

A HISTOLOGICAL STUDY OF THE SKIN LESIONS OF PELLAGRA.¹

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PLATE V.

Although, during the past decade in Europe and more recently in this country, pellagra has been the subject of careful study, the pathological phenomena have received but little attention. Certain investigators, working upon the hypothesis that the disease is due to the action of a toxine produced by some of the fungi ingested along with food stuffs, have made an extensive study of the metabolic changes in pellagra. These studies, together with empirical methods of treatment and prophylaxis and close observation of the results of these, have undoubtedly resulted in an advance in our knowledge of the disease. At present, however, it may be said that no constant pathologic lesions have been accepted as characteristic of the disease.

Clinically the disease is recognized by a syndrome of symptoms which may be classed as nervous or functional, trophic, and, to a less marked extent, organic. To many observers one of the most helpful signs in the diagnosis of the condition is the presence of skin lesions. All writers are more or less impressed by the fact that the appearance of the lesions varies markedly in different cases and, in general, comparatively little effort has been made to correlate the diverse manifestations. Dyer (1), in particular, speaks of the diversity in the characteristics of the lesions of the skin. He says: "The cases seen by me had certain points in common, but were sufficiently dissimilar to suggest the probability that the skin evidences of pellagra are more apt to be the direct reflections of the associated etiological factors than a separate integral symptom."

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He does not, however, note what associated factors he considers potent in the production of the lesions in the different parts of the body.

The resemblance of the gross skin changes in pellagra to those of erythema solare, have been noted by several observers, especially as the affected parts in pellagra are usually those which are either exposed to light or are less sufficiently covered than the remaining skin surface. The essential changes in the skin which bring about the clinical appearance of erythema, bullæ formation, and, finally, pigmentation and scaling, has received practically no attention. If it is possible to determine that the different phenomena are the result of essentially the same pathologic process, a decided advance will have been made. If, further, it can be shown that the lesions in different parts of the body are in similar tissues, the factor or factors causing these lesions remain to be investigated.

The presence of cutaneous lesions upon the arms, legs, or other parts of the body have been looked upon as essential phenomena of the malady. If, therefore, it can be shown that their character and situation is more or less accidental, and that their absence or severity depends as much upon secondary factors as upon the pellagrous process itself, the clinical diagnosis will be facilitated. In the explanation, too, of the cutaneous changes, a clue will be given as to the nature of lesions in the buccal, intestinal, and other mucous membranes.

The skin lesions in pellagra were first described by Casel (2) in 1735. Raymond (3) drew attention to the occasional rapid appearance of the skin lesions in patients already suffering from other manifestations of the disease.

Merck (4) describes the cutaneous lesion as a more or less diffuse erythema which subsequently became pigmented and scaly, the pigmentation and hyperkeratosis continuing as characteristic of the disease. He says that the tissues are frequently swollen as the result of an excess of blood and serum in the derma and, in consequence, wrinkling may occur subsequently. The lesions usually begin at the base of the fingers and upon the dorsum of the foot. In the former situation they spread and form a pigmented, scaly, triangular area, the apex of which is at the olecranon and the

base at the metacarpal-phalangeal joints. In a similar manner the lesions commencing upon the foot may spread toward the knee. Occasionally lesions appear on the face, around the neck, and down the front of the sternum (the so-called "Casel's neck-tie"). Other parts of the body, for instance, the buccal mucosa and genitals, are occasionally affected, but in these situations the lesions are not analogous to the dermatitis here described. In the severer forms vesicles or bullæ are present early in the process.

Babes and Sion (5) were the first to study microscopically the lesions of the skin. They describe a slight serous exudation and leucocytes in the erythematous stage, together with the presence of peculiar homogeneous metachromatic masses of what they considered to be coagulated albumin. These observers did not note changes in the nerves. In the stage of desquamation and hyperkeratosis, the papillae of the corium contained lymphoid and plasma cells, and a few mast cells. The sweat glands were atrophied. They consider that the thickening of the skin is the result of increased blood supply. They mention, also, the swollen appearance of degenerating elastic tissue fibrils in the superficial layers of the derma. In the cases which ulcerate, the phenomena they describe are the same as those observed in ordinary chronic ulcerations. Harris (6), confirmed, in general, the findings of Merck and Babes and Sion, stating, however, that an erythema does not always occur.

