaning on or rubbing an area of the face, pressure from helmets, tight collars, wrestling, and other contact sports. At times, local physical factors can be severe enough to the degree that usually effective therapy appears at best to be merely containing the process instead of suppressing the formation of new inflammatory lesions. Failure to perceive the role of friction often leads the therapist to switch from one antibiotic to another in a fruitless search for the “best antibiotic.”

Emotional Factors. While rigorously controlled studies with endocrinological monitoring have not been done, there is general agreement that emotional factors can play a significant role. The probable mechanism is the production of adrenal androgens which lead to increased seborrhea followed by crops of inflammatory lesions. Women appear to be more susceptible, possibly because their sebaceous glands are not as maximally stimulated as those of men and any increase in circulating androgens will have a proportionally greater effect. The ultimate expression of this factor occurs in women and is often referred to in texts as pyoderma faciale. Actually, this is an explosive form of acne almost exclusively seen in women. Classically, a severe emotional stress precedes the onset of marked seborrhea which is then rapidly followed by the onset of deep nodular and pustular lesions. This form of acne is extremely difficult to control, and in addition to the usual therapeutic maneuvers, some form of tranquilizer or sedation is necessary.

Ultraviolet Light. Most dermatologists would agree that ultraviolet light is helpful in acne therapy. Acne patients in general appear to improve in the summer. However, such improvement may more accurately reflect seasonal variation in the disorder which is unrelated to ultraviolet light. Recently, Kligman and Mills have incriminated ultraviolet light in that erythemic radiation actually enhances the comedogenic activity of materials such as coal tar and free fatty acids in both humans and in the rabbit-ear model.21 Further work is needed in this area to discern just what happens to the acne patient who spends his summer on the beach and appears to improve and require less therapy.

Cosmetics. Many cosmetics including cleansing creams and moisturizers contain chemicals which can aggravate acne.22 The mechanism appears to be that of inducing the derangement of keratinization which results in horny cells sticking together and eventual impaction of the follicle. Cosmetics do not produce a physical obstruction of the follicular orifice, rather the mechanism appears to be due to a chemical induction of comedo formation. The follicular epithelium is induced to form horny cells which stick together and eventually result in comedones.

Therapy.

With the basic concepts of pathogenesis as outlined above, our approach to acne therapy is as follows:

1. Diet. No evidence exists to substantiate the common belief that certain foods aggravate the acne process. Dietary restrictions are useless and ineffective.

2. Skin care. Acne patients are oily and want to remove the objectionable feel that excess oil produces. No “special soaps” are necessary. Patients should be instructed to wash gently two or three times daily to remove surface oil,
but under no circumstances should they scrub or abrade their skin. This leads to an intensification of the inflammatory aspects of acne. Blackheads are 4 mm deep and cannot be washed away—as most acne patients eventually discover. Local friction to the acne areas is to be avoided at all costs.

3. A primary and perhaps the central therapeutic maneuver involves the topical use of retinoic acid (Retin-A*) which reverses the abnormality in follicular keratinization. This material is applied once daily to the entire area of involvement, not just to clinical lesions. Application must be only to bone dry skin (no closer than 15 minutes to the last facial washing) to avoid unnecessary local irritation. Patients who also have atopic dermatitis may be able to apply this agent only once or twice a week. Retinoic acid unseats existing comedones in 8 to 12 weeks and prevents the formation of new lesions. As such it is the backbone of acne therapy. It is continued till the patient is free of new lesions for several months and then slowly withdrawn.

4. Antibiotics are indicated for patients who have moderate to severe inflammatory lesions. Tetracyclines and erythromycin have been time-proven safe and efficacious choices. The usual dose is 500 to 1,000 mg/day in divided doses initially and then gradual withdrawal as inflammatory lesions disappear. In combination with topical retinoic acid, most patients will not need antibiotics for more than 3 or 4 months. More recently, properly formulated topical antibiotics have been introduced. Currently, there are several formulations of benzoyl peroxide which are extremely effective. Many patients, however, cannot use both benzoyl peroxide and retinoic acid simultaneously because of excessive local irritation. More recently, 2% erythromycin free base has been shown to be effective, but it is not yet readily available.

5. If there is excessive emotional tension or pressure, then this too must be counteracted by a mild tranquilizer.

6. The excessive use of cosmetics especially moisturizers, cleansing lotions, and face creams should be discouraged.

The successful management of acne involves a careful detailing of the factors involved in pathogenesis to insure confidence and cooperation with the now quite successful therapeutic maneuvers available.

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Skin Signs of Systemic Disease

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The subject of this McGuire Lecture series, the skin, is a relatively enormous organ vulnerable to an enormous variety of external and internal insults. Its total visibility is both a blessing and a curse. Its very size and the protean nature of its disorders may paradoxically make it easy to ignore: it may so overwhelm the neophyte that he is discouraged from the proper training of his retina.

A famous and wise Chicago dermatologist, Dr. W. A. Pusey, wrote many years ago, "Skin diseases occur on the surface of the body, where everyone can see them but few recognize them." Indeed, there is often a great gulf between seeing and recognizing, seeing and comprehending. For example, I wonder how many of us have passed the site of these lectures numerous times and failed to recognize the distinctive abstract mummy design of the cast iron fence posts outside? Or how many of us have somehow missed knowing about the significance of this landmark Egyptian Building in American architectural history?

Our powers of recognition are easily overwhelmed by all of the other buildings, people, and traffic around here, just as our recognition of skin disorders and their significance may be impaired by the plethora of things that can appear upon the skin.

