CUTANEOUS MANIFESTATIONS OF SYSTEMIC DISEASES*

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More than a half a century has elapsed since cutaneous medicine became established as a recognized special field. The development of specialties in general has come about rather slowly, receiving initiative from the great epochs of modern medical science, notably the rational pathology of the Virchow school and the application to the theory and practice of medicine of the principles of modern bacteriology and immunity.

Dermatology may be said in some respects to have had an unfortunate and precipitous birth. It did not develop gradually but was rather abruptly established as a result of the classification of dermatoses based upon pure morphologic characteristics by the early founders of the Vienna school. This has resulted in the development of a cumbersome, awkward, and somewhat irrational nomenclature.

The early interpretation of pure morphologic pictures as these occur in the skin, led away from, rather than toward the concept of general morbid processes. The natural result of this schism from the domain of general medicine was the development of a field with its own peculiar pathology, and with an ever widening breach between its confines and the pathologic processes which affect other systems.

A science based upon such superficial characteristics could not long endure as such. The last two decades, therefore, have seen a great change in the interpretation of disease processes in the skin. The recognition of the integument as an organ of fundamental importance in the

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general physiology of the body, its function as a vast heat-regulating mechanism, as an excretory and secretory organ, and more latterly its recognition in the important biophysical and biochemical activities of the organism, are rapidly aligning disease conditions in the skin to the general pathologic state of the individual. Each year sees more and more so-called essential dermatoses proved and accepted as the cutaneous reflections of systemic morbid processes.

Cutaneous medicine therefore concerns itself with the concept of the skin and its appendages as a complex organ which graphically reflects systemic disease processes in a vast variety of what might be termed reactions. Conversely, it also serves as an excellent yardstick whereby may be evaluated and measured standards of good health.

The so-called essential skin diseases have in the course of the last few years been narrowed down to local infections, both bacterial and mycotic, and to a few benign and malignant growths. The several unexplained inflammatory diseases in the skin such as lichen planus and psoriasis, may in our ignorance still be regarded as peculiar to the integument. The ultimate elucidation of their nature, however, may well show them to be the manifestations of a general rather than a local pathologic condition.

It is manifestly impossible in the allotted time to enumerate or to discuss in detail the various skin manifestations of systemic disease. It would, I think, be far better to emphasize the theme suggested by taking two texts: first, the subject of focal infection in its relation to cutaneous disorders; and, second, the intimate relation of the skin to the group of so-called lymphoblastomatous diseases.

Among the many theories elaborated to explain the phenomena of morbid processes, none has seemed at first glance so attractive, so readily applicable to many diseases as that of bacterial foci from which systemic infections take place. Following, as it did, in logical sequence, the identification of specific microbes as causative agents in the pro-

duction of disease, and the subsequent knowledge of bacterial sepsis, it is readily comprehensible why the theory of focal infection should have been readily applied to hitherto unknown etiological entities.

That focal infection has passed from a scientific theory to a proved principle cannot be gainsaid. The work of Billings, Rosenow, Holman and many others in this country and abroad has established beyond a peradventure that its application to certain disease processes fulfills all scientific postulates. However, it must also be admitted that, like uric acid, the theory of focal infection has had woven about its application as much of fiction as of truth.

There is a basic misconception and rather widely current confusion in the minds of many who have written and spoken on this subject, between the terms, focus of infection and focal infection. The two are frequently loosely and synonymously applied in both writing and discussion, when in fact they should be sharply differentiated.

Billings described a focus of infection as a circumscribed area of tissue infected with pathogenic organisms. Holman has pointed out, therefore, that any condition resulting from the systemic dissemination of bacteria from the source or focus becomes a focal infection. It is therefore self-evident that focal infection results from foci of infection and the two terms, although related sequentially, have different identities and must not be confused (and we must at all times distinguish between them).

Perhaps the simplest example of proven focus and consequent focal dissemination is the chancre of syphilis; here we have a nidus of pathogenic organisms leading to more or less rapid dissemination and to remote morbid processes in the skin, viscera and mucous membranes, thus representing admirably a focal infective process.

It seems quite natural that in the ten or more years since Billings' first paper on focal infection the theory should have found favor among dermatologists, and an earnest

effort should have been made to apply it to our many obscure etiological problems.

When the initial wave of enthusiasm passed, it was found as in other advances in medical science, that something new had been added to our knowledge of disease cause, but much was left over to be explained on other theories. It is safe to state that at some time or other almost every etiologically obscure dermatosis has been said to result from a focus of infection, but only a few have stood the rigid scrutiny of scientific accuracy and have been established as of such origin.