Roher (7) considers that pellagra is a granulomatous disease, basing his view upon the occurrence of collections of spindle-shaped and small round cells surrounding a central necrotic area. These nodules, he considers, are usually present in the vessels in the lungs and brain. Roher's observations have not been confirmed by others or by the author in the cases examined in the course of this study.

Merck's description of the gross appearance of the skin is sufficiently accurate, and no additions will be attempted. According to him, the essential features of the gross lesions are their limitation, usually, to the arms and the dorsa of the feet, early erythema or bullous formation followed by pigmentation, scaling, swelling, and wrinkling. By far the most common manifestation of the disease is the dry, pigmented, scaly skin.

Material and Method.—The material upon which these studies are based was procured from eleven cases autopsied in the Charity Hospital in New Orleans. The cases were diagnosed as pellagra by clinicians thoroughly accustomed to the different phases of the disease, and the autopsies were performed at periods of from two to eighteen hours after death. The tissues were removed, fixed in Zenker's fluid and 10 per cent. formaline, and were imbedded in paraffin. The sections were stained with eosin and methylene blue. For the determination of special tissues Mallory's connective tissue stain, Mallory's phosphotungstic acid hematoxylin stain, and Unna's orcein elastic tissue stain, were used. In the identification of pigment bodies, silver impregnation, after the manner of Levaditi, was resorted to.

Unfortunately there is little opportunity at autopsy to note the acute lesions. As a consequence no vesicles or bullæ were examined. The phenomena noted in several of the earlier cases have explained; however, the probable cause of these formations. In two cases the rash was erythematous in character; the other cases have shown a more or less marked pigmentation and scaling; in one case a brownish-black, dry, thickened mass of integument, measuring from 1 to 2.5 mm. in thickness was present over the dorsum of both feet.

Since the lesions in all the tissues that were examined are similar, a detailed description is given only of those cases which demonstrate the essential changes.

Case 1.—The patient was a white man, thirty-five years of age. At death the skin lesions consisted of a dry, pigmented scaliness over the dorsum of both feet, over the back of the hands, and below the olecranon of each arm. About the periphery of the darkened area over the forearm, a narrow zone of redness was present. Portions of the skin from the forearm and from the dorsum of the foot were studied.

The microscopical sections consisted of epithelium, corium, sebaceous and sudoriferous glands, etc., with a small amount of subcutaneous fatty tissue. The corium was normal in thickness and the skin appendages appeared negative. The superficial portion of the corium was very irregular in appearance, the normal papilliform arrangement being largely absent; the whole surface was, however, thrown into deep folds and projections. Over the outer surface of this papillary layer the epithelium was arranged. The deeper cells of the epidermis varied very much in character and followed the irregular outline of the fibrous tissue. In the *flatter* areas the columnar cells were shorter than usual in their long diameter. The prickle cell zone was composed of only one layer, and the stratum granulosum of but one or two layers of cells. In the *indented* portions the columnar cells were chiefly spindle-shaped, morphological differentiation between these and the underlying fibrous tissue cells being almost absent. Spindle-shaped columnar cells formed the greater part of the cellular thickness of the epidermis. The more superficial cells of this shape were prickled, there being no distinct polyhedral-shaped prickle layer. In the spindle columnar cells brownish-green pigment was present in the form of very minute granules; but it was practically absent in the cells covering the flatter portions of corium. There was a slight increase in the number of so-called Langerhans

cells (cells with long projections between and about the basal epithelial cells). Over the whole section there was a marked hyperkeratosis, the line of demarcation between the narrow zona granulosum and the keratinized layer being very clearly marked. The superficial layer of horny material is stained deep purple and appeared to be composed of four distinct layers. Beneath this purple-stained layer was a zone of about equal thickness consisting of pink-staining vacuolated bodies which had the general outline of cell bodies but were devoid of nucleus or other evidence of cell life. Throughout this area were numerous small, round and oval hyaline bodies similar to those described by Russell (8) in degenerating epithelium.

A similar hyperkeratosis was present throughout the walls of the hair follicles. It was especially marked beneath the skin surface. Diffusely throughout the corium, the tissues were separated by clear areas of edema.

In the superficial layers of the corium the blood vessels were increased in number and dilated. In the perivascular spaces collections of lymphoid cells were present. There were also a few lymphoid cells throughout the superficial layers of fibrous tissue. The papillary layer contained an unusually large number of cells, the nuclei of many of the fibrous tissue cells were large, and the protoplasm was irregular. Immediately beneath the epithelium were several cells whose morphology was equally suggestive of fibrous tissue and epithelial cells. These cells had fibers entering the deeper epithelial layers and contained no pigment. The sweat glands and nerves appeared normal.