In this lecture, I want to point out a few important landmarks on the skin that should attract our attention no matter what else is around, lesions we should be able to select out of the morass of 600-odd skin disorders to warn us that something may also be amiss elsewhere in the body. These associations of skin pathology with pathology elsewhere: They may be grouped by pathogenetic mechanisms, by organ systems, or by various conventional categories of disease. Some of the skin findings are rather nonspecific and some may appear in a variety of associations, while others may be very specifically related to a disease state.

First, let us consider some disorders grouped by organ system, those neurocutaneous syndromes with rather specifically associated skin lesions. Neurofibromatosis is a classical example: we all can recognize from a block's distance the patient with dozens to thousands of varying sized and shaped soft tumors that tend to invaginate the skin when pressure is applied ("buttonholing"). We know that this patient may also have neuromas wherever neural tissue is found in the body, that there is a 2% to 5% incidence of malignant degeneration of those tumors, and that there may be other associated defects. We know, too, that the patient will have numerous macular areas of hyperpigmentation called café au lait spots, and that the presence of six or more spots of greater than 1.5 cm diameter and of the freckling is almost pathognomonic of Recklinghausen's disease. The presence of these lesions is almost pathognomonic of a neurocutaneous syndrome. In the patient with Recklinghausen's disease, the presence of six or more spots of greater than 1.5 cm diameter and of the freckling is almost pathognomonic of Recklinghausen's disease, and they may be found early in infancy. Informing the parents of the dominant inheritance of this disorder may properly dissuade them from further childbearing. Knowing the diagnosis may also give ready explanation for bizarre neurological findings that can appear, sometimes in the relative absence of skin tumors.
Another neurocutaneous syndrome in which early recognition is of crucial importance is tuberous sclerosis. Patients with this disorder also may have a few café au lait spots, but the significant dermatologic finding is at the other end of the pigmentary spectrum: 90% of these patients will at birth have macular hypopigmented areas of varied size and configuration, some of them with a characteristic ash leaf outline. Examination with a Wood's lamp facilitates their discovery in light-skinned individuals. Early in life these white patches (they are not true vitiligo: some melanocytes are present) may be the only cutaneous manifestations, because the lesions of adenoma sebaceum, ungual and gingival fibromas, and shagreen patches appear much later. Here again is a dominantly inherited disorder in which early recognition and proper parental counseling may prevent further tragedy. Here also is a clue to otherwise unexplained neurological phenomena: a child with these light spots and unexplained seizures very likely has tuberous sclerosis.

Considering the neural crest origin of melanocytes, it is not surprising that yet another neurocutaneous disorder, ataxia-telangiectasia (Louis-Bar syndrome) occasionally displays hyperpigmented and hypopigmented macules. Here, however, they are not the leading clues to the diagnosis. Rather, the appearance of telangiectases of the skin, particularly in sun-exposed areas, and of the cornea provides the diagnosis in the patient who has cerebellar ataxia and choreoathetosis. That patient will also have recurrent sinopulmonary infections, related to his low levels of IgA (and, in 30%, of IgG), which may eventually cause his death, if he does not die sooner of lymphoma. Genetic counseling is of lesser importance here, this disease being inherited in a recessive fashion, but earlier recognition may benefit the patient by causing heightened awareness and more effective management of the complicating illnesses.

Structures as contiguous and continuous as skin and gut could well be expected to share close disease associations. The most dramatic example is pyoderma gangrenosum in which the painful, chronic skin ulcers are counterparts of gut ulceration, most often ulcerative colitis (50%), but sometimes also regional ileitis or even gastric and duodenal ulceration. It is worth noting that the skin ulcer may precede clinical evidence of the bowel lesions. Another clear-cut association is found in Peutz-Jeghers syndrome, dominantly inherited, in which acral and periorificial freckles are so vividly described by Shelley as "... entrance signs to tell us there are polyps within!" The benign hamartomatous polyps may be anywhere in the bowel (and also in the nose, bronchi, and genitourinary tract). They get the patient into trouble because of intussusception or bleeding: recognition of the skin freckling may readily explain the trouble when one is confronted with a patient who has unexplained abdominal colicky pain or melena. Despite the benign nature of the polyps, these patients do have a greater-than-normal tendency to develop carcinoma of the colon and stomach. There is also a 10% incidence of ovarian tumors in women who have the Peutz-Jeghers syndrome.

Another useful "entrance sign" is found in the Rendu-Osler-Weber syndrome, in which superficial telangiectases of the skin signal the presence of similar lesions in bowel as well as other internal structures. Again, recognition of the skin component provides immediate explanation for internal bleeding. A further vascular association is the correlation of spider angiomas and red palms with the failing liver. A most specific correlation, this time involving unexplained occlusion of small blood vessels, is found in Degos' disease (malignant atrophic papulosis). The atrophic, porcelain-white skin papules surrounded by a telangiectatic border are matched by similar bowel (and other organ) lesions which are prone to perforate and cause death from peritonitis within a short time of onset of this rare disease.

Cutaneous signs of endocrine malfunction are unparalleled for playing the game of diagnosing-from-the-foot-of-the-bed. Few things can be as grossly visible as the striae, atrophy, acne, hypertrichosis, moon facies, and buffalo hump of Cushing's syndrome, or the cool, dry, puffy, carotenemic skin and the loss of hair (including sometimes the lateral one-third of the eyebrows) of hypothyroidism. In contrast, the hyperthyroid patient exhibits warm, moist, soft, smooth, flushed skin which is occasionally overlaid with acne papules, distal onycholysis (Plummer's nails), hyperpigmentation and even vitiligo; hair growth may also decrease. More dramatically, the hyperthyroid patient, most likely after treatment, may develop flesh-colored or erythematous or brownish nodules or plaques on the shins and elsewhere, called pretibial or localized myxedema. The same patient usually has exophthalmos.

