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ORIGINAL MEMOIRS.

MULTIPLE CARCINOMATA FOLLOWING CHRONIC X-RAY DERMATITIS.*

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THE recent death of Prof. Fuchs of Chicago from metastatic X-ray carcinoma leads me to report in detail the history and present condition of another case of multiple epithelial carcinomata which has been under my care since 1897.

In delaying this report until the present time I have been greatly influenced by my personal regard for the patient; but the above case, the fourth fatal one in the United States, and a slowly increasing list of undoubted instances of X-ray carcinoma, here and abroad, makes it imperative that the attention of dermatologists and surgeons should be thoroughly aroused to the great *danger* of *all persistent X-ray ulcerations* and especially to those which have followed, with a few years interval, the chronic skin lesions of the earliest operators.

The first published account of the injurious effects of the X-ray with which I am familiar, was a paper by Marcuse,

* Read by title at a meeting of the American Surgical Association held at Washington, May, 1907.

"Dermatitis und Alopecie nach Durchleuchtung mit Röntgenstrahlen" in the Deutsche med. Wochenschrift, No. 30, 1896.

From 1897 the literature of this subject has grown each year. The earlier articles dealt with the immediate effects of the X-rays, dermatitis and burns; then it soon became recognized that these lesions were most excruciatingly painful and extremely slow to heal; further experience showed that some lesions closed with great difficulty only to break down again and again, and finally formed chronic ulcers:—then came the first report of cancer developing in a chronic ulcer, and finally the first death from metastatic carcinoma.

In an excellent article written by Dr. Richard Mühsam, and published in the Archiv für klinische Chirurgie, 1904, No. 74, "Über Dermatitis der Hand nach Röntgenbestrahlung" may be found a full bibliography of the literature up to that time and a brief résumé of the histology of the characteristic lesions with which we are unfortunately too familiar.

CASES OF X-RAY CANCER.

I and II.—In 1903 Sick reported two cases, both in X-Ray operators, the first, after years of severe changes in the skin of the arms, neck and face, finally developed an ulcer upon the back of the hand, which soon took on the typical appearance of a carcinoma, and required amputation at the shoulder joint.

The second, with similar skin lesions of six years duration, also developed a chronic ulcer on the hand, which was excised and showed upon microscopic examination the typical picture of a skin cancroid, with cancer nodules in the cutis—the material from these cases was examined by Unna.

III.—Dr. Blacker of England, mentioned in *Medical Record,* Oct. 22, 1904, for a long time suffered from an X-ray burn of the hand which was neglected till the cancer which had developed had extended up the arm and involved the axillary glands, when it was too late for operation.

IV.—Clarence Daly. Personal communication from Dr. Samuel Lloyd of New York and Dr. W. B. Graves of East Orange, N. J.

This patient was very seriously burned on both hands years before, in working with X-Ray tubes. He was treated at many different hospitals. Skin grafting was tried without result, until finally epithelioma developed on the right hand and on the base of the little finger of the left hand. At the time of Dr. Lloyd's first examination the right hand was infiltrated with carcinoma and the axillary glands were involved.

The arm was amputated at the shoulder joint and the glands above and below the clavicle removed. Amputation of the left hand was advised but refused. This was August 8, 1902. The ulceration gradually increased in size and depth and the left arm was amputated by Dr. Graves on March 16, 1904. Death followed from mediastinal recurrence in October, 1904.

V.—Epithelioma of finger of X-ray machine manufacturer (communication from Dr. Lloyd).

VI.—Personal communication from Dr. W. B. Coley, Surgeon of Rochester, New York. For five years had been using X-Rays continuously. Ulcerations present for six months on the backs of both hands, specimens from which were examined by Dr. Welch and found to be undoubted epithelioma. Amputation of right hand above wrist and thorough excision of ulceration on left hand October 10, 1904. Subsequent recurrence in axilla and death.

VII.—Bertha Fleishman, San Francisco, death. Quotation from New York *Sun*, April 24, 1907.

VIII.—Foulterton's Case. *Lancet*, May 6, 1905. At a meeting of the Pathological Society of London, Foulterton reported the case of a surgeon who began systematic work with the X-rays in 1897. In May, 1903, had a severe attack of dermatitis, blistering of the skin on back of index and middle fingers of left hand, ulcers resulting healed in about four months. New skin was thin and tender and showed nevoid looking patechiæ. The nails fell out and new ones were hard and brittle. In December, a second attack of dermatitis again caused ulcers on first and second fingers. Ulcers on index finger remained open and in April, 1904, began to assume a malignant character. In September of that year, finger was amputated at the metacarpo-phalangeal joint. Sections of index finger showed typical squamous celled cancer.

IX.—Personal communication from Dr. L. L. McArthur of Chicago, dated April 26, 1907. Patient was the first photographer to develop X-ray plates in America. "He early developed the chapped and fissured hands which go with the exposure to the ray, *especially* in those who combined the development of their plates with their X-ray work. For the last three years he has been having, from time to time, minor surgical procedures in the way of removal of a phalanx now and then, until three fingers of the right hand and two on the left had been sacrificed. After various plans of local treatment and a trip to Europe in search of remedial agents, he came to me for the first time with an enormous axillary involvement. This was indubitably squamous celled carcinoma. The radical operation with removal of portions of the pectorales and a dissection of the axilla en bloc failed to effect an arrest of the trouble. Recurrence took place very promptly, and within three months again filled the axilla and involved the supraclavicular glands. Deeming it hopeless to subject him to further surgical interference, trypsin injections were given, with a resulting liquifaction of the axillary mass to a nonpurulent, sero-sanguinolent fluid containing immense masses of epithelial cellular detritus, as was shown on opening and draining the same.

After lingering for six weeks he finally succumbed to a multiple metastasis on April 23, 1907."

X.—"The second case was that of a physician who combined his electrical therapeutics from his static machine with the taking of pictures of his surgical cases. He, too, developed his own plates and constantly had his hands stained with the photographing solutions. He had the usual history of a chronic dermatitis with ulcerative processes that refused to heal, and required removal of the terminal phalanges on his left index and middle fingers. When he came to me it was with a typical epithelioma on the remains of the left index finger, and numerous senile keratoses on the back of both hands. I amputated the finger, which microscopic section demonstrated to be carcinomatous. I removed by a deep shaving-like cut the senile keratoses and grafted the same. I secured primary union in the grafts, had a mild infection along the stitch line in the amputation and an aseptic result in the axilla which I cleaned out radically though no glands were distinctly palpable at the time of the operation. No metastases were found in those lymph glands removed from the axilla which were examined. At present he is in good health."