Case 2.—The skin was from the dorsum of the foot of a negro man, thirty years of age. At autopsy, over both forearms and hands, but more especially over the dorsum of the feet, there was a marked thickening which was dry, scaly, and almost black in color. The sections consisted of epidermis, corium, and a small amount of subcutaneous tissue.

The epidermis was slightly thickened. It was divided distinctly into two layers. The outer layer, which was somewhat thicker than the inner, was composed of keratinized material; the inner layer was wrinkled, the distance between the indentations of the wrinkles measuring from .2 to 1 mm. There was no regular arrangement of the underlying corium, some places being flatter than usual, others showing deep projections of the epithelium. The cells of the Malphigian layer were normal in appearance and deeply pigmented, with the exception of one or two areas in which epithelial cells were placed below the regular epithelial border. The cells of the stratum granulosum were poorly differentiated from one another. The prickles on the cells in the deeper zones were very distinct. No mitotic figures were seen.

The upper layer of the corium was much rarefied and the collagenous fibrils were fine and sparse. There was an increase in the number of cells in this area, many of which resembled fibroblasts. Numerous pigmented, spindle-shaped, and branched cells were present. The smaller blood vessels were much dilated, and in the neighborhood of many of them numerous lymphoid cells were seen. The deeper layers of the corium were dense, the collagenous fibrils forming large masses, some of which were cloudy in appearance. Several of the larger vessels in the corium and in the subcutaneous tissue showed a separation of the muscle cells caused apparently by edematous fibrous tissue. In the hair follicles a marked hyperkeratosis was present. The musculares pili were swollen. The

sudoriferous glands were present, but were degenerated, as was evident from the presence of vacuoles and fine reddish granules in the epithelial cells. The nerves were apparently normal.

Case 3.—This patient presented the most aggravated form of the chronic lesion. Over the anterior aspect of both feet were large irregular areas of thick, dry, brown-black scaly eruptions. Similar eruptions, though less marked, were seen over the anterior aspect of both forearms just below the elbow and also over the dorsum of the hand, being especially marked in the triangular space between the metacarpal bone of the index finger and thumb.

Sections—The skin from the dorsum of the foot consisted of epithelium and corium, together with a small amount of subcutaneous areolar tissue. The epidermis measured 2 mm. in thickness. With the low power of the microscope it was seen to be divided into two distinct layers, the superficial layer being composed of degenerated keratinized cells devoid of nuclei and taking a pale purplish stain.

Throughout the entire length of the section the layer of epithelium lying upon the corium was distinctly differentiated from the keratinized layer. The basal layer of epithelium dips down to a marked extent into the hollows between the papillæ of the corium. In places the individual basal epithelial cells projected irregularly into the rarefied corium. The cells forming the Malpighian layer were apparently normal. No mitotic figures were seen. In general the cells of the prickle layer were normal and the prickles were distinct. Over the papillæ were seen but one layer of prickle cells and but two layers of the stratum granulosum. Between the cells of the stratum granulosum and throughout the keratinized layer were numerous hyaline red staining bodies. Over the prolongations downward, the number of prickle cells was increased and the cells of the stratum granulosum consisted of three to four layers. The cells of the Malpighian layer contained a large amount of pigment. The cells of Langerhans were increased in number, their prolongations also being apparently somewhat longer than usual. These cells were especially numerous between the columnar cells and immediately beneath the epidermis, where they were identical in appearance with the chromatophores in the corium. A moderate amount of pigment was seen throughout the entire epithelial structure.