Patients with diabetes mellitus also have a propensity to develop pretibial lesions of two types. One, necrobiosis lipoidica, is characterized by sharply de-
marcated, brownish-yellow, atrophic areas. Sixty-five percent of patients with necrobiosis lipoidica have overt diabetes. Of the remainder, three-fourths have abnormal glucose tolerance tests or a family history of diabetes. The second type of lower leg lesion is found in 46% of diabetics and is characterized by smaller, somewhat atrophic patches called "brown spots" or "diabetic dermopathy." The spots tend to look like ordinary trauma scars, but probably represent yet another manifestation of diabetic microangiopathy. There is a multitude of other visible problems associated with diabetes: lipodystrophy; excoriations because of itching; carotenemia; ulcers and gangrene; Dupuytren's contracture; bacterial, mamilial, and dermatophytic infections; acanthosis nigricans; hirsutism; vitiligo; idiopathic bullae; xanthomas; flushing and anhidrosis as complications of neuropathy. Then, there is "bronze diabetes": hemochromatosis. Therapy of diabetes introduces other problems, ranging from localized and systemic reactions to insulin preparations through photodermatoses induced by oral hypoglycemic agents.

The photodermatoses occupy a niche of particular clinical and research interest in dermatology. There is always one great clue to their diagnosis: the distribution of the dermatosis must be in sites exposed to light. Beyond that, the differential diagnosis may be tedious and taxing, because one must consider all the topical and systemic agents capable of producing a light eruption, the entities such as polymorphous photodermatitis and solar urticaria that exist unto themselves without known cause or systemic consequence, and the several diseases with internal correlates which may be triggered or worsened by light exposure. Pellagra is a classical example of the last group; we still expect to see it every spring when the poorly nourished emerge from their hibernation to enjoy the warmth of the sun, but find themselves developing acutely inflammatory skin lesions, perhaps even with bullae. Those with any variety of porphyria other than the acute intermittent form find themselves similarly afflicted.

Two of the collagen vascular diseases, lupus erythematosus and dermatomyositis, are notable for the development of characteristic lesions as a result of sun exposure and indeed for having internal manifestations worsened by that exposure. Although only 40% of lupus patients are at any one time photosensitive, one cannot readily know which patients will be so or when. Therefore, all must be carefully taught that sun is poison. The well-circumscribed inflammatory plaques with atrophic centers, the expanding red borders, and the follicular plugging of the characteristic discoid lupus erythematosus lesion can be readily recognized. It is most reassuring to be able to tell the patient he has only a 1% to 5% chance of ever developing the systemic form of the disease, but discoid and systemic lupus truly form a continuous spectrum and the possibility of development must always be remembered. The availability of the LE cell test and antinuclear antibody determinations have greatly aided in the differentiation. At some point in their disease history, as many as 83% of patients with systemic LE will have skin lesions. Fifteen percent will have what appear to be typical discoid lesions, only one-third will ever have the "butterfly rash" (most patients we see with something in the butterfly distribution have only seborrheic dermatitis or rosacea), and some will have only what may be passed off as sunburn or urticaria. The skin lesions of dermatomyositis may be equally vague to the careless observer, and the prime clue is again the distribution. Another helpful sign in both systemic lupus and dermatomyositis is periungual telangiectasia. Either of these diseases may at some time exist in a crossover form with sclerodermatous manifestations, but scleroderma is not a photodermatosis. Scleroderma's many manifestations, including turgid, bound-down skin, telangiectasia, and hyperpigmentation, occur without respect to light exposure.

Let us now consider that most nonspecific of all cutaneous indicators of systemic disease: pruritus without primary skin lesions. The great problem is always to rule out a primary dermatosis, because its hallmark may have been eradicated by the excoriations, abrasions, lichenification, crusts, and ecchymoses superimposed by the uncomfortable patient's hands. One must always consider particularly dermatitis herpetiformis, glass fiber dermatitis, scabies and other infestations, and simple dry skin, which will be the most common cause of unexplained itching in the winter months. Psychogenic causes will explain the problem in another large group of patients. Once the foregoing have been considered and eliminated, and the itching is unresponsive to usual measures, the clinician must proceed to careful physical and laboratory evaluation of other possibilities. Pruritus may be associated with and may be the presenting symptom in a variety of disease states: internal neoplasms; diabetes mellitus; chronic renal failure; hepatic disease; hyperthyroidism and, rarely, hypothyroidism; polycythemia vera; systemic lupus
erythematous; paraproteinemias; juvenile rheumatoid arthritis; parasitic infestations; certain nutritional deficiencies; gout; neurological disease including tabes, thalamic tumors, pre-eruptive herpes zoster, and the syndrome of hereditary localized pruritus. Drug history must also be evaluated: itching may be the only evidence of drug allergy or may precede the obvious eruption; cocaine and opium derivatives are pruritogenic; amphetamines can induce repetitive picking and scratching of the skin. Like urticaria, erythema nodosum, and erythema multiforme, unexplained itching must be considered a symptom complex, demanding a foray into the etiological forest.