From a careful search through the literature and some personal inquiry these ten cases of undoubted X-ray cancer are all which I have been able to find. I have purposely excluded a few recorded cases of carcinoma developing in lupus tissue after Röntgen treatment, and one or two cases of epithelioma, following burns, for I wish to limit the question under discussion to cancer resulting in the X-ray operators who for years have followed their work in spite of previous inflammations of the skin and persistent lesions.

If my case be included, there are eleven cases, of which five have proved fatal, and as one of Sick's, reported in 1903, had to submit to a shoulder joint amputation, it is probable that this result was also a fatality. The prognosis in X-ray cancer would therefore appear appalling if it were not for the very great likelihood that all fatal cases have been published while no record has been made of the much larger number of sufferers, who after excisions or minor amputations have as yet shown no evidence of recurrence. Though it is obvious that surgeons will very naturally hesitate, in the case of a brother physician, to add publicity to misfortune, there are so many unfortunates throughout the country, suffering from chronic lesions of all grades of severity, that it is now a duty

I think for all who have charge of these cases to publish their experiences in order that our knowledge of this difficult subject may be increased.

The case which I have to report is that of an X-ray operator, who, as a *young man,* first began X-ray work with a large static machine in March, 1896; after October of the same year a powerful twelve-inch coil was used. Exposure lasted for several hours each day, at a very *short distance* from a *low vacuum* tube. About the middle of November hands became red and dry, and in a few days very painful and greatly swollen. Under black-wash the dermatitis subsided, but the finger nails first became dry and striated, then softened and finally sloughed off (the patient felt convinced that this condition of the nails was greatly aggravated by the use of chromic acid in development of the X-ray plates). In spite of the fact that one per cent. orthoform ointment had to be used almost continuously to relieve the intense pain, work was continued until April 1, 1897, when the onset of another very severe dermatitis, with the formation of enormous blisters, and pain "beyond description," necessitated ward treatment for a month. White-wash gave considerable relief. All forms of treatment by ointments, powders, and washes, which Prof. J. C. White could suggest, proved useless; the chronic ulceration which now involved most of the backs of the fingers of both hands refused to heal. Orthoform ceased to relieve the pain. At the suggestion of the patient Reverdin grafts were applied on July 10, 1897, to the tip of the left forefinger, which presented the appearance of a sluggish ulcer, with rather exuberant granulations and unhealthy-looking edges. These pin-point grafts "took" and grew. Accordingly on August 13, 1897, under ether, all the ulcerated areas were cleaned up, shaved down to an apparently normal base, and Thiersch-grafted; fourteen different grafts being applied. Contrary to all expectations, the great majority of these grafts adhered and "*have never broken down since,* nor do they show the eczematous condition, which now exists on the areas not grafted." "Pain ceased absolutely from the time of operation, and areas then grafted are in good condition to-day." "Epithelioma has *never* developed in any graft which *completely* took at this time." (I quote from a letter which the patient wrote me in 1905.)

Though all X-ray work was stopped for a year ulcers developed upon the fingers, and again in spite of all treatment refused to heal until excision with skin-grafting was carried out; after several operations all the chronic lesions were successfully grafted or healed spontaneously, except some very persistent ulcers on the ends of the ring fingers of both hands and the little finger of the right hand, which in spite of six or seven operations refused to heal.

In July, 1902, the persistent ulcerations at the tip of the ring fingers were again excised and grafted. The grafts did not take. The specimens sent to the pathologist were misplaced and not until October, 1902, was the report received that both ulcerations showed unmistakable evidence of carcinoma. In the meantime these finger tips had become excessively sensitive and painful and showed an angry-looking ulcer, with somewhat raised and indurated edges. On or near October 31, 1902, both of the ring fingers were amputated at the knuckles.

I. The ulcer on a ring finger is shown in Fig. 1.
II. The gross appearance under a low power in Fig. 2.
III. The microscopic picture in Fig. 3.

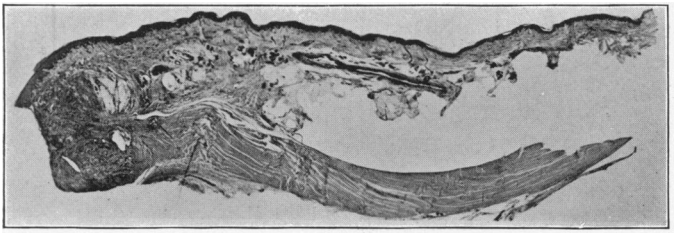
During the period from October, 1902, until June, 1905, a dozen or more operations under ether were performed—amputation of the middle finger of the left hand, removal of the tips of the second and third fingers of the right hand, and numerous excisions of keratotic areas or chronic ulcerations on the dorsum of the remaining fingers or backs of the hands. Figs. 4 and 5 show the conditions of the hands.

In June, 1905, for the first time in eight years, the patient was free from pain and no dressings had to be worn. Both hands could be placed in his trouser pockets. The left hand was soundly healed; the right showed one superficial ulceration at the base of the third finger, with considerable thickening of the skin about it and numerous other keratotic areas. Unfortunately during the summer the favorable condition did not endure, but steadily, though slowly, several places on both hands began to break down. Under date of November 8, 1905, the following notes were made: "For three months following a slight bruise and subsequent infection, there has been a great deal of pain in the tip of the stump of the little finger on the right hand; gradually an ulcer formed,

FIG. 1.