The whole corium was edematous. The superficial layers contained a markedly increased number of fibrous tissue cells; the collagenous fibers were decreased in number and very fine. There were also numerous oval cells with a deep red-staining protoplasm and a somewhat bean-shaped vesicular nucleus (young connective tissue cells). Numerous chromatophores were also present, especially beneath the epithelium. Many of the oval pigmented cells contained but one or two moderate-sized, brownish pigment granules; others which were much longer and narrower were completely filled with a similar pigment. In many places the prolongations of these cells projected in between the basal epithelium. The blood vessels in the superficial parts of the corium were numerous and dilated. About the blood vessels were moderate numbers of lymphoid cells. The lymphatic spaces were markedly dilated. No plasma or mast cells were seen. In that part of the corium which showed rarefaction of the collagenous fibers, there was a complete absence of elastic tissue fibrils. Deeper down were a few very fine fibrils, and in the deeper layers, which appeared normal, the

usual arrangement of elastic tissue was seen. One blood vessel, situated in the subcutaneous tissue, had a diameter of 1.5 mm. and showed a markedly thickened wall. The thickening was due, in part, to an increase in the medial layer, which was hyaline in appearance and contained few cells, but more especially to a proliferation of the endothelial lining with degeneration of the cells nearest the internal elastic lamina. The internal elastic lamina was broken up and much twisted. Numerous smaller blood vessels in the subcutaneous tissue showed a similar though less marked change. The epithelium of the sweat glands had degenerated, as was evidenced by vacuolization and the presence of round hyaline-staining bodies. No hair follicles were seen in the sections examined. The nerves appeared normal.

An area on the forearm showing a slight scaliness was also studied. The section of this consisted of epithelium and corium. The corium was similar to that in the last section, with the exception that the increase in the number of cells in the superficial layer was less marked. The elastic tissue fibrils in the superficial layers of the corium were swollen and apparently increased in number. This increase is, however, relative, and the result of the change in the intervening collagenous fibers. The sweat glands were normal. The epithelial layer was extremely narrow. The keratinized layer was normal or slightly increased in thickness. In general, the normal papilliform arrangement was absent, although there was some wrinkling over the greater part of the section. The prickle cells constituted but one layer, and the spindle cells of the stratum granulosum formed only one or two layers. The Malpighian layer was normal.

Another section from a part of the forearm, showing moderately well-marked hyperkeratosis, presented an appearance similar to that noted in the section from the dorsum of the foot, although the increased thickness of the epithelial layers was less marked.

The edema present in all these sections cannot be the result of local changes, since all the tissues of the body were water-logged, caused, apparently, by a general degenerative change in the smaller vessels. The alterations seen in the vessels in the subcutaneous tissue can, therefore, hardly be attributed to the local process, since the whole body presented a more or less marked general vascular change.

The lesions here are to be traced to a primary degenerative change in the corium followed by a reactionary process. The first change consists in the degeneration of the collagenous fibers with consequent rarefaction of the papillary layer of the corium and dipping down of the epithelial covering in search of a firmer base. The author questions that the changes in the blood vessels (*e. g.*, the dilatation of those in the superficial layers of the corium) cause the degeneration in the connective tissue, as has been suggested. To

him it seems more probable that the capillaries dilate as a result of the loss of support consequent upon the rarefaction of the surrounding tissue. Certain it is that the formation of new vessels is an active process and part of the reparative change. As a result of this increase in vascularity, the epithelial cells proliferate with the formation of the hyperkeratosis, which is characteristic of the lesions.

Although somewhat retarded, the changes in the elastic tissue are similar to those in the fibrous tissue. There is, in the earlier lesion, a swelling of the elastic tissue, with some fragmentation, and this is followed by complete destruction, as is evidenced by the absence of elastic tissue in the more advanced lesions. Replacement of the tissue apparently begins in the deeper zones.

Following the degeneration there is an attempt at repair, as is shown by the increase in the number of connective tissue cells and the presence of fibroblasts. The fact that such a reparative process took place, although the disease itself progressed, proves that the essential factor causing the degeneration comes from without and that it is not the result of toxic bodies in the blood stream. The presence, too, of an enormous increase in the pigmentation of the epithelium and the large number of chromatophores suggests that this irritant is sunlight or, at least, the ultra-violet rays, since we know that the production of pigment is the attempt of nature to protect the underlying tissues.

Case 4.—A section from the skin of the forearm, showing moderate pigmentation and scaliness, was impregnated with silver, reduction of silver taking place only in certain tissues in the upper layer of the corium and in the epithelium. The cells of the rete Malpighii were almost completely filled with black granules corresponding in size to the pigment granules noted with simple stains, but the black material in these sections was more abundant than the pigment seen in the sections stained by eosin and methylene blue. The granules were arranged chiefly about the periphery of the cell, a clear zone surrounding the nucleus. Owing to the extreme clearness of the sections, the protrusions of the basal epithelial cells into the corium were very distinctly seen, some of the fine prolongations projecting twelve microns or more into the connective tissue layer. The cells of the prickle layer and stratum granulosum also contained a large number of fine black granules. In general, the cells of the Malpighian layer contained the most silver, the stratum granulosum and stratum lucidum almost as much, and the prickle cells the least. The branching cells of the epidermis were most distinctly demonstrated and filled with silver deposit. A

definite net-work formed by the projection of these cells was present in the deepest layers.