With the clear-cut definition of a focus of infection as a nidus of pathogenic organisms, and of focal infection as the expression of systemic invasion by these organisms, very rigid criteria should be applied to a disease, together with convincing experimental evidence, before it may be accepted as an example of a focal infective process.

In by far the majority of examples in cutaneous medicine where focal infection has been suggested as the cause of symptoms, the case has been made on suggestive criteria and on clinical data. Thus, one observer with a series of cases of, let us say, alopecia areata, in which dental caries has co-existed, expressed the opinion that the latter as foci caused the former. His view was perhaps strengthened by the clinical observation that the alopecia disappeared after removal of the alleged foci. I shall hope to show later that while such evidence is perhaps suggestive or presumptive, it lacks scientific accuracy and does not sufficiently support accepted postulates for cause and effect in disease.

At some time or other the following conditions have been considered to be due to foci, and therefore examples of focal infective processes: urticaria, urticaria pigmentosa, eczema, the erythema multiforme group, cutaneous tuberculosis and the tuberculides, hemorrhage, petechiae, purpura hemorrhagica, herpes zoster, pemphigus, derma-

titis herpetiformis, lupus erythematosus, keratosis blenorrhagica, and many others.

It now appears that in a few cases focal infection adequately explains certain cutaneous diseases in which up to now, to the best of my knowledge, that cause was not suggested for them. Such are the trichophytides, sporotrichosis, tularemia, and probably vaccinia and certain of the contagious exanthems.

It might be well at this time to apply rigid scientific criteria to the above groups, and to see to what extent focal infection is proven in one group, presumptive or likely in a second, and unlikely or improbable in the third.

In the proven group stand out syphilis, sporotrichosis and tularemia with their portals of entry in an injury, cases of systemic blastomycosis, the petechial and hemorrhagic lesions of bacterial sepsis, the trichophytides, scarlet fever, vaccinia, and the many extraordinary mutation forms of skin tuberculosis, including the sarcoid of Boeck, the deep tuberculosis of the hypoderm, and many of the so-called tuberculides.

It may well be argued that systemic or blood-borne tubercle bacilli are difficult to determine, and that with all the evidence not at hand in every case, it would seem improper, for example, to class lupus vulgaris in its many clinical forms, sarcoid tumor, lupus miliaris, and lichen scrofulosorum as examples of tubercle implantation from a remote focus.

Admitting the validity of this argument, it is nevertheless true that the overwhelming preponderance of opinion favors the view that these are endogenous blood- or lymph-borne infections, and the weight of clinical evidence, together with some experimental proof, supports this view.

When we come to the tuberculides, however, we face a group of conditions which in part fit in with the concept of focal infections, and in part do not.

It seems to be accepted that certain tuberculides are actually hematogenous tuberculous lesions. Bacilli have at times, with difficulty to be sure, been demonstrated, or occasionally animal inoculation has shown the lesions to contain bacilli. Others, on the other hand, are widely if not generally accepted as evidence of tissue changes due to tubercle toxin liberated from a tuberculous focus. To include such a group, providing the hypothesis of their nature is correct, in the class of focal infections, would necessitate a wider interpretation of our theory than we postulated at the outset.

In the interest of scientific accuracy, therefore, it would seem wiser to limit the term focal infection to those conditions in which systemic dissemination of pathogenic organisms occurs, and to place the group of toxic tissue reactions from remote foci, in a class which might properly be called, *focal irritative processes.*

Following the researches of Jadassohn, Bloch, and their students, we may now place in the group of proven focal infections the generalized dermatoses due to the hematogenous dissemination of mycelia and spores, originating in such local lesions as the kerionic ringworm.

To these lesions the name of trichophytides has been given. The identification of this group and the demonstration of the entity as a systemic infection is a scientific achievement of considerable importance.

The petechial hemorrhages and purpura which are seen in the skin incident to bacterial endocarditis and to general sepsis, also fulfill the postulates of focal infections as do the rose spots of typhoid fever.

Scarlet fever is, of course, as good an example as is syphilis of a focal infection if we accept the throat as the portal of entry of the streptococcus which produces the septic erythema.

The weight of evidence also supports the view of a focal infection for the other contagious exanthems as well.

Until we know more about the smallpox virus and the infectious agents of measles and chickenpox, however, we must place the entire group aside from scarlet fever and vaccinia as presumptive but not yet proven cases.

Sporotrichosis and tularemia are strikingly similar in their mode of onset as starting with lymph-borne infections, which occasionally develop septic manifestations. Both conform admirably to the criteria of focal infective processes.

Yaws in all probability fulfills the conditions of a focal infection, but until its epidemic character and method of transmission are better known, it is best not to include it in the proven focal infectious group at this time.