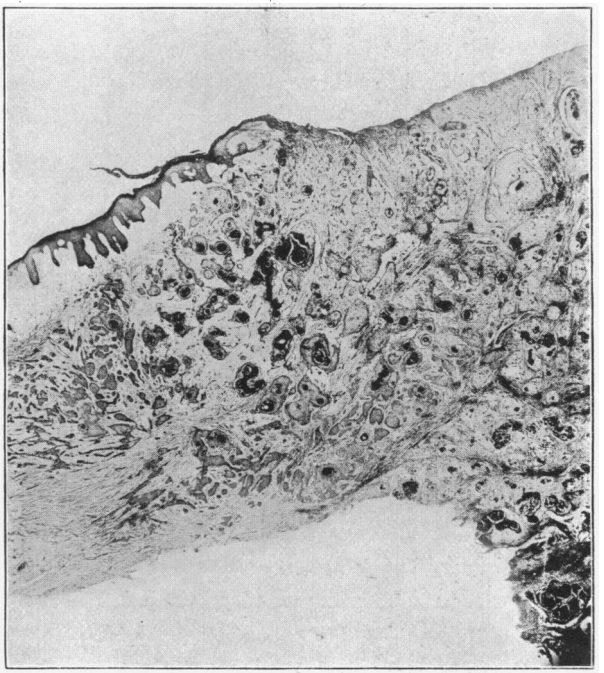
Ulcer at end of amputated ring finger, Oct., 1902.

FIG. 2.



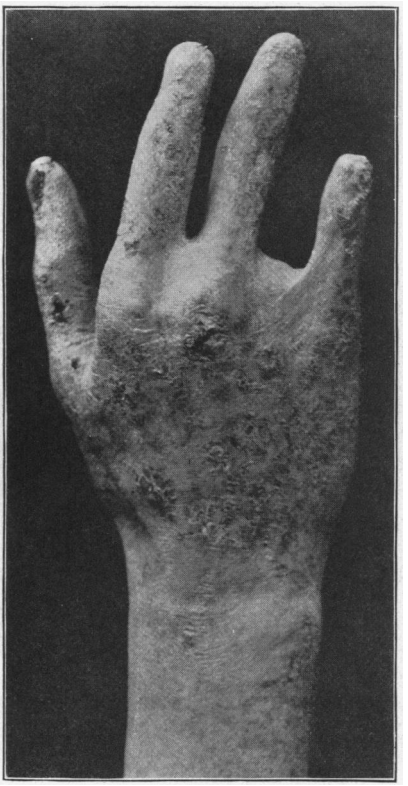
Ring finger, 1902. Low power.

FIG. 3.



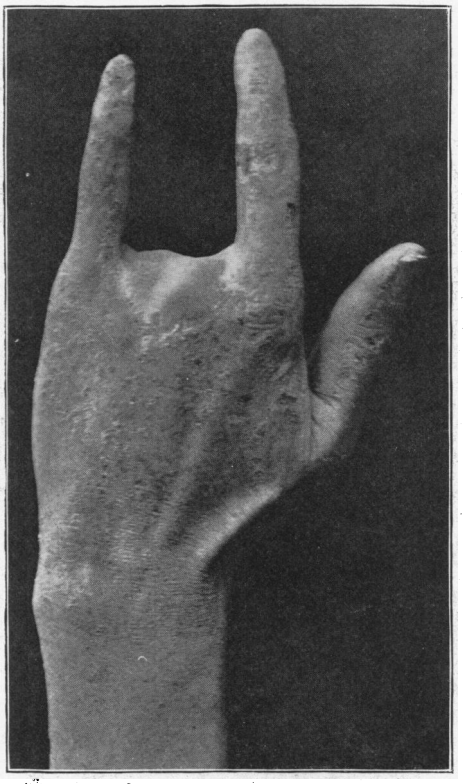
Ring finger, 1902. High power.

FIG. 4.



Condition of hand, June, 1905.

FIG. 5.

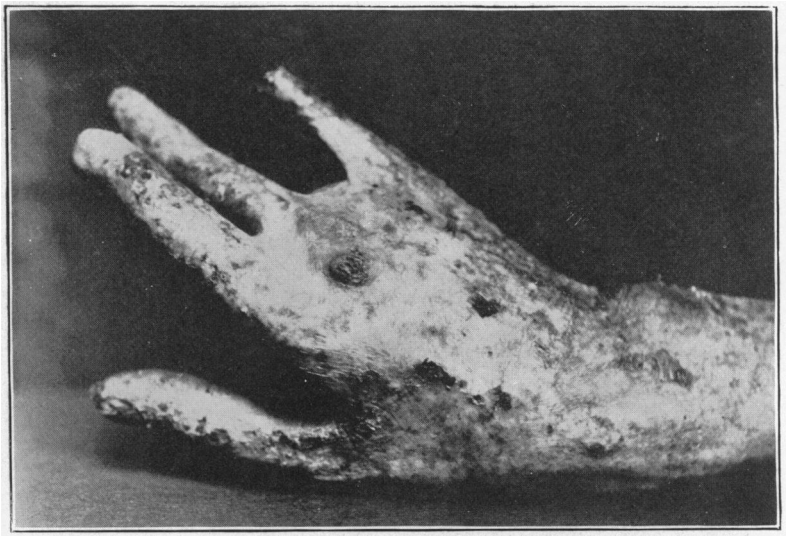


Condition of hand, June, 1905.

FIG. 6.

Ulcer at end of little finger, Nov., 1905.

FIG. 7.



Keratoses on back of hand. Carcinoma at base of middle finger. Nov., 1905.

about the size of an old-fashioned three-cent piece, which looks very angry and resembles those found in the ends of the fingers in 1902."

Figs. 6 and 7 show the condition. At operation the end of the little finger was removed and a suspicious ulceration at the base of the third finger throughly excised. The back of the forefinger over the second phalanx showed a superficial unhealthy-looking ulceration which involved the old graft; on the ulnar side of this finger were several macerated warts, which had been excessively sensitive and painful. On the radial side were numerous cracks and fissures, with some keratoses, but nothing suggesting anything malignant. All these lesions were excised, as were seven other places on the backs of the hands and Thiersch grafts were applied. All of these grafts took except those on the back of the forefinger, which sloughed and left exposed the white and glistening but not necrotic aponeurosis of the extensor tendon. Dr. Wright's examinations showed that the ulcer on the end of the little finger was not malignant, but that the specimen removed from the base of the third finger was a typical epithelioma. One or two others suggested beginning cancerous degeneration.