In addition to the epithelial cells, there were seen, throughout the papillary layer of the corium, numerous cells of irregular shapes which were more or less filled with black granules. These cells were chiefly irregularly spindle-shaped, some were circular, and others were oval. In form these black cells resembled closely the chromatophores found in the sections stained with eosin and methylene blue; there were, however, a larger number present in this section than in the sections above described. It is noted, also, that, although the granules in many of these cells were very dark, they were slightly more brownish in color than the intense black granules in the epithelium.

Sections from two portions of skin from the first patient (p. 101) were similar to the one just described. In neither of these, however, was the gross lesion so marked and in neither was there such a large number of black cells in the corium, although both contained many cells with black granules. In the lesion showing least hyperkeratosis and least subepithelial rarefaction of the connective tissue, the number of cells with granules was smaller than in the one in which these changes were most marked.

The irregularity of the outline of the basal epithelium upon the connective tissues and the number and length of the prolongations in all sections varied, apparently, directly with the rarefaction of the corium; that is, with the loss in connective tissue fibrils.

Tissues from other cases, sectioned and infiltrated with silver, all showed similar changes, the number of granulated cells in the epidermis varying in all cases according to the extent of the rarefaction.

Apparently, then, in sections impregnated with a soluble silver salt, which was subsequently reduced, the pigment granules in the epithelium were found to be filled with metallic silver. The chromatophores of the corium and branching cells of the epidermis also contained particles of the metal. Not only does the brownish pigment, which is seen by other methods, take the salt in a manner which permits its reduction, but other bodies in similar cells also present the same reaction. In the absence of a like appearance in

other tissues, it seems probable that by this means we have a method for demonstrating the pigment bodies before they have become brown as well as after they have lost their color, as in the keratinized layer. This idea is also borne out by the larger number of black cells in the corium, demonstrated by the silver method, than brown pigmented cells seen in sections stained by simple methods.

In 1908 Schrieber and Schneider (9), as a result of observations based upon the preparation of foetal eyes by means of the Levaditi method, came to the same conclusion with reference to the deposition of silver in a reducible form in cells which contained melanin and also in cells in which the pigment as such had not appeared. They stated that not only colored pigment bodies, but also the antecedent colorless material, as well as the end products of the destruction of melanin, were capable of demonstration by means of this method. My own observations appear to corroborate their findings and conclusions.

The increase in pigment is one of the most constant changes in all skin lesions of pellagra. It is marked in those lesions which show the most advanced gross and microscopic lesions as evidenced by the hyperkeratosis and rarefaction of the corium. The pigment, which is greenish-brown in color, does not contain iron in a demonstrable form, occurs in small granules, and is, apparently, the same in both epithelium and mesoblastic cells. Nowhere is found an appearance suggestive of hematogenous pigment.

Councilman and Magrath (10) and others consider that the formation of pigment in such lesions is primary in the cells of the corium and is thence transmitted to the epithelium. The view has also been brought forward that the chromatophore of the corium derives its pigment from the epithelial cells. This latter view, however, may be almost excluded, since in the frog and other lower forms of life, chromatophores similar in appearance to those in the corium and containing a pigment indistinguishable from that in the skin, are present in the heart and other internal organs which contain no epithelial tissue. In the retina, a tissue composed exclusively of epiblastic cells, the production of pigment is more marked than in any other tissue of the body, proving the potentiality of epithelial cells to form melanin. The author considers, therefore,

that both epithelial and mesoblastic cells produce an autochthonous pigment, and that there is no reason for believing that the pigment, after production in the latter, is transmitted to the epithelial cells. It would be hard to explain the manner in which pigment so far removed from the surface could be directly turned over to the epidermis. The fact that pigmented mesoblastic cells lie, in some places, in very close proximity to the epithelium is explained more readily by considering that they occupy this position for the reason that the nearer the pigment lies to the surface of the body, the greater will be the protection to the susceptible connective tissue, than by assuming that they are passing their prepared melanin on to cells which appear quite capable of producing pigment.