Although Rosenow has shown bacteria in some of the lesions of erythema multiforme, notably in erythema nodosum, and demonstrated similar strains in the tonsils and elsewhere, I do not believe the evidence at this time is sufficiently convincing to place this very large and varied group of cutaneous reactions with the proved cases of focal infection. The weight of clinical evidence, to be sure in cases such as erythema nodosum in association with rheumatic fever, points to bacterial dissemination. However, it seems quite likely that many forms of erythema multiforme, perhaps the majority, are toxic rather than microbic processes. Many, indeed, very definitely refer back to such causes as foreign protein and drug reactions, thus establishing for them other etiologic factors than infective foci.

While for the entire erythema multiforme group, foci of infection, therefore, as a cause do not fit, in isolated cases we may occasionally be dealing with hematogenous bacterial dissemination.

Toxins rather than infective organisms explain even more readily the urticaria group of dermatoses. These at one time may be due to local toxic irritations and at others to systemic intoxications, as from enteric protein sensiti-

zation or from toxins associated with gall bladder and hepatic disease. While frequent clinical evidence supports the view of foci of infection as the cause of urticaria, the local manifestation is never an evidence of systemic sepsis. It is a *focal irritative* rather than a focal infective process.

Herpes zoster is another disease probably definitely specific and due to an infective focus. The remote lesions on the skin, however, can very properly be regarded as focal irritative rather than focal infective sequelæ. The immunity usually conferred by herpes zoster, moreover, does not fit in with the ordinary history of a focal infective condition where recurrence and chronicity are the rule. It stands out, however, as an admirable example of a change in a remote portion of the body dependent upon a focus of irritation.

A disease which may at some time be shown to be a focal infection, in which the evidence thus far is supported only by clinical evidence, is pityriasis rosea. The frequency of an initial plaque in this disease, the sudden explosion of satellite lesions support the view that we are dealing with a systemic dissemination of an infectious agent from a primary plaque. My own experiments with this disease, extending over five years, while inconclusive, strengthen my belief that a specific blood-borne infectious agent is its cause.

Alopecia areata has been supported by many as an example of a focal infective disease. It is certainly true that the removal of carious and abscessed teeth has frequently resulted in the cure of this condition. Likewise, the uncovering of visual difficulties, sinus infection, and other foci of infection or irritation in the head, has resulted in spontaneous cure of the baldness.

There is to my knowledge, however, no direct experimental evidence to show that alopecia areata can, in the strictest sense of the word, be a focal infection. If the vast preponderance of cases cleared up upon removal of infectious foci, which in fact does not occur, the disease

could at most be placed, like herpes zoster, in the group of *focal irritative* processes.

Many of our deductions as to the focal infective character of a disease are based first, upon the establishment of a focus of infection, second upon the disappearance of the general process after the removal of the alleged focus.

Both hypotheses are open to criticism. Most individuals can be shown to have some demonstrable focus of infection in the teeth, tonsils, gall bladder, appendix, prostate, or elsewhere. The finding of a focus is, therefore, only suggestive. Thus, if a tuberculous focus were found in a lymph node or tonsil in the presence of a cutaneous tuberculosis, the case would at once suggest the relationship between the two conditions, which might, however, be difficult of actual proof.

The clearing up of a systemic condition or of a dermatosis upon the removal of a focus of infection, morever, has importance where bacteriologic proof is lacking, only when it occurs with great regularity, and only when other causes cannot operate to produce the same condition. Under these circumstances, focal infection may be assumed, but its ultimate proof still requires the demonstration of a pathogenic organism in both cause and result.

Where occasional cure of a dermatosis occurs upon removal of a focus, it is more likely that this results from the relief of inhibitory forces which such a focus may exercise on general conditions; or it may be a response to general well being, resulting from the removal of the focus. These factors will explain the cases of lupus erythematosus and of dermatitis herpetiformis, which occasionally clear up rapidly upon removal of infected foci. In both of these conditions the weight of evidence is against their being true focal infective processes.

It may properly be pointed out that occasionally the removal of a focus which, without doubt, is the causative factor of a dermatosis, is not followed by involution or even im-

provement in the focal infection. The demonstration and removal, for example, of a tuberculous lymph gland in the neck would effect little, if any, change in a resulting patch of lupus vulgaris, although it might well be a preventive measure against the development of new lesions. Irreparable tissue damage due to hematogenous germ dissemination cannot be followed by restitutio when the source of the infection is laid bare and removed.

In conclusion, it may be emphasized that foci of infection play either a causal or a casual rôle in the etiology of many dermatoses, or their presence may have nothing whatever to do with the disease in question.

