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. There are numerous ways of classifying these dermadromes, 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 will also have axillary freckling. There will be little help to offer this patient. Had we been able to diagnose the disorder in infancy, we might have prevented the birth of a younger sibling who would also have the disease. Therein lies the greatest significance of the café au lait spots: 5% to 10% of the normal population may have one or a few, and such spots are also found in Albright's syndrome, but 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.

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Another neurocutaneous syndrome in which early recognition is of crucial importance in genetic counseling 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!"[1] 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 brown, 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, monilial, 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

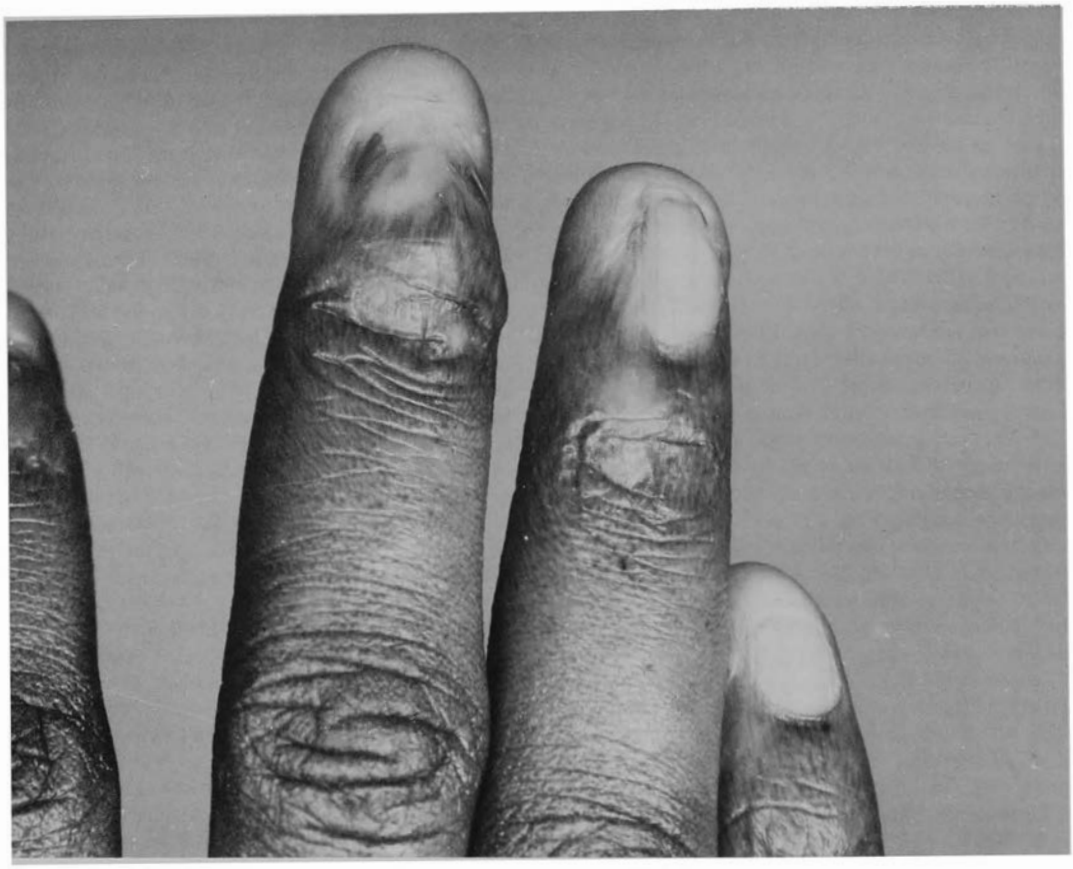

Fig 1—Partial and total anonychia in patient with dyskeratosis congenita.

erythematosus; 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.[2] 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 thrombodytopenia.

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.[3] 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.[4] 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 dermadromes, 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[5–10] 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 Degos' 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.

Fig 2—Distinctive pattern of reticulated hyperpigmentation with interspersed islands of normal and hypopigmented skin in dyskeratosis congenita.

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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