During the winter and spring of 1906 these areas broke down further, and the middle joint of the first finger, from sloughing of the extensor tendon became flexed and discharged synovial fluid. For a time there was some infection, but this soon passed away. During the summer the patient suffered much from this persistent ulceration. The back of the middle finger also began to break down.

In November, 1906, under ether, the ulceration and unhealthy granulations on the back of the first finger were again excised. Examination by Dr. Wright of frozen sections showed epithelioma, or at all events invading epithelium; accordingly the excision was extended into apparently sound tissue at the margins, and the base was removed down to the bone. The dorsum of the third finger was thoroughly scraped with the knife, the tip of the little finger of the left hand removed for persistent ulceration, and several suspicious areas excised. All open surfaces were grafted successfully except the backs of the second and third fingers. A subsequent report from Dr. Wright confirmed his diagnosis of superficial epithelioma in the tissues

removed from the back of the forefinger; the ulceration on the third finger was negative.

By January 1, 1907, there was some evidence of healing from the edges in both ulcerations. The patient wished very much to delay radical treatment of the first finger, for as the third finger was stiff, amputation meant almost total disability of the right hand.

The condition of the hands on April 25, 1907, is shown in Figs. 8 and 9—*the result of ten years of treatment and twenty-five operations under ether.*

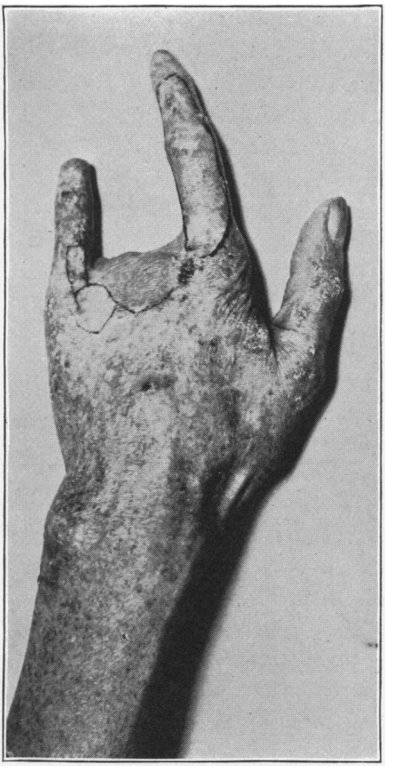
On the left hand the thumb is sound and serviceable. The forefinger is stiff, but shows no lesions. The third and fourth fingers have been amputated. The little finger lacks a terminal phalanx. On the back of the hand there are a few keratoses, but no ulcerations. *On the right hand* the thumb is useful, but at its base is a small ulceration, and the whole ulnar side is covered with thickened epithelium. The forefinger is flexed and presents an ulceration over its middle which is undoubtedly malignant. (This finger will be amputated in June.) The middle finger is stiff. There are a few sluggish granulating areas on the dorsum, but these are healing in. The fourth finger is lacking, as is also the end of the fifth. There are numerous keratoses, but no other ulcerations on the back of the hand.

The palmar surface of both hands is normal. The skin grafts, which are outlined in black, are soft, movable, and some of the thicker ones have almost the appearance of normal skin.

The axillary glands have been somewhat enlarged for many years, but show no evidence of increase in size.

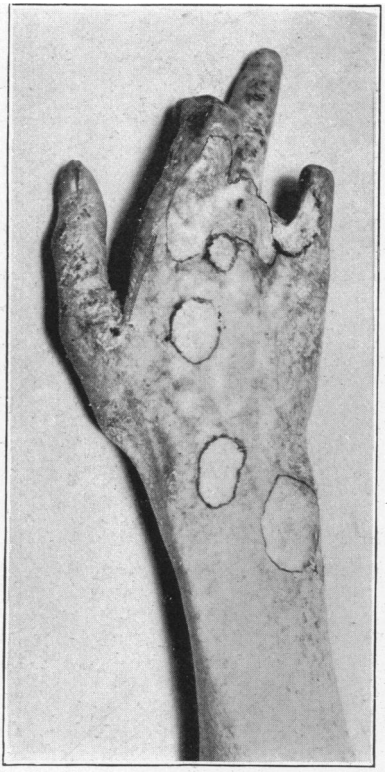
From the first demonstration of epithelial cancer in 1902 on the tips of the fourth fingers, undoubted malignant degeneration has been found in eight other areas, so that we have the extraordinary development of ten different epitheliomas in one case in five years. As the report by Dr. White will show, from such a condition there are all grades of what might be termed precancerous changes, down to simple ulceration or benign keratosis. In this as in the other reported cases, persistent ulceration has for a time, from three to six months, always preceded cancer.

FIG. 8.



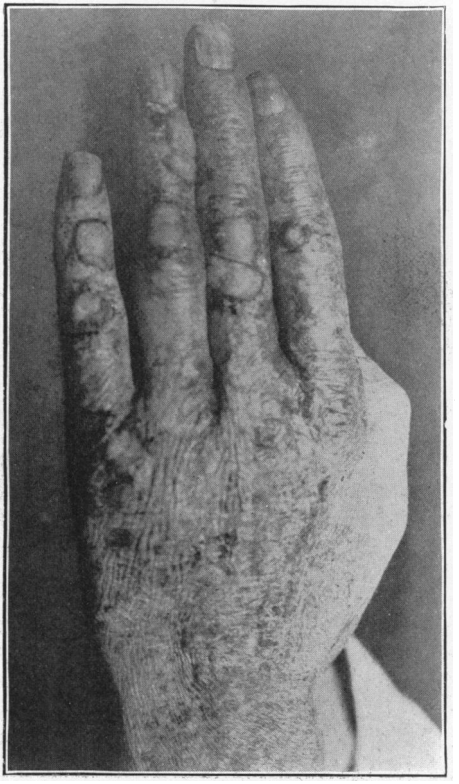
Condition of hand, April, 1907.

FIG. 9.



Condition of hand, April, 1907.

FIG. 10.



Hand of G., May, 1907.

FIG. 11.

Hand of G., April, 1907.

In addition I will report a second case of chronic but much less severe dermatitis to show the advantage of skin grafting for recurring fissures; and the report of Dr. Mallory upon the recurrent growth which may prove to be a sarcoma.