Where the foci are causal, we are dealing with true focal infection as determined by blood-borne dissemination of the pathogenic organism from the focus to the satellite lesion.

This occurs in a proven fashion in syphilis, cutaneous tuberculosis, certain tuberculides, the trichophytides, sporotrichosis, tularemia, systemic blastomycosis, vaccinia, and scarlet fever.

A casual relationship occurs between foci and certain dermatoses with such frequency as to merit notice, and possibly to constitute a contributory etiologic factor in such conditions as erythema multiforme, dermatitis herpetiformis, and alopecia areata.

Finally, to the focal infective process might well be added a group in which foci of infection play a direct rôle in the causation of satellite cutaneous lesions, in which pathogenic organisms are not present, but in which the tissue damage is apparently due to a toxic process. This occurs in herpes zoster, in some of the so-called toxi-tuberculides, in many of the multiforme erythemas, and occasionally in urticaria. This group might properly be referred to as *focal irritative* processes.

During the past twenty years I have had a most unusual opportunity of studying a very large number of cases of

what formerly was termed the lymphadenoses of the skin. In this connection I have been singularly fortunate in the exchange of views with my late colleague Warthin, who throughout his active life contributed much to the pathology of these conditions. In 1929 there were reported from my clinic by Keim twenty cases of various clinical types, of which ten came to autopsy. A great diversity of opinion exists as to the proper classification of diseases of the lymphatic hæmapoietic system. Those which are frequently found in the skin and occasionally occur there before their demonstration in other parts of the body are leukemia, both myeloid and lymphatic, lymphosarcoma, Hodgkin's disease, and granuloma fungoides. From our studies of this group of diseases we have come to the belief that genetically they are closely related, occasionally occurring as combined pictures or changing from one clinical form to another.

From the clinical standpoint the most frequent cutaneous manifestation of the so-called lymphoblastomas occurs as a persistent scaling erythroderma. So frequently is a true lymphadenosis ushered in by a universal scaling dermatitis that the chronicity of this condition should always lead to suspicion of its grave nature. The condition may occur with or without changes in the circulating blood stream. In the majority of cases these are absent at the outset and develop only later in the course of the disease. In a few of our cases marked lymphocytic deviations in the blood occurred only shortly before death. In the large majority of cases a marked lymphadenitis is present, though not usually developing until the disease has been present in the skin for some months. I have, however, seen a few cases in which there was general lymphatic enlargement preceding the development of the erythroderma. Of greatest diagnostic import in determining the lymphoblastomatous nature of an erythroderma is the early biopsy. Even in the very early period the picture is quite characteristic—an infiltrate of lymphoblastic cells occurring in the upper portion of the corium either in clumps or as a

sharp band-like infiltrate quite similar in its architecture to that seen in lichen planus. The biopsy of the lymph glands shows enormous hyperplasia and the same type of lymphoblastic cells as are seen in the skin. In two cases of an unusual type of cutaneous lymphatic leukemia I have seen an ordinary exfoliative dermatitis, unassociated with lymphadenitis and with no unusual blood picture, entirely remit for several months, then reappear with associated lymph gland involvement, and finally remain in a state of chronic cutaneous lymphadenosis with the blood changes of a chronic lymphatic leukemia. In one case of true cutaneous leukemia with marked changes in both the blood and lymph glands, spontaneous recovery took place after four years of observation, during which time the patient on several occasions was considered dangerously ill. Since this observation I have seen spontaneous recovery in a second similar case.

In myeloid leukemia the cutaneous manifestations are considerably more rare. Quite apart from the cutaneous hemorrhages and purpura, one occasionally sees tumors of varying size and density, more particularly occurring on the face. Their appearance on the skin very occasionally antedates or is coincident with the first symptoms which lead to an examination of the blood and the establishment of the diagnosis. The tumors are pure myeloid in structure, and many exist only as transitory cutaneous manifestations of the disease. I have seen one universal type in which large tumors of a purplish-red color appeared all over the body, some of which ulcerated. The resemblance of this type of case to the entity of mycosis fungoides is quite striking.

In Hodgkin's disease one may recognize on the skin the so-called essential types of eruptions. These take the form of definite nodules. The architecture of the latter conforms exactly to that of the pathologic picture seen in the lymph glands. The so-called non-specific lesions occurring in Hodgkin's disease take the form of prurigo-like nodules and excoriations and pigmentation. These are

alleged to be toxic reactions of the disease rather than examples of true cutaneous Hodgkin's disease.

In at least one case, however, in which prurigo-like nodules occurred, I was able to demonstrate very definite pathologic architecture typical of the disease.