Certain syndromes involve such a multiplicity of organ systems that they defy easy categorization. Some of the genodermatoses in particular are of such complexity that many years of study by multiple investigators are required to unveil the whole picture. Even then, the discovery of a basic defect, that one hopes is correctable, often awaits the discovery of some new piece of basic biochemical or physiological knowledge. For example, we were asked several years ago to see a patient on another service because of her peculiar fingernails. This teen-aged girl had been hospitalized for treatment of a recurrently fractured femur. Her fingernails were most unusual, being partially to totally absent (Fig 1). Further examination revealed a distinctive pattern of reticulated hyperpigmentation of the skin (Fig 2), intraoral patchy hyperpigmentation and leukokeratosis, poor dentition, sparse hair, palmar and plantar hyperkeratoses, ab-
sent dermatoglyphics, and absent lacrimal punctae. She also had chronic, refractory pancytopenia. This constellation of findings added up to the diagnosis of a very rare disorder, dyskeratosis congenita. More investigation uncovered five other involved family members in three generations and some previously undiscovered unique features: dominant inheritance, chromosomal abnormalities, and certain immunological defects. Studies of this family have involved dermatologists, orthopedic surgeons, hematologists, biochemists, immunologists, radiologists, pathologists, and geneticists. Despite all of these studies, we have not yet uncovered a basic unifying defect. Neither have we been able to offer much therapeutic benefit. One family member has died of carcinoma, another eventual component of this disorder, and another has died of accidental injuries, his death probably being related in part to his profound thrombocytopenia.

To offer a more successful example, Dr. Lowell A. Goldsmith, a dermatologist-biochemist at Duke University, has recently shown what therapeutic benefits may grow from careful observation and study of a similarly rare disorder. Earlier he had found rather serendipitously that patients with the Richner-Hanhart syndrome had extremely elevated plasma tyrosine levels. At a regional dermatology meeting last year he found an infant who had the typical findings of herpetiform corneal ulcers that eventuate in blindness, punctate palmar and plantar keratoses so painful that they limit use of hands and feet, and mental retardation. This child had plasma tyrosine levels fifty times that of normal. Following biochemical logic, he placed the patient on a low tyrosine-low phenylalanine diet. Now, several months later, this child has normal vision and healed keratoses, which should allow normal walking and development of the lower extremities. It isn't every day we enable the blind to see and the lame to walk, but it is the hope of that sort of result that keeps us inquisitive.

In concluding this review of some dermatomes, I do not want to leave the impression that it has been comprehensive. Many other skin-systemic disease correlates may be pursued further in general and specific reference sources. Neither do I want to leave the impression that we dermatologists devote most of our practice hours to diagnosing such rare entities as tuberous sclerosis or Degas' disease. On the contrary, we expend most of our efforts on the common dermatoses which fortunately have no relationship to disease elsewhere. That does not lessen their importance, for perhaps the most important functions of medicine after all are to reduce the annoyance of common afflictions, make our brief passage more comfortable, palliate in the highest sense.

There is, nevertheless, a peculiar excitement generated by the recognition of a skin lesion that immediately tells us that something, perhaps very specific, in a less accessible site may also be diseased. Even more exciting is the realization that the whole saga is not and never will be written. Any of us on any day may have the opportunity to recognize a new correlation between skin and systemic disease and, as a result, may be able to do more to benefit the patient who has the disease.

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Cutaneous Manifestations of Venereal Disease

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There has been a dramatic increase in the incidence of venereal disease, and these disorders have become one of our major national health problems. It is obvious that if this chain of infection is to be broken, individuals with these diseases must be treated as early as possible in the course of the infection before there is a chance for it to spread to others. We have been implored to help find the sexual contacts of these individuals, and it is essential that we use the excellent epidemiological investigators of our health departments for this purpose.

From the physician's viewpoint, it is particularly important to recognize these disorders early and treat them as soon as possible, and in order to do this we need to recognize the lesions we see. Many of these disorders have their first manifestations on the skin and mucous membranes, and our purpose is to present a somewhat panoramic view of the many and varied types of skin lesions that may lead to the diagnosis of one of these disorders.

The first part of this discussion will deal with gonorrhea because it is the most common of venereal diseases. It not only has the highest incidence among venereal diseases, but it has also become one of the most common of all infectious diseases. There were at least two and a half million cases in the United States last year.1 The disorder usually begins with genital infection and in the male is a relatively simple problem. There is urethral discharge, marked dysuria, and the patient is so uncomfortable that he rapidly presents for treatment. Most of the time he even tells you what he has. Diagnosis under these circumstances is not difficult.

The problem is the female who is asymptomatic in many instances.2 She has only mild vulvovaginitis or cervicitis, and she has very little in the way of symptoms. It is obvious that she will not be treated unless the physician makes sure that she is through his treatment of her male contact who presents with symptoms. Internal involvement may occur with this disorder in the form of progression of the organism to the internal genitalia resulting in salpingitis. Sometimes this may lead to pelvic inflammatory disease and sterility.

There are very few lesions on the skin and mucous membranes. Rarely, there will be localized cutaneous lesions in and around the genitalia. These may involve the lower abdomen, the upper medial thighs, and the genitalia themselves, and may take the form of pyoderma-like infections. These lesions may appear as folliculitis or abscesses.

About 1% or 2% of individuals with gonorrhea, if left untreated, will develop generalized cutaneous gonorrhea.3 These lesions usually begin as erythematous macules and progress to papules or vesiculopustules (Fig 1). They most frequently are located on the distal extremities and sometimes take on a hemorrhagic appearance. Organisms reach this destination apparently by hematogenous spread, and these lesions are commonly associated with fever and arthralgia. The arthritic involvement most frequently occurs in the large joints, particularly the knees, wrists, and ankles. The typical hemorrhagic papules on the distal extremities though few in number should be enough to suggest this diagnosis without any of the other findings, but if they are accompanied by fever.