Mr. J. G., X-ray operator, has suffered for many years with the milder varieties of X-ray lesions such as atrophy of the sweat glands, more or less persistent eczema, marked atrophy and longitudinal ribbing of the finger nails, with the characteristic X-ray telangiectases and keratoses. During the winter most painful fissures occurred over the extensor surfaces of the joints. It is of interest to note that none of these lesions are present over the proximal phalanx of the ring finger, which was protected from all early exposures by a broad gold ring.

In May, 1906, the keratoses and fissures on the back of the right hand were excised and grafted. Fig. 10 shows condition ten days after the operation. All of the grafts took. These were prominent and raised above the surface for a month, but at the end of that time were level with the surrounding skin and remained solid until September 15, when a spot on the terminal phalanx of the ring finger became ulcerated. Under gas and ether on October 18 this ulceration was freely excised and the radial fourth of the nail with its matrix extirpated. The skin at the margin of the nail was approximated with plaster and another graft was applied. In ten days the wound was completely healed and free from pain. This finger remained painless and healed until the middle of March, 1907, when the distal part of the graft on the radial side began to increase in size and show well-marked vascularity. After two weeks there was a slight discharge near the edge of the nail.

Examination by Dr. Wright of this specimen led him to make a diagnosis of spindle-celled sarcoma, though by some the growth was thought to be a granuloma.

By April 23, 1907, the growth had become decidedly larger and was apparently extending backward into the proximal graft. See figure 11. After careful consideration of the possibility of the return of the growth excised in October, but chiefly influenced by the anatomical conditions, which could not, in all probability, be rectified by removal of the nail and grafting, the

terminal joint was amputated under gas and ether. The wound was completely healed in a week.

Examination of tissue from finger of J. G. following exposure to X-rays by Prof. Mallory, of Harvard Medical School.

The section shows an oval, cellular mass of tissue partially surrounded by more or less normal fibrous tissue. The cellular mass at its outer end is ulcerated and covered with fibrin, cells and dried necrotic tissue. The more normal tissue is covered with epidermis. The oval, cellular mass of tissue is quite sharply defined and is limited by a layer of dense, fibrous tissue. It is composed of rapidly growing connective tissue cells and of a small number of thin-walled blood vessels. The connective tissue cells are typical, that is, they have flat, oval nuclei and contain one to three coarse chromatin masses. The cytoplasm is made out with difficulty. In places the cells are bordered by very delicate fibroglia fibrils. Everywhere the cells are separated from each other by a relatively large amount of ordinary (collagenous) fibrils. The cells and their fibrils tend to form small bundles which run in all directions. Mitotic figures are numerous, one to three showing in nearly every oil immersion field. While the cellular mass of tissue at its base is sharply defined, on both sides, it gradually blends with the adjoining connective tissue.

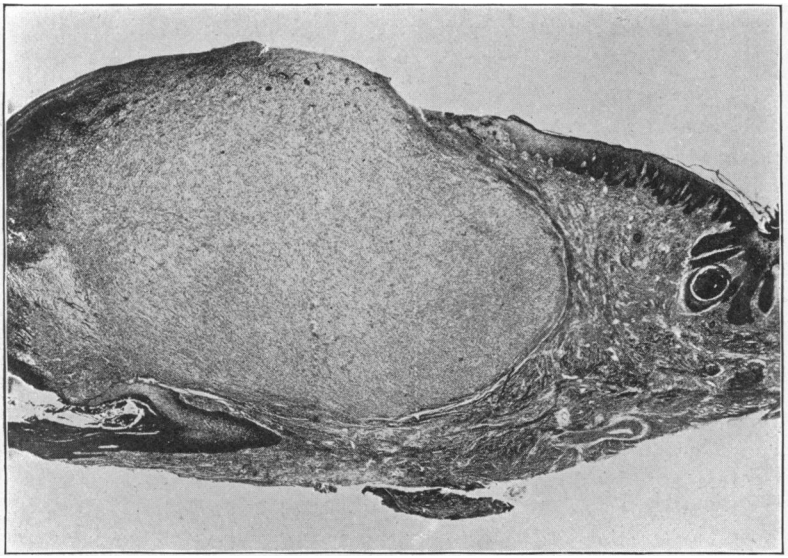
The adjoining tissue of the finger shows infiltration with numerous groups of lymphocytes. Otherwise there appears to be no change in it. It is difficult to give a positive diagnosis in this case. The rapidly growing mass of connective tissue may be either an unusual form of reparative action on the part of connective tissue or it may be a connective tissue new growth, namely, a rather slow growing spindle-cell sarcoma. Personally I favor the former view owing to the lack of any definite evidence as yet of invasion.

F. B. MALLORY.

The microscopical appearances under the low and high power are shown in Figs. 12 and 13. Note beginning epithelial infiltration at the extreme right of the photograph.

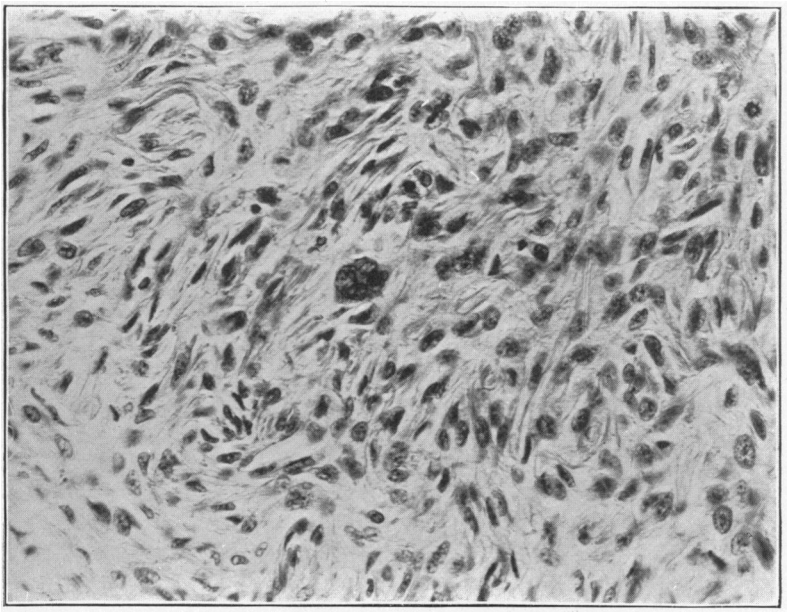
During my long experience with the first case I have learned many things about skin grafting, and now have no hesitation in recommending it, as the best treatment for all chronic X-ray lesions. Early in the history of this case, the tissues were remarkably vascular. There frequently occurred little hemorrhages in the skin, which were often the starting-point of subsequent ulceration; there appeared to be an almost complete vaso-motor paralysis. Owing to the chronic eczema no adequate disinfection was possible so that most of the early

FIG. 12.