The pigmentation seen in Hodgkin's disease is sometimes of a very bizarre nature. I have at present under observation a young man who was admitted for an exfoliative dermatitis which rapidly cleared up on topical remedies. He returned to the hospital less than a month ago with a zone or band of deep brownish pigment extending around the waist and onto the upper portion of the thighs. There was also hyperpigmentation of the axillæ and sufficient thickening of the skin to suggest at least a diagnosis of acanthosis nigricans—a pigmentary disorder discovered by your fellow member Pollitzer many years ago and shown by him to be a frequent accompaniment of abdominal neoplasm. In addition to the pigmentation there was marked enlargement of the inguinal and axillary lymph nodes. A biopsy taken from these and from the overlying thickened skin showed typical early Hodgkin's disease.

With regard to lymphosarcoma, the cutaneous manifestations are extremely varied. One may have, as in leukemia, a scaly erythroderma, apparently benign at the outset and leading to the diagnosis of simple exfoliative dermatitis from one cause or another. Subsequently a marked enlargement of the lymph nodes leads to the suspicion of the lymphoblastomatous nature of the eruption, and the biopsy, both skin and lymph node, readily establishes a diagnosis of small or large round-celled sarcoma. In the late stages of this condition actual metastatic nodes to the skin may occur in large numbers in various parts of the body. In other cases lymphosarcomatous nodes may appear in various parts of the otherwise normal appearing skin, to be followed at a later time by the generalized involvement of the lymph nodes. The picture of the erythrodermatous type is therefore indistinguishable clinically from leukemia and from occasional cases of Hodgkin's disease.

I have before referred to the occasional combination pictures which are seen in these various conditions. So closely may they simulate each other that a clinical diagnosis must occasionally be changed from time to time during the course of the disease.

I shall show lantern slides of two cases illustrating this point. In one, definite lymphosarcomatous nodes were removed from the skin of a young boy who at the time showed little or no change in his blood. He later developed severe hemorrhages into the skin, hemorrhages from his mucous membranes, following which he developed a rapidly fulminating type of lymphatic leukemia from which he died. A second case which I still have under observation is that of an elderly man with multiple lymphosarcomatous nodes in the skin and lymph glands in whose blood at this time there are changes suggesting at least leukemia.

Many years ago there was demonstrated before the Dermatological Section of this Academy a patient in whom at the time it was believed both leukemia and granuloma fungoides were present. The case which I cited before of a young boy who died of myeloid leukemia in whose skin a large number of large ulcerative nodules occurred is, I believe, the analogue of this condition.

An interesting question arises in connection with those cases of lymphoblastoma in which a scaly erythroderma of an innocent type antedates the more serious phase of the disease. The suggestion in this type of case is that the cutaneous insult may be a primary factor in the activation of the lymphadenosis. In cases biopsied during the early period there may be no suggestion of a lymphoblastomatous infiltrate. While the majority of the cases are undoubtedly lymphadenoses from the outset, it is nevertheless a tenable hypothesis that in a few cases at least the lymphadenosis may be secondary to a prolonged skin insult. The analogy at least is present as regards occasional infection and acute lymphatic leukemia.

My own studies have convinced me that the lymphadenoses are reflected in the skin in three different ways. First, and perhaps more rarely, one may find in the incidence of lymphadenotic blood pictures the cutaneous expressions as infiltrations and tumors, together with hyperpigmentation. These are true metastatic lesions. Second, one finds pictures in which the cutaneous lymphadenotic infiltrations antedate the chronic involvement of the blood and lymph glands. In this group are found large numbers of cases of exfoliative dermatitis of great chronicity, as well as isolated tumors and infiltrations. The third group includes particularly scaly erythrodermas and occasionally also localized infiltration in which transitory deviations from the normal are found in the blood stream, together with characteristic hyperplastic changes in the lymph nodes. In this group occasional recovery may take place with complete restitutio even after several months or years. In such cases I believe the skin pathology rather than reflecting systemic changes may by cutaneous insult act as a causative factor in the production of secondary lymphadenotic changes which simulate closely the typical primary cases.

The group of lymphoblastomas illustrate admirably the cutaneous manifestations of systemic disease. They represent a very small although important group which serve merely as a text upon which to elaborate the theme you have been good enough to ask me to discuss. One might with equal profit, if the time permitted, discuss the cutaneous manifestations of glycosuria, the unique changes in the skin incident to the disorders of fat metabolism such as occur in xanthoma, the atrophic changes of arteriosclerosis and senility, the remarkable changes in the integument with endocrinous disfunctions, and the subject of the skin as a reflector of emotional states. These and many others, if time permitted, could each be taken as a text to illustrate that, apart from its protective function, its thermostatic control, and its secretory and excretory functions, the skin admirably reflects and intimately takes

part in many, if not most, of the morbid processes of the body.