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and arthritis, the diagnosis is almost certain, and it is basically a clinical one. Unfortunately, Neisseria gonorrhea usually cannot be cultured from the cutaneous lesions, but frequently can be identified by means of fluorescent staining techniques. Therefore, we have to depend on the clinical combination of these three manifestations, and sometimes a culture can be obtained from the cervix of the female.

While gonorrhea actually has very little in the way of findings on the skin, syphilis probably has the most varied number of cutaneous lesions of any infectious disease. The primary phase has an incubation period which averages about three to six weeks, but may stretch all the way from ten to ninety days. The first sign is an indurated papule which soon becomes eroded and leaves an ulcer. Most patients will have regional lymphadenopathy or so-called satellite buboes. In the male, most of these lesions are located on the penis, frequently on the glans or on the area of the coronal sulcus. They have a clean base, slightly rolled edge, and are firmly indurated if palpated with the gloved hand of the examiner. Typical lesions in this area are readily suspected. Most of us would immediately think of primary syphilis. On the other hand, the primary lesion in the female is most frequently on the cervix, and if it is not suspected and an examination with a vaginal speculum is not done, it will be missed. In addition, the lesion may appear as almost any nonspecific type of erosion. The second most common location of lesions in the female is on the external genitalia.

Another problem is the increasing incidence of extragenital primary lesions. These do not occur on the genitalia, but may occur anywhere on the anatomy. They are frequent in the perianal region, and this is particularly true in our ever-increasing homo-
sexual population. These lesions may appear as almost any nonspecific erosion of the anal area, appearing to be an anal fissure or erosion. Another common extragenital location is the perioral region including the mouth, pharynx, lips, and tongue. Again, because of the location, many would never suspect the diagnosis of even a classical lesion. Extragenital lesions can occur in rare locations such as fingers where they are sometimes seen in medical, dental, and paramedical personnel.

Secondary syphilis is by far the most varied cutaneous phase. The incubation period is a great deal longer, and the patient is not as suspicious of any contacts he may have had because the average incubation from the time of infection to the beginning of the secondary phase is somewhere around two to three months and may be as long as six months. There are sixteen different types of cutaneous lesions listed in Table 1, and the main point to emphasize is that almost any type of cutaneous lesion can occur in the secondary phase of syphilis. The one major exception to this rule is that in adult secondary syphilis vesicles and bullae rarely, if ever, occur.

Some types of lesions are more characteristic than others. Annular lesions, split papules, palmar and plantar lesions, alopecia, mucous patches, and condylomata lata fall into this category. The patient in Figure 2 has an erythematous macular, morbilliform type of eruption which could easily be mistaken for a drug eruption or any viral exanthem. A VDRL was reactive at 1:128. Lesions on the palms and soles are probably the hallmark of secondary syphilis. These lesions may take any form: macules, papules, pustules, and even an exfoliative process may be seen. Most of them are hyperpigmented macules with an overlying fine white scale, but they may be much more impressive with pustules leading almost to exfoliation. If one sees a patient with lesions on the palms and soles that are symmetrical and are not vesicular or bullous, this diagnosis should at least come to mind.

Alopecia is usually described as being patchy in nature or, classically, as being moth-eaten in appearance. Once again, almost any patchy type of alopecia should be suspected. There are some exceptions to this rule, and probably the most common type of patchy alopecia is alopecia areata. However, without a ready explanation or diagnosis such as alopecia areata, the physician should consider secondary lues.

Condylomata lata begin with flat-topped papules which coalesce to form masses, usually in intertriginous areas particularly around the genitalia and in the perianal region. These lesions are flat-topped and this appearance helps to differentiate them from the pointed lesions of condylomata acuminate or venereal warts which may occur in the same area. Condylomata lata may become quite massive and be surrounded by marked hyperemia, and if a dark field is done from these lesions, it is readily positive because they are moist and usually teem with spirochetes.

Annular lesions are among the most characteristic type for this phase of syphilis. These are lesions with an active advancing border and a healed center. They may occur in other disorders such as sarcoidosis or granuloma annulare, but once again, if they are seen, secondary syphilis should be included in the differential diagnosis. Split papules may occur at any crevice such as along the corner of the nose, behind an ear, or at the corners of the mouth where they may be difficult to separate from perlèche. Mucous patches are white stuck-on-appearing lesions that may occur on any mucous membrane such as the cervix or oral area. Sometimes these lesions are difficult to differentiate from lichen planus, moniliasis, and even leukoplakia.

Because of its varied forms of presentation, secondary syphilis is often confused with several other disorders. Pityriasis rosea is one of the most difficult to separate from secondary lues. A patient who does not have the classical herald patch and the classical Christmas tree distribution of pityriasis rosea, is suspect. The palms and soles should be examined and if they are clear, the patient probably does not have syphilis, but the physician should be thinking about the possibility and a serologic test should be done.