Tissue from hand of G. Low power. April, 1907.

FIG. 13.



Same as Fig. 12. High power.

operations were somewhat influenced by sepsis, yet in spite of this the grafts often took surprisingly well. Hæmorrhage proved to be most troublesome, not only at the time of operation, but subsequently, when blebs would form under the grafts, and unless speedily snipped with scissors would detach them. Hæmorrhagic infiltration of the grafts was often noticed on the second or third day, doubling their thickness.

As a rule I applied a finger tourniquet before excising, as much of the work had to be done with great care, especially when dealing with a suspicious ulceration over an aponeurosis or tendon sheath. Fortunately, no deep infiltrations have yet occurred. After excision firm pressure by gauze was applied to the raw surfaces for ten minutes, and the hands were then exposed to the air and held aloft. No grafts should be applied until all bleeding has ceased. So far as possible an attempt should be made to bevel the edges of the wound. After shaving off granulations to get a smooth surface, the base of the wound is next examined for vascularity, in order to determine the thickness of the graft which should be used. While the ultimate result, if successful, which a thick graft gives, is most desirable, I feel sure that I have occasionally jeopardized healing by attempting to place a thick graft upon a very small spot, or upon such bloodless tissues as the backs of the fingers. I now use thinner grafts. If these fail, another operation should be done when the surface has become covered with granulations. A very small spot upon the fingers is most difficult to graft. I have had the best results by cutting a special graft for each place, thickest in the middle and gradually thinning towards the periphery, in order that it may fit evenly into the concavity of the wound. When possible, the whole forearm was firmly fixed with adhesive plaster to a well padded palmar splint before any of the grafts were applied. More than once from a sudden movement of the patient or an assistant, many of the grafts have been brushed off. The patient should be kept under full surgical anesthesia until the dressing is completed.

After having tried all the methods of dressing the

grafts with which I am familiar, I have adopted the following technique, and after-treatment. The grafts are so cut and arranged that they *do not overlap* either the edges of the wound or each other. If on the back of the hand, they are covered with a piece of rubber protective tissue which extends not more than ⅛ of an inch beyond their edge; if on the fingers, narrow strips of protective, arranged in an imbricated fashion, encircle $^2/_3$ of the finger, and are stuck in position with blood, which soon coagulates. A small absorbent gauze pad is then placed over the protective and then *direct downward* pressure is applied by a piece of gauze or bandage, which is tied with a surgeon's knot on the palmar side of the splint. I was forced to resort to this manœuver by the discovery that the smaller grafts now and then were carried from left to right by the ordinary application of the bandage. Owing to the amount of exudation which occurs immediately after the operation, I have found it unwise to adopt immediate exposure to the air, as is now customary in *normal* skin-grafting. After twenty-four hours, with the hand continuously elevated, the protective is carefully removed. Longer delay in this case has almost always been followed by maceration of the grafts.

At the first dressing, blebs, if present, are snipped with the scissors and their contents gently expressed. Any lateral movement of the graft must be avoided. All the *edges* of the individual grafts are then greased with lanolin, or with the following ointment which was found to be less macerating.

Benzoinated lard.....	175
Lanolin	25
Ichthyol	4
Silver citrate.....	1

The grafts were then covered with a cage and allowed to dry, exposed to the air, and so treated for the next week whenever possible. Often, however, the sensitiveness and pain after half an hour's exposure were so great that the whole surface had to be covered with the ointment.

Almost without exception the pain in these ulcerated areas as well as in the X-ray burns which I have excised, has ceased from the time of operation. It is interesting to note that in one instance thick grafts grew even on the base of an epitheliomatous ulcer, but within three weeks became excessively hypertrophic. After subsequent amputation of the finger, sections showed carcinoma invading the bottom of the œdematous graft.

Though future events may prove that my treatment of this patient has been too conservative, his present condition would seem to justify it.

In order that the abundance of material which has resulted from all these operations may prove of value to dermatologists, interested in the study of the pathological conditions induced by the X-rays, Dr. C. J. White has kindly made a careful examination of all the slides which have been preserved, and his exhaustive report forms a most valuable addition to my paper.

The clinical appearances of the chronic X-ray dermatoses, suggest a precocious and extreme senility of the skin; microscopic examination, also, shows the most extraordinary changes, always of a degenerative character, unequalled in their severity and chronicity by the effects of any other agent.

In view of these facts and the histories of the eleven cases reported, I think the following conclusions are justified:

1. For the atrophic condition of the skin and the telangiectases nothing can be done.

2. Hypertrophic changes, keratoses and warts may with safety be treated in the usual manner. If such treatment fails, excision with or without skin grafting, will probably relieve the pain and result in a cure.

3. Excision and grafting will prove to be the best treatment for recurrent fissures.

4. All ulcerations, which, under ordinary treatment, remain open, after three months, should be thoroughly excised, and very carefully examined. The subsequent treatment de-

pending upon the result of the microscopic examination, should be skin grafting; further excision and grafting, or amputation.

5. As the history of almost all of these cases of severe and chronic dermatitis dates back to early exposures, with the protection which our present knowledge demands, it is to be hoped that the number of victims of too enthusiastic work in an untried field, will steadily diminish.

6. In the meantime, I have no hesitation in recommending the *early excision* of all *persistent X-ray ulcerations,* in order that subsequent malignant degeneration may be prevented.

PATHOLOGICAL REPORT.