Discussion

William R. Williams
New York

Doctor Wile's paper is so clear and convincing that there is no place for controversy in a discussion of it.

It is important to define, as he so definitely does, the precise limitations of the terms relating to focal infections. Such distinctions foster more accurate thinking in dealing with the nature and the cause of lesions throughout the body as well as those within the realm of dermatology.

The changed point of view of dermatologists that tends to a broader outlook upon skin conditions and that links them with more general disturbances of the physiology of the body is obvious to those of us who are struggling with the problems of internal medicine. The knowledge of the dermatologist has become an invaluable aid to the internist.

Diagnosis has always been very difficult. Those surprising individuals who find it easy neither convince nor excite emulation on the part of the rest of us. We must elicit with great care the case history, the development of symptoms, the result of all the various examinations of the patient, including many investigations by the clinical laboratories, the x-ray and others.

After all this has been done it too commonly happens that we have failed to find enough that is crucial to justify a conclusion as to diagnosis, or even to direct a lead as to a line of farther search. If then, as we keep the patient under observation, we detect a skin lesion that can be seen and touched our hopes rise and we seek from the dermatologist a suggestion as to the nature and cause of the illness that may be associated with such cutaneous symp-

toms. Very often his discussion of the case is not only helpful to us but also is of great benefit to the patient.

In therapeutics, also, we listen to the dermatologist. When we send a patient to him it commonly happens that the patient is sent back to us for treatment along special lines and this treatment may prove to be indispensible for the restoration of health.

For these reasons we call upon the dermatologist much more frequently and with greater confidence than formerly when we were wont to ask chiefly for "the name of this lesion."

The internist has always focussed his attention on certain of the external symptoms and has relied upon them very largely for diagnosis. Conspicuous examples of such diseases are the usual exanthemata.

In conditions characterised by purpuric lesions great difficulties are encountered. Here a broad outlook is indispensible and we must consider such widely diverse causes as a hæmophilic tendency and very severe fatal sepsis. Then too there are the arthritic purpuras that no one has quite satisfactorily classified. Certainly here the visible lesions usually have their chief importance because of their relation to the underlying general causes.

Doctor Wile's remarks about the lymphoblastomatous states are of the first importance. This group of diseases frequently offers hard problems in diagnosis. There are so many atypical pictures that baffle us for a long time both in estimating the nature of the disturbance and in planning our therapeutic attack. Obviously we must learn from Doctor Wile that a study of the condition of the skin may give the earliest hint as to the diagnosis. The fact that two of his patients presenting a condition that was legitimately classed as leucæmic, have recovered tends to lighten a trifle the gloom that hung over the prognosis of this disease.

In conclusion I wish to thank Doctor Wile for his paper

this evening and to express to him the pleasure that internists feel in cooperating with those of his group for the welfare of our common patients.

Discussion

Howard Fox
New York

It is always a pleasure to listen to Dr. Wile's thoughtful contributions to dermatology and we are specially glad to do so tonight and thus show appreciation of our former Fellow in the Academy.

Dr. Wile has done well to confine his attention to two phases of tonight's subject. He has clearly indicated the diseases of the skin which can be properly considered as focal infections in contradistinction to those which might be called focal irritative processes. He has also helped to clarify the difficult subject of cutaneous lymphoblastomas, especially the universal erythrodermas, which we see fairly often and the significance of which it is so hard to determine.

In the time at my disposal I would like to give some idea of the immense number of cutaneous lesions which denote systemic disease. Only a portion of these lesions are however treated by the dermatologist, whose advice is sought for diagnosis and for treatment of particularly obstinate dermatoses. It is in the teaching of dermatology (including syphilis) that the relationship to systemic disease is manifest and it is largely due to this fact that the comparatively liberal share of a crowded curriculum is devoted to this subject.

There are numerous systemic infections which cause cutaneous lesions, many of which do not properly come under the class of focal infections. Leprosy is an important disease which is usually treated by the dermatologist,

though many of its lesions are neurological. Even leprosy might be classed as a possible example of focal infection arising in the nasal mucosa though this has not been definitely proven. Anthrax, glanders and the rare cases of diphtheria cutis are examples of systemic bacterial infections with lesions of the skin. Purpuric eruptions are invariably seen in typhus, cerebro-spinal meningitis and Rocky Mountain spotted fever. The exanthemata are systemic infections in which the cutaneous lesions are essential for diagnosis.