Having talked about the so-called major venereal diseases because they have the highest incidence, I would like to turn the discussion to those that are sometimes considered minor, but are certainly not
minor to persons who have them. Chancroid has the so-called soft chancre, as opposed to the hard chancre of syphilis, because it is not usually indurated. The lesions are multiple and extremely tender and all of these characteristics help clinically to separate it from syphilis. The lesions are usually located on the genitalia, and most of these patients will have inguinal adenopathy. The ulcers frequently have a dirty, necrotic, shaggy base. They are extremely tender and because there is so much necrosis they may emit a foul odor. Often it is difficult to differentiate this disorder from syphilis, and unfortunately the available laboratory tests for chancroid are not satisfactory. Occasional patients will have fairly clean-based lesions unlike the typical lesions of chancroid, but if these lesions are multiple, there is less chance of primary syphilis which usually is solitary. Tenderness also suggests chancroid, but one cannot be sure without ruling out syphilis by means of a negative dark field examination and negative serologic tests. If these are not done, the clinical diagnosis of chancroid cannot be made.¹

Next, are two disorders which are frequently confused because their names are similar: lymphogranuloma venereum and granuloma inguinale. They really are not very much alike except that they occur on or around the genitalia. Both are considered to be venereal in nature. In lymphogranuloma venereum, the primary lesion is a papule or erosion of brief duration and is not very impressive. Most physicians have never seen one and probably never will because it is small and often overlooked by the patient. Soon after the primary phase in the male, large, tender lymph nodes appear. These are referred to as buboes. In the female, lymphatic drainage is partially to the perianal area, and therefore proctitis may occur as well as resultant stricture. The lymph nodes are usually large, fluctuant, and tender. They may be unila-

Fig 2—Palmar and plantar lesions are extremely suggestive of secondary syphilis.
teral or bilateral, and both the inguinal and femoral nodes may be involved.

Granuloma inguinale, on the other hand, does not primarily involve the lymphatics. It is basically a disease of large slowly growing ulcers which have a beefy red appearance, and there is not usually lymphatic involvement unless secondary bacterial infection with other organisms supervenes. These lesions may be markedly destructive. The beefy red, granulomatous appearance is typical as is partial destruction of the genitalia.

It should be noted that occasionally individuals with one venereal disease may have another. It is not rare to see a patient with gonorrhea and syphilis at the same time, and any combination of these disorders is a possibility. Consequently, appropriate investigation should be done to rule out such simultaneous occurrences.

Finally, there is another problem which is increasing rapidly in numbers of cases. This problem is genital infections with herpesvirus. This is almost always with herpesvirus type 2, although occasionally type 1 will become involved. The lesions most frequently are vesicular and they quickly erode to leave shallow ulcerations which are usually somewhat tender. These will resolve in a period of a couple of weeks in most instances. The diagnosis is basically clinical and the physician usually is able to tell what it is by simple examination. However, if there is doubt, other venereal diseases must be ruled out. A culture can be done for the virus, and a Tzanck prep may be very helpful.

The lesions in the primary phase of infection around the genitalia are numerous. They may involve the whole area from the genitalia to the perianal region. There frequently is some fever and generalized illness with malaise, some edema, and sometimes a purulent discharge which occasionally is mistaken for gonorrhea. However, this is not the phase that is usually seen. Usually localized clusters of vesicles occur over and over in the same location, and if this history is available, it is easy to make the diagnosis. However, even more frequently the vesicles have already eroded by the time the patient presents in the physician’s office, and only simple small erosions are seen. Then the physician has to depend on the history that vesicles have occurred previously.

One final point: there has been an increasing amount of evidence in recent years that there may be some relationship between carcinoma of the cervix and herpesvirus type 2. This was initially discovered by cytological exams of individuals who had both premalignant and malignant lesions of the cervix. These exams were noted to have the cytological appearance typical of herpes infections, and there is also an increased number of these patients who have more antibodies to herpesvirus type 2 than do control groups. The significance of these findings is not clear, but some workers now feel that at least women with this type of infection should have more frequent pap smears, maybe one every six months.

REFERENCES

Management of Cutaneous Malignancy—
A Review

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Skin cancer is the most frequent type of cancer, accounting for about 20% of all cancers in the State of Virginia, and the most common type of skin cancer is the basal cell carcinoma. The basal cell carcinoma is a tumor which is not considered highly malignant because, in general, it does not metastasize, although there have been a few instances in which metastases have occurred. However, such lesions may be quite destructive at times. The typical basal cell carcinoma presents as a waxy, papular or nodular lesion which has a gelatinous or somewhat translucent appearance. Coursing across the surface from the normal skin toward the center of the lesion, one will often see fine telangiectatic vessels. At times the lesions may be somewhat deceptive because of their location, and this is particularly true in the inner canthus where they may be missed until they are fairly large. Some basal cell carcinomas will remain relatively quiescent for long periods of time; others will become much more aggressive and grow rapidly. The tumor may, at times, be much like an iceberg with only the tip appearing, and this is particularly a problem with lesions on the nose. In treating a lesion in this location one has to be very cautious and be prepared to perform grafting, if this is required. It may, at times, be difficult to differentiate a basal cell carcinoma from small lesions which we call sebaceous adenomas, which occur frequently on the faces of elderly individuals. These are small waxy, creamy elevations usually on the forehead and they are the result of hyperplasia of sebaceous follicles.

Basal cell carcinomas are occasionally quite atypical. The so-called superficial basal cell carcinoma often looks very much like an eczematous process. One could easily mistake such a lesion for psoriasis or nummular eczema. However, at the edge of such a lesion one will see the small thread-like, pearly or waxy border. Bowen’s disease also may look very much like superficial basal cell carcinoma, but it is, in fact, an in situ squamous cell carcinoma. Another atypical type of basal cell carcinoma is the morphea-like or sclerosing basal cell carcinoma. As the tumor extends at the periphery, scarring will take place in the center, and the center of the lesion will actually disappear and be replaced by scar tissue. It is often not recognized that basal cell carcinomas may have a considerable amount of pigment. The pigmented basal cell carcinoma may be very difficult to differentiate from a malignant melanoma because it has many of the characteristics that we associate with malignant melanoma, such as pseudopods of pigment.