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The pathological report which follows is based upon the study of forty-three microscopic slides presented by Dr. Porter. The sections were already stained, for the most part by the hæmatoxylin-eosin, iron-hæmatoxylin and methylin blue-eosin methods. It is to be regretted that no fresh material was at hand for the special staining of connective tissue and elastic fibrils. The first sections date from July 17, 1902, and were as follows:

1. *Finger of Right Hand.*—Keratosis moderate. Rete somewhat hypertrophic and shows an increased tendency toward downward proliferation. Corium normal and presents no marked signs of inflammation. The deeper horizontal vessels, however, exhibit serious changes. In places veins appear displaying extraordinary mural thickening. No interior alterations are present beyond a slight enlargement of the cells but the outer coats are greatly hypertrophied. Here and there arteries are totally obliterated by endothelial overgrowth.

2. *An Ulcerated Area.*—The rete, where existent, is totally abnormal. The stratum corneum consists of a few lamellæ of non-nucleated cells. The stratum granulosum is absent. The stratum spinosum is made up of greatly dilated cells, the extra-nuclear protoplasm being much rarified and the nuclei shrunken, murally placed, or entirely gone. The palisade layer, however, shows comparatively normal elements. Here and there are masses of red blood cells, suggesting golden pigment granules and filling the whole depth of the rete.

As the ulcer is approached the spinous cells show more distinct

configuration but are horizontally elongated and interspersed with erythrocytes.

Corium.—Below this abnormal epidermis there are occasional masses of plasma cells accompanied by a rare mast cell. The papillary and subpapillary vessels are dilated and many are clogged with red cells. Larger deeper vessels are choked with endarterial masses of nucleated cells. This condition is extraordinarily abundant—the lumen of some vessels of great size being entirely obliterated.

Invading the entire corium are polymorphous masses of epithelial cells ranging from small strings to great clumps with many smaller epithelial pearls. The epitheliomatous masses are outlined by a limiting band of deeply staining cells. Within these peripheral bands the cells are often oval and greatly enlarged with correspondingly hypertrophic nuclei containing one or two nucleoli. Some of the cells are really enormous (fusion?) while around them appear epithelial cells whose limiting membranes are indistinct and whose nuclei have disappeared. The epithelial pearls are large, some of them consisting of a nucleated centre surrounded by 15 to 20 concentric hyaline rings.

Mitoses are rare and between these epithelial masses are numerous cells.

3. *From a Finger.*—For the most part the epidermis is normal although the rete is somewhat hyperplastic. In one place, percontra, the spinous layer has receded to three or four layers of somewhat amorphous cells illy defined from the underlying corium and exhibiting deeper proliferation suggestive of epithelioma while above a nucleated crust appears.

The corium shows in the middle and lower layers a few highly dilated lymph spaces and some moderately enlarged blood vessels surrounded by dense plasmomata with an occasional mast cell; while still deeper are seen blood vessels presenting an obliterating endothelial change, and again others with persistent but distorted lumen and thickened walls surrounded by dense envelopes of connective tissue.

4. *From a Finger.*—Within the lobules of epithelioma are many large oval and round, swollen, pale-staining cells—some of great size. The progressive steps towards the formation of pearls can be demonstrated easily. Again mitoses are rare.

5. *Finger of Left Hand* (see photograph 3).—*Rete.*—Where the epidermis is intact there is a marked parakeratosis and acanthosis. The horny layer is decidedly thickened and nuclei persist; the stratum granulosum is absent; the upper layers of spinous cells are flattened and elongated and more or less devoid of nuclei and the whole rete somewhat hyperplastic. In several places the epidermic origin of the epithelioma is plainly manifest and broad masses of tumor cells are seen in direct continuation with the overlying rete.

Throughout the depth of the corium are seen lobules and whorls of epitheliomatous cells between which the collagenous bundles form a delicate meshwork in which are lodged masses of mononuclear cells—for the most part plasma cells—and very numerous, small, dilated vessels. Before any degenerative alterations have developed the cells of the outer

layers of the lobules retain their prickles undiminished. With the onset of degeneration, however, we note a disappearance of these spongioplastic prolongations and a concentric arrangement of the cells. Within these onion-like lamellæ the cells assume a roundish configuration with occasional great perinuclear halos while in the centre of the mass appears a basic-staining substance reminiscent of keratin. These conditions well illustrate the epidermic derivation of the tumor masses by their analogy to the progressive cornification of the normal epidermis.

In other parts of the section the epidermis shows less keratosis while the rete produces long finger-like projections into the corium. Finally, in still other areas, there is ulceration. The lowermost layers of the rete alone persist as round or oval, swollen cells; while again all signs of the epidermis are wanting and the surface is formed by a highly cellular corium.

The vessels are everywhere dilated. The papillary and subpapillary channels are delicately widened and the interlobular passages show the same condition while in the non-epitheliomatous parts of the section the deep vessels are very conspicuous and here and there form great reservoirs like those seen in cavernous angiomata. These veins do not exhibit dilatation simply, for their walls are manifestly hypertrophic.

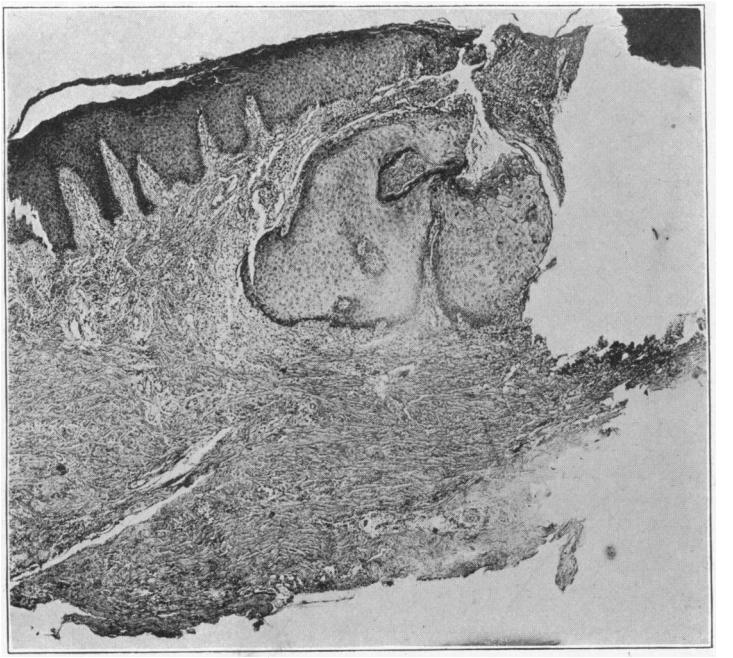
Curiously enough, pigmentation, which we associate so strongly clinically with X-ray dermatoses, seems to play no rôle throughout all these sections and hæmatin or melanin granules are conspicuously absent.