Fungous infections which cause severe systemic symptoms include actinomycosis and coccidioidal granuloma, while protozoal infections are represented by malaria which may be accompanied by both types of herpes, by pigmentation and at times by gangrene.

Infestations by Vermes may result in elephantiasis of the legs and scrotum due to the Filaria sanguinis hominis or the curious soft tumors caused by the Guinea worm. Tape worms from both human beings and dogs may occasionally produce curious swellings in the skin suggesting sebaceous cysts.

Impairment of the general circulation is shown not only by the common diffuse type of passive hyperemia with bluish, cold and clammy hands, but also by the reticulated type (livedo reticularis) which occurs chiefly in children or adolescents and usually disappears in adult life. Ordinary chilblains and lupus pernio have a poor circulation as their basis. Striking circulatory disturbances occur in Raynaud's disease and in peripheral syphilitic arteritis, which shows similar cutaneous phenomena.

Gastro-intestinal disturbances are often accompanied by skin lesions, the frequent association of hives and toxic erythemas with indigestion being recognized even by the layman. In the average case of rosacea there is a history of indigestion and the frequency of hypochlorhydria makes it proper to administer hydrochloric acid as a routine procedure. The effect of alcoholism is most apparent in the

severe hypertrophic type (rhinophyma) which is only seen in men.

The relationship of diabetes to certain diseases of the skin is unquestioned as shown in some cases by the effect of diet and the administration of insulin. The list of skin affections seen in diabetes includes pruritus, pigmentation, furuncles, carbuncles, eczematous lesions, rare cases of xanthoma and gangrene. Greenwood, from a study of 500 cases of diabetes, concluded that the diabetic patient showed a higher incidence of skin diseases including skin infections, than do other persons.

Disturbances of the lipid metabolism is represented by xanthoma tuberosum, though there are many gaps in our knowledge of this disease, valuable contributions to this subject having been made by our guest, Dr. Wile. We are ignorant of the real cause of this disease as nothing is known of the location or action of the mechanism which regulates lipid metabolism.

Various neurologic diseases may cause skin lesions, such as perforating ulcers of tabes and leprosy, the trophic changes of syringomyelia and the vesicles of herpes zoster. While many cases of the latter affection are undoubtedly infectious some are toxic such as those following administration of arsenic.

One of the most interesting examples of skin lesions related to mental disease is dermatitis factitia accompanying hysteria. While the diagnosis of a self inflicted eruption can usually be made by an expert on the appearance of the skin alone, in many cases it is easy to recognize stigmata of hysteria, such as absence of corneal and pharyngeal reflexes, areas of anesthesia and altered personality. Neurotic excoriations are usually seen in the neurotic type of individual and the same is certainly true of those who have the peculiar habit of pulling out the hair, without apparent cause (trichotillomania). The importance of the effect on the skin of emotional and nervous states, acting through the gastro-intestinal tract, has lately been

shown in an exhaustive paper by Stokes. The action of mental emotion upon common and juvenile warts, though the lesions themselves are due to infectious agents, has been scientifically demonstrated by Bloch.

The relationship of endocrine dysfunction to cutaneous lesions is capable of definite proof in only a few of them. In many others it is probable and in still others possible. Owing to our lack of knowledge of the physiology and pathology of endocrine glands, we must, as Bloch says, be content for the present to collect material and classify cases in which an endocrine origin is either certain or highly probable. The rest must be left to future research. A definite endocrine relationship is known to exist in myxedema, Addison's disease, and certain affections related to the gonads, particularly in women. The basis of acne in either sex is undoubtedly an endocrine disturbance. Dysfunction of the ovaries causes certain changes during menstruation and pregnancy including pigmentation, herpes gestationis, so called dysmenorrheal dermatoses and impetigo herpetiformis. Numerous cutaneous lesions occur with more or less regularity in Graves' disease and in hypopituitarism though none are absolutely diagnostic. There is strong evidence that scleroderma represents an endocrine disturbance and various observations suggest the same causation for vitiligo, some cases of alopecia and acanthosis nigricans, ichthyosis, cutaneous calcinosis and various atrophic conditions such as essential telangiectasia and striæ atrophicæ.