Ehrmann (11), as the result of a comprehensive study of pigment production in the lower forms of life as well as in human embryos, considers that all pigment found in the adult epithelium has been primarily produced in cells which he says are neither connective tissue cells nor epithelium, and which he calls "melanoblasts." These "melanoblasts," according to his ideas, include the chromatophores of the corium as well as the branched cells seen in the epidermal layer, namely, the so-called Langerhans cells. He states that they are present in the latter position as a result of wandering from their original situation between the epiblast and mesoblast. As there appears to be no means of proving the source of the Langerhans cells of the epidermis, in this paper their histogenesis will not be discussed: nevertheless, as there is apparently undoubted evidence of the ability of the epithelium to manufacture pigment, I see no reason for using the term melanoblast, this term suggesting the future transposition of the pigment.

The degeneration and the reaction of the superficial layers of the corium, as shown by the loss in collagenous fibrils and degeneration in the elastic tissue, together with an increased cellularity and infiltration of the corium with lymphoid and plasma cells, is evidence of the effect of some irritant acting upon these tissues. The presence of an enormous increase in the pigmentation of the epithelium and, in particular, in the appearance of pigment-bearing cells in the corium is at least suggestive that this irritant is light. The presence of lesions uniformly and primarily in areas which are uncov-

ered or which are insufficiently protected against the sunlight, violet, or ultra-violet rays, is also evidence in favor of the importance of light in the production of the degeneration which precedes the reactive changes.

Several observers (12) have been successful in inducing an acute onset of erythema or vesicles by exposing to sunlight patients who, although suffering from pellagra, did not show skin manifestations. The fact, as demonstrated by Fox (13) and others, that once the lesions have appeared, protection from light is not effective in the cure of the conditions is explained by the fact that, with the exception of the initial lesion, the histologic phenomena are those of reparation rather than progressive degeneration.

If it be accepted that the changes are the result of the action of sunlight, some special predisposing factor must be present rendering the tissues less resistant than normally. Either this change takes place in the connective tissue of the corium or it is the result of some physiological alteration in the epidermis whereby the sub-epidermal tissues are not sufficiently protected.

In the early lesions of pellagra characteristics are noted which are histologically similar to those in an erythema caused by exposure to excessive sunlight and examined after the healing process has begun. There is dilatation of the blood vessels and lymph spaces together with a moderate serous exudate. Babes's (5) finding of polymorphonuclear leukocytes in cases showing vesicles is easily understood in the light of our general knowledge of the reaction of the tissues to injuries which are sufficiently acute. The meta-chromatic bodies described by him are probably degenerated collagenous material, and this we should expect to be most marked in severe lesions. In the material studied in this series, these early changes must be, in part, inferred. At first the epidermis is atrophied, and the prickle cells and stratum granulosum are decreased in thickness and show a tendency toward early keratinization.

Following the primary degenerative changes there is a reactive process consisting of a dilatation of the blood vessels and hyperplasia of connective tissue cells. As the disease progresses, in the superficial layers of the corium an infiltration of the perivascular tissues with lymphoid cells is seen. An increased

activity on the part of the epithelium takes place, together with an augmentation in the production of pigment. Although the deeper layers of epithelium are found to be growing rapidly and show a tendency to dip down into the rarefied corium, the upper layers, especially the stratum granulosum, show early degenerative changes resulting in the hyperkeratosis. The nerves at no time showed evidence of degeneration or fibrous tissue proliferation.

As pointed out by Wolbach (14) in his studies on X-ray dermatitis, the changes in the epithelium are apparently secondary to those in the corium. The histological appearance of the lesions of pellagra are, in many respects, strikingly similar to those described as the result of the action of the Roentgen light. There is the same degeneration of the collagenous and elastic tissue fibrils with secondary rarefaction and increased cellularity. These changes are followed by dilatation of the blood vessels, atrophy of the sweat glands, and, finally, by hyperplasia and rapid keratinization of the epithelial structures. The analogy between these two lesions is so marked that we are justified in considering that the direct agents in their production are probably similar.

Councilman and Magrath (10), from their investigations on xeroderma pigmentosa, in which, again, changes were found, similar to those in pellagra, are of the opinion that xeroderma develops as the result of some congenital condition, in consequence of which children are especially susceptible to the action of some irritable agent which is responsible for the development of the lesions. They consider that in all probability this causitive agent is sunlight, especially the ultra-violet rays. They refer to the apparently undoubted relationship between the formation of pigment and the action of light. According to their observations, atrophy of the corium is an essential lesion of xeroderma pigmentosa and is primarily responsible for the subsequent hyperkeratosis and tumor formation.