At times we see individuals who have a very extensive process in which many hundreds of basal cell carcinomas may occur, starting oftentimes in childhood, and continuing with development of new lesions, into adult life. Most of these individuals do not survive to late adult life because of the severity of this process. In addition to the presence of these basal cell carcinomas, there are other features which allow us to make a diagnosis of the nevoid basal cell carcinoma syndrome. Individuals with this condition have frontal bossing, lantern jaw, and appear grotesque. They may have jaw cysts, abnormalities of the ribs such as biled ribs, and small pits on the palms and soles.

Treatment of basal cell carcinoma is quite var-
WEARY: MANAGEMENT OF CUTANEOUS MALIGNANCY

Lesions can be excised surgically, are amenable to x-ray therapy, and may be adequately treated by electro-desiccation and curettage. The recommended way to use this latter modality is to desiccate the lesion, curette it and then repeat the same procedure with a final light desiccation to control bleeding. If this is done properly, the cure rate should approach 95% to 98%, and this is as good as one can get with any form of management. Many dermatologists now are turning to the use of cryosurgery, liquid nitrogen in particular, for treatment of basal cell carcinomas. One may use a large cryotherapy unit with either a probe or spray, and the recommended treatment is to insert thermocouples beneath the skin at approximately the base of the tumor. The thaw. With this type of approach, the cure rate should be very high.

It is known that topical 5-fluorouracil has significant destructive effects on various cutaneous tumors. Unfortunately, application of 5-fluorouracil alone to a basal cell carcinoma has been ineffective, probably because the surface epithelium overlying the tumor is intact. My rationale is to combine cryotherapy with subsequent application of 5-fluorouracil so that one destroys the overlying epidermis and a portion of the tumor, thereby allowing the 5-fluorouracil to penetrate into the depths of the lesion and destroy any pseudopods of tumor which might persist. With this approach one can apply the liquid nitrogen on a cotton-tipped applicator stick to the lesion for a period of perhaps one to two minutes. While the lesion is frozen, we take a small curette and simply scoop out a small portion of the tumor for histologic verification (no local anesthesia is needed). Bleeding afterwards can be controlled by application of aluminum chloride. The patient commences that evening, and twice a day thereafter, application of topical 5-fluorouracil in the form of 5% Efudex ointment to the lesion. I usually have the patient cover the site with an occlusive Blenderm tape dressing. Treatment is continued for a period of two to three weeks, depending upon the depth and size of the lesion. With this treatment I have treated perhaps 400 to 500 such lesions in the last four years. The cosmetic result is superb and the amount of recurrence is no more than one would expect to see with the other more conventional modalities.

Epidermoid or squamous cell carcinoma is the second most common type of skin cancer. Most such lesions arise from sun-damaged skin. The association of squamous cell carcinoma and actinic exposure is very well appreciated, and we think that the actinic keratoses or cutaneous horn is oftentimes a precursor. Squamous cell carcinoma arising from actinic keratoses is a much less aggressive tumor than other types of squamous cell carcinoma, often remaining well confined to a localized area for a long period of time, being slow to metastasize and quite amenable to treatment by cryosurgery, electro-desiccation, surgery, or radiation therapy. Surgery is probably the best-accepted treatment for such lesions. When squamous cell carcinoma arises in pre-existing dermatoses, long-standing ulcers, burn scars or sites of old radiation dermatitis, which is not a rare sequence of events, the lesion is much more aggressive, more apt to be anaplastic, metastasize early, and has to be treated, therefore, in a much more aggressive fashion. If one encounters an area of chronic ulceration (stasis, decubitus, burn) which does not show signs of healing, it is very important to consider a biopsy to be sure that one is not dealing with such a tumor.

Bowen's disease, a form of in situ squamous cell carcinoma, is a disorder which may be very slow to change and it may be present for many months or years without undergoing rapid enlargement or without becoming an invasive carcinoma. Most of these lesions will probably become invasive if they are allowed to remain in place indefinitely. Lesions of this sort are very amenable to treatment with cryotherapy and topical 5-fluorouracil, or in some instances, the use of topical 5-fluorouracil alone. They should be biopsied and followed carefully to be sure that all of the lesion is removed.

There is a condition we call keratoacanthoma which looks clinically very much like squamous cell carcinoma. Microscopically, as well, it may be somewhat difficult for the histopathologist to differentiate such lesions from squamous cell carcinoma unless he has the entire specimen or very adequate specimen. The one feature about keratoacanthoma which is so distinctive is its rapid growth. A lesion may attain a size of 1 to 2 cm in a period of three to four weeks. Characteristically, the lesion exhibits a heaped-up or rounded border with a central horny plug. Occasionally, one will see multiple lesions of keratoacan-
thoma. Keratoacanthoma is called a benign, self-healing epithelioma and it is true that most such lesions, if left alone, will heal spontaneously. Unfortunately, the scar that results when they heal spontaneously is often not a satisfactory one and a more suitable cosmetic result is obtained if these are excised or treated with one or another modality. In addition, there have been a few instances in which keratoacanthoma seems to have progressed to the development of squamous cell carcinoma, and even occasionally into a metastatic squamous cell carcinoma. Keratoacanthomas are usually treated by excision. They can also be treated by electro-desiccation and curettage, but unfortunately, with such treatment, one does not have an adequate specimen. I now freeze such lesions with liquid nitrogen and, while they are frozen, shave-excise a major portion of the lesion for a pathologic specimen. I then have the patient apply topical 5-fluorouracil and an occlusive dressing as with a basal cell carcinoma. The end cosmetic results are very good.