Of the pigmentary changes in the skin, other than those due to endocrine changes, jaundice is the commonest. Somewhat like jaundice in appearance is carotinemia, though it differs from the former in not affecting the sclera and in showing a tendency to certain localization. This disease which follows ingestion of food containing carotin is of special interest on account of the relationship or possible identity with vitamin A. Their effects at least are the same. Acanthosis nigricans, first described independently by Pollitzer and Janovsky, is usually accom-

panied (in the adult type) by malignant disease in the abdominal cavity. Pollitzer subscribes to Darier's theory that interference with the function of the abdominal sympathetic is the immediate link in the causation of cutaneous manifestations. The curious disease called pinta, though known by various names in the American tropics is an interesting example of one which has long been considered to be a fungous infection of the skin, but which now seems in all probability to be a systemic disease. My work on this affection in Mexico and Colombia which agrees with that of the Pinta Commission in Mexico, convinces me that neither aspergilli nor any other fungi are causative. In over ninety per cent of the cases the Wassermann test is strongly positive and marked improvement results from treatment by arsphenamin or bismuth. The suggestion that the disease is a spirochetosis affecting the vegetative nervous system seems reasonable.

Among so called deficiency diseases which present cutaneous lesions are scurvy, beri-beri and probably pellagra though the last word has not been said about this curious affection.

To the above mentioned groups of diseases could be added the long list of cutaneous changes of senility; pruritus associated with internal malignancy; hydroa vacciniforme which in the majority of cases is caused by the presence of hematoporphoryn in the tissues which sensitizes them to ultraviolet rays; sclerema neonatorum so often associated with dehydration following severe diarrhea and in some cases showing definite fat necrosis; and finally the important subject of allergy in eczema, urticaria and angioneurotic edema which will doubtless be discussed by Dr. Coca.

While certain diseases or abnormalities are confined solely to the skin, enough has been said to show that there are innumerable cutaneous manifestations of systemic disease.

Discussion

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Dr. Wile has remarked that one cannot in one evening cover the entire field indicated by the title of his discourse, and it may have been on account of his knowledge that I was to discuss this subject from the serological point of view that he has omitted from his paper formal mention of the group of dermatoses which are the cutaneous manifestations of allergic disease.

The cutaneous manifestations of allergy differ in their etiology, their mechanism and their histopathology. The clinical forms are:

First, urticaria. Second, atopic (inherited) eczema. Third, contact dermatitis; and Fourth, the cutaneous tuberculin reaction.

Dr. Wile has mentioned the toxic urticaria such as that produced by insect bites and stings, nettles and other direct irritants.

Allergic Urticarias are of two types—the reaginic and the non-reaginic.

The reaginic urticaria is seen, for example, when an overdose of an excitant of hay fever or asthma is injected into the subjects of these conditions. The reaginic wheal can be produced experimentally by the local intracutaneous injection of these excitants into asthmatic or hay fever subjects. It is always due to the irritative effect of the reaction between the specific excitant and the peculiar human antibodies known as reagins.

The non-reaginic allergic urticaria is often due to idiosyncrasies to foods, for example, strawberries; although the exciting cause is often not discovered. It is a remarkable fact that even the known excitant of non-reaginic urticaria usually fails to elicit a wheal upon its intracutaneous injection. The absence of reagins in the blood of

the subjects or of any other demonstrable sensitizing antibodies leaves us with no clue to the mechanism of this kind of urticaria.

The urticarial lesion does not depend upon any inherited abnormality of the skin; this is evident in the fact that any normal skin can be sensitized with the serum of a hay fever or asthmatic subject so that the injection of the specific excitant into the sensitized site will result in the formation of a typical wheal.

Atopic Eczema, on the contrary, seems to be due to an inherited abnormality of the skin because it is so often found in patients presenting a personal or family history of asthma or hay fever, and especially because of the evidence presented recently by Balyeat in an extensive series of cases, in which the influence of heredity is shown to be the same as that in the other atopic diseases. Whenever a specific excitant of the atopic eczema is found, reagins are always present in the blood.

Contact Dermatitis differs from atopic eczema, first, in the absence of an hereditary factor; second, in the fact that the sensitivity is confined strictly to the skin; third, in the absence of reagins in every instance; and fourth, in the fact that the excitants of it are all non-antigenic, whereas the specific excitants of atopic eczema are always antigenic.

The cutaneous sensitivity to tuberculin typifying the so-called hypersensitiveness of infection or infectious allergy is always dependent upon a previous infection with the corresponding bacteria. It is not subject, so far as we know, to an hereditary influence. The fully developed cutaneous lesion is said to resemble tuberculous tissue. All efforts to discover an antibody representing the specific mechanism of the tuberculin reaction have failed.

In conclusion, referring to Dr. Wile's suggestion that the skin manifestations of scarlet fever are due to a streptococcus septicemia, I may mention the fact that these

lesions in their typical development, including desquamation, have been produced by the injection of the sterile toxic filtrate of cultures of the streptococcus. They seem, therefore, to be an expression of an intoxication rather than the result of a localization of the bacteria.