It has been demonstrated by physiologists that if the sun's rays be examined spectroscopically, after having passed through the cornea or other colorless epithelial tissue, certain rays at the violet and ultra-violet end of the spectrum are cut off. It is also known that the violet and ultra-violet rays are harmful to animal tissues,

and that they are apparently particularly harmful to connective tissues. If, as a result of an altered metabolism in the epithelial covering of the body, the substance, as yet not isolated, which normally filters out these ultra-violet rays, is not formed, the underlying connective tissue will be subjected to the detrimental action of these rays.

In my opinion it is more reasonable to suppose that the degeneration in the corium in both pellagra and xeroderma pigmentosa, is due, not to predisposition on the part of these tissues to the action of the violet and ultra-violet rays, but to an altered physiological function on the part of the epithelial cells, causing these to allow the passage of rays injurious to the subepithelial tissues. In exposure to the action of the Roentgen light, on the other hand, the surface of the body is influenced by rays against which there is no normal resistance on the part of the epithelium, with the result that there is a destruction of the upper layers of the corium.

The series of phenomena leading to the dermatitis of pellagra are, then, primarily, alteration in metabolism of the epithelial cells, whereby their power of preventing the ultra-violet rays from reaching the connective tissue of the upper layers of the corium is destroyed; as a result, the subepidermal tissues are subject to the action of these rays and are injured. The resulting degenerative process is followed by a stage of reparation accompanied by an increased vascularity, in consequence of which the epithelium proliferates rapidly with the development of the hyperkeratosis which was noted clinically.

It may be, also, that a similar loss of resistance on the part of the mucosa of the intestines, analogous to that found in the skin, predisposes to the development of lesions with symptoms referable to the intestines. Dysentery, or, at any rate, severe diarrhœa, is commonly met with during the course of the disease, and frequently the evidences of an acute colitis are found at autopsy. As has been shown by observations in our laboratory, the dysentery bacillus was in many cases the cause of the intestinal disturbances so frequent in the course of pellagra. It is now believed that the acid producing dysentery bacillus is present in many individuals as a normal inhabitant of the intestinal tract. It is, moreover, reasonable to

infer that, as the result of any circumstance leading to a lessened local resistance of the parts, autoinoculation takes place and the organisms develop pathogenic properties. This supposition is borne out by common experience. Other organisms, also, such as the colon bacillus and streptococcus, are recognized as being potent to induce, under certain conditions, catarrhal and other inflammations of the intestines. It seems unreasonable to suppose that the essential factor in the production of pellagra, whatever this may be, should produce a lessened resistance to one irritating body only. Up to the present, no histological changes in the intestines have been described to account for the occurrence of the diarrhoeas, and although it is possible that a functional insufficiency on the part of the nerve plexuses may be the cause, this explanation is not very satisfactory. On the other hand, there is cause to believe that, whereas, in the case of the epidermal covering of the body, this loss of resistance is against the ordinary irritating agent to which it is accustomed, namely, sunlight, the loss of resistance upon the part of the entodermal lining may, in a similar manner, be against an irritant to which it is normally subjected, namely, the bacterial flora of the intestinal tract and their toxines. In a similar way functional changes in the epithelial cells of the mucosa in the mouth and genitals would cause the lesions described in these situations. If this theory be accepted, the occurrence of at least two important evidences of the disease can be explained, and also the lack of either or both in any individual case.

Pellagra is a disease characterized by certain organic changes in the skin and intestines, but more especially by certain nervous manifestations, for which, up to the present, no constant histological factors have been recognized. If the changes in the skin be explained primarily by an altered function on the part of the epithelium, may it not be that the symptoms referable to the nervous system are the result of an altered metabolic activity of the nerve cells, which are also epithelial in origin? Such an explanation, in the absence of histological alterations in the nervous system, seems tenable.

It is my belief that pellagra is a disease in which, under the influence of some toxic substance or microorganism, there is an altered function on the part of the epithelial tissues throughout the

body, rendering them less resistant than normally to the action of different injurious agents. Whether the altered function on the part of the epithelium be the result of the toxic action produced by low forms of vegetable life outside the body or the action of some unknown microorganism or protozoon in the body, need not be discussed in this paper.