About 2% to 3% of internal malignancies may metastasize to the skin. Recognition of these lesions, of course, may allow one to make an early diagnosis of an internal malignant process. Characteristically, metastatic carcinoma is stony hard to palpation rather than doughy or rubbery like a sebaceous cyst or lipoma. The color may be normal skin color or various shades of brown, pink, or red. At times these lesions appear to be very vascular. When they occur on the scalp, which is not an infrequent site, the hair overlying such lesions is lost. In general, the incidence of metastasis from an underlying malignancy parallels the incidence of these tumors in the population. In other words, the two most common tumors to metastasize to the skin are the two most common tumors in the population—carcinoma of the breast in females and carcinoma of the lung in the male. Metastasis to the skin of an internal tumor generally takes place in relative proximity to the site of the tumor. A pelvic tumor might, therefore, be expected to metastasize to the perineum, a carcinoma of the lung may metastasize to the chest wall. They may metastasize either by the blood, along the lymphatic channels, by implantation at the time of surgery, or by actual growth of the tumor in underlying tissues out to the skin, presenting there as a nodule.

Malignant melanoma is the most malignant of skin tumors and it is important to realize that 50% of malignant melanomas arise de novo rather than in pre-existing nevi. The average individual has between 20 and 40 pigmented lesions on the skin so it is a total impossibility to remove all such lesions. Some textbooks state that all pigmented lesions on the hands, the feet, and genitalia should be removed. This is due to the fact that lesions in this location are largely junctional in nature, and we know that malignant melanoma arises most often from junctional lesions. It is now known that one out of five individuals has a pigmented lesion on the hands, feet, and genitalia and, therefore, in order to prevent one malignant melanoma, one would have to remove 10,000 such lesions: obviously an impracticality. On areas of the hands and feet subjected to significant degrees of pressure or friction, pigmented lesions probably deserve removal. We have all heard the statement that moles that are on areas subject to friction from clothing should be removed. There is very little really good evidence to substantiate this concept. In order to establish any real association, one would have to do a comprehensive, prospective study to really determine whether rubbing from clothing is enough to cause lesions to become malignant. We do at times remove such lesions if the patient shows an obvious concern, but I am not inclined to remove them simply because I am worried about malignancy in general.

Lesions which are dome-shaped, uniform in color, lightly colored brown, tan or skin colored, with well defined edges, are usually benign. Variation in color is probably one of the most significant and important features which would cause us to be suspicious of malignant melanoma. Small blackish areas occurring in a nevus which has been uniformly colored previously, and particularly blue-black coloration, is highly suspicious. Not all black coloration of a nevus will be due to dark discoloration in the depths of the lesion, however, and many times dark keratinous material may accumulate on the surface in little crypts to form black plugs. Lesions which show pseudopods of pigment at the edge, or the edges of which are irregular and indistinct, may be active lesions and should definitely be removed. Lesions with alternating color, perhaps even hypopigmentation at times, probably should be removed.

Lesions arising in the proximal nail fold which disperse pigment into the nail plate itself, producing longitudinal pigmented bands, may indicate the presence of a pigmented nevus in the matrix of the nail. Such lesions occurring in Caucasians should all be removed, but pigmented bands in the nails of black individuals are common and usually benign. Pigmented lesions on mucus membranes or transitional
mucosal surfaces should be removed because they have a high incidence of malignant alteration. Occasionally, one will see a so-called bathing trunk nevus, often quite large and hairy as well as pigmented. Malignant melanoma occurring prior to the age of puberty is a very uncommon circumstance, but when it occurs, a number of melanomas have arisen in such large nevi. Sometimes these bathing trunk nevi cover 75% to 80% of the body surface, and it is very difficult to remove the entire lesion, but as much as can be removed with suitable grafting should be accomplished as early in life as possible.

Lentigo maligna is a lesion which occurs mostly in older individuals, frequently on the face, and characteristically will be present for many years, very slowly growing at the edge, oftentimes with a grayish or slate color. There may be a significant degree of pigment variability from one area to another. After a period of many months or years the lesion may develop very dark or jet-black areas or a small nodule. When this happens, the lesion, which was previously benign, has crossed the border into the malignant category. It is important to recognize that the melanoma that arises in such lesions is a much less aggressive type of melanoma than that which arises in the average pigmented mole. It will metastasize first to the regional nodes and often fairly late in the course, whereas malignant melanoma of the usual type may bypass the regional nodes and metastasize early to distant sites. Lentigo maligna can be treated by simple excision or by cryotherapy, if malignancy is not present. A biopsy should be done of the most suspicious areas before one uses cryotherapy to confirm the fact that one is not dealing with a malignant process.

Two other special lesions should be mentioned in conclusion. The blue nevus because of its blue color may be mistaken for a melanoma. It occurs most often on the distal extremities and usually by the time the patient is seen he may have had it for many years. If a patient comes in with a lesion such as this, of recent onset, we might be suspicious that it is a blue nevus, but because we cannot always be sure that it is not a malignant melanoma, we remove a small number of benign blue nevi. Blue nevi may occasionally become malignant, but this is certainly an unusual circumstance. The halo nevus is essentially a benign nevus about which a halo of depigmentation arises usually in the process of autodestruction of the nevus. Generally speaking, we do not advocate removal of the lesions because we know that most of them will not become malignant. Occasionally, malignant melanoma may have a surrounding halo of depigmentation and thus each such lesion should be carefully examined. If you do remove a halo nevus, be sure to tell the pathologist that this is a lesion that you suspect of being a halo nevus, because microscopically such lesions have an intense inflammatory response around them, and the inexperienced pathologist looking at such a lesion may misinterpret this as evidence for a melanoma.
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