SUMMARY.

The cutaneous lesions in pellagra consist of an early erythema, or, in occasional cases, of vesicles or bullous formations which are followed by hyperkeratosis and pigmentation, resulting in a dry, dark brown scaliness. These various lesions are similar to those normally produced by the action of sunlight, but are much more marked. The histological phenomena of the erythematous and bullous stage are those of a mild acute inflammatory reaction, together with a degeneration in the superficial layers of the corium.

Following this degeneration, which involves not only the general connective tissue but the connective tissue of the blood vessels, there is a reparative change evidenced histologically by an increased cellularity of the corium and the presence of fibroblasts. The capillaries also are increased in number and much dilated. Apparently as a result of this increased vascularity of the corium, there is an increased proliferation of the epithelium resulting in a thickening of the epidermis. This increase in thickness of the epithelial layer is especially marked in the prickle cells and the stratum granulosum. In the later stages, in an effort to secure a firm basement membrane, the epithelium is seen to dip down deeply into the rarefied connective tissue. About the blood vessels during the reactionary process are found collections of lymphoid cells, a few plasma cells, but no mast cells or eosinophiles.

That the irritant producing the degeneration in the corium is sunlight in the presence of some predisposing factor, is suggested by the enormous increase in pigment formation in the epithelial cells and by the large number of chromatophores in the superficial layers of the corium. This pigmentation is autochthonous in both types of cell. There is no reason for believing that the pigment is formed in the cells of the corium and thence discharged into the epithelium, or that the reverse process takes place.

The predisposing factor inducing the changes in the corium is, apparently, a lessened resistance of the epithelium to the violet and ultra-violet rays, due to some metabolic insufficiency on the part of the epithelial cells.

Further observation may justify the conclusion that throughout the body, pellagra is a disease essentially of the epithelium, including the nervous system, this pathological condition manifesting itself by an insufficient or altered function.

In conclusion I wish to express my thanks to Dr. Duval and the clinicians of the Charity Hospital for many helpful suggestions.

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EXPLANATION OF PLATE V.

FIG. 1. Photograph of the hands of a pellagra patient who had worn rings. Those portions of the fingers protected from the sunlight are free from the skin lesions. I am indebted to Dr. C. C. Bass for the use of this photograph.

FIG. 2. Section of skin from case 3, showing hyperkeratosis and dipping down of the epithelium into the rarefied corium. Note the extreme dilatation of the vessels in the superficial layer of the corium.

FIG. 3. Specimen prepared by Levaditi's method, showing a large number of pigment cells in the corium.



FIG. 1.

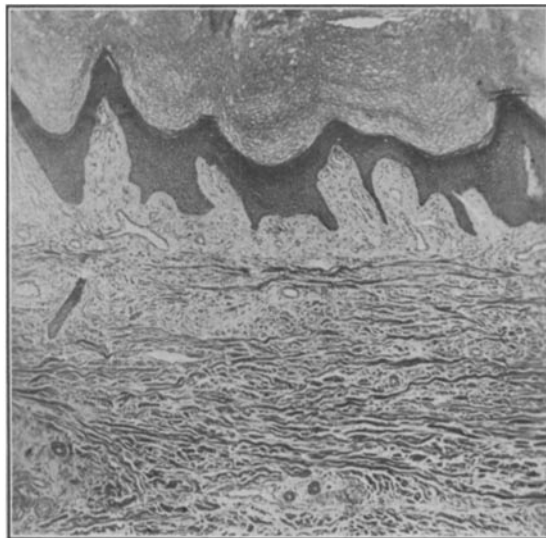


FIG. 2.

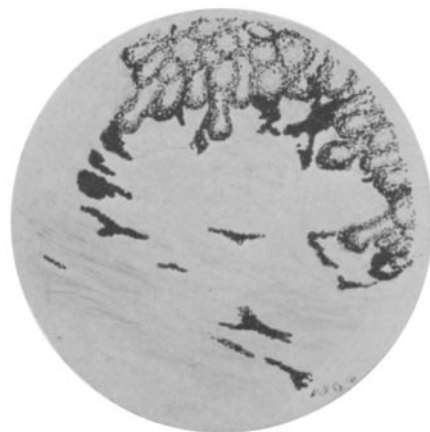


FIG. 3.