6. *Ulcer: Tip of Third Finger of Right Hand.*—This area presents a central ulceration with comparatively normal epidermis on each side. The floor of the ulcer is composed of string-like serpentine masses of epithelioid cells, groups of erythrocytes, polynuclear leucocytes and rather inconspicuous bundles of collagen. Lower down the field becomes less troubled. The pus cells and red corpuscles disappear. The epithelioid masses grow less numerous while mononuclear elements and connective tissue cells replace them. The epithelioid elements for the most part form worm-like processes; but in places this configuration is lost, branches develop or irregular masses are produced. These figures are composed of cells exhibiting large, oval or round nuclei which contain many nucleoli and are surrounded by meagre protoplasm with no retaining envelop. Here and there are especially large cells which seem to be pushing their way through lymph spaces.

7. *From a Finger.*—Here the epitheliomatous process is young. The epidermis shows a loss of the stratum corneum. The granular layer is practically wanting save for an occasional attenuated cell with but few granules. The upper layers of the rete are elongated and more or less devoid of nuclei. The germinal cells on the other hand are conspicuously numerous, absorb the stains deeply but show an irregular demarcation from the subjacent corium and exhibit occasional downward buds.

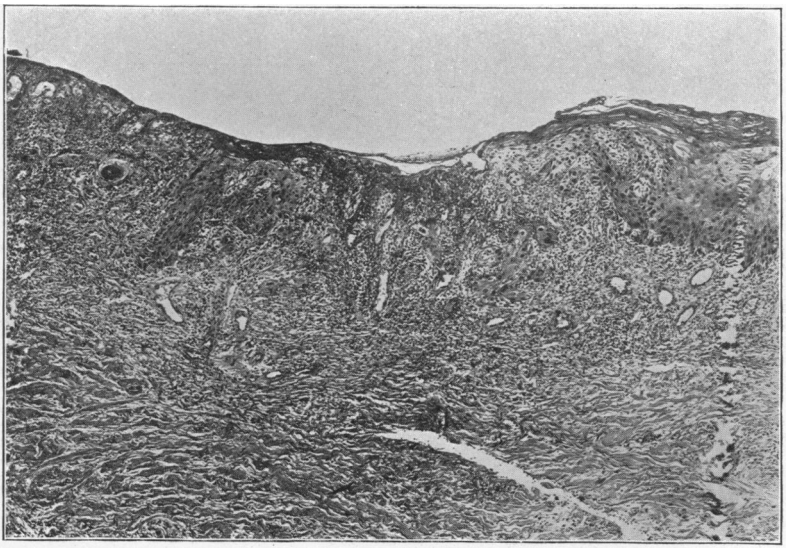
The corium presents dilated subpapillary vessels with hypertrophied endothelial cells while the deep veins are enormously enlarged with frequent great thickening of their several coats. In the sub-papillary layer there are striking masses of plasma cells with infrequent mast cells

FIG. 14.



Section from periphery of ulcer on back of right wrist, December, 1903.

FIG. 15.



Section from base of ulcer on back of right wrist, December, 1903.

especially about the vessels. Here again can be seen delicate string-like masses of epithelioid cells which wind through the lymph spaces. Where these masses widen out their component cells display large swollen nuclei. Evidences of chromatophores or of free pigment granules are once more wanting.

Where epitheliomatous changes are absent the connective tissue nuclei are appreciably elongated and enlarged.

Thus far these sections date from the operations of July 17, 1902.

Back of right wrist December 23, 1903 (Fig. 14). The epidermic structures are normal with the exception of a slight tendency toward irregularity where the palisade layer and corium meet and here certain nuclei are surrounded by clear spaces while others have dropped out and are replaced by inflammatory cells.

The papillary vessels are dilated with hypertrophied endothelium. The corium is very dense and is filled with mononuclear cells not particularly grouped but generally distributed.

At the periphery of the section, however, where the section ends abruptly through ulceration (?) there are two lobules of epithelial cells. One suggests the epidermis irregularly cut (cross section?), the other contains œdematous cells, some without nuclei, others swollen with large vesicular nuclei, others containing granules of keratohyalin—in fact the whole picture is strongly reminiscent of the epidermic changes seen in molluscum contagiosum. The whole structure is surrounded by inflammatory tissue.

8. *Back of Right Wrist.* (December 23, 1903, Fig. 15.)—To one side of the ulcerated area shown in the photograph the epidermis is greatly modified. The palisade layer forms a straight but broken line owing to the disappearance of the papillæ. The cell nuclei are round or oval rather than elongated, show one or more sharply staining nuclei and are filled with chromatin granules. The intercellular spaces are irregular and often enlarged. The overlying layers of the rete are thickened and present swollen, œdematous, loosely opposed cells mostly free of nuclei and spines. The granular layer is represented by free kerato hyalin granules only, all other evidences of granular cells having disappeared. Lastly, the stratum corneum is composed of many dense lamellæ with numerous persistent nuclei. Thus the whole epidermis presents acanthosis and parakeratosis of pure type.

In the corium the absence of papillæ has already been alluded to while the subpapillary vessels are widely dilated and exhibit hypertrophic endothelial cells. Below, the collagen is comparatively normal save for occasional swollen bundles. Moderately numerous plasma cells and rare mast cells are present, sometimes grouped about a distended vessel. Finally, deep down in the corium appear prominent veins now enothelially now totally thickened.

The ulcerated portion (Fig. 15) presents a complex picture of masses of polynuclear leucocytes and red cells lying in a mediumly coarse reticulation with interspersed large dilated vessels filled with erythrocytes and coagulated fibrin and with occasional processes of epithelial cells with

grossly vesicular nuclei growing in from the sides or persisting as remnants. Below these abnormal elements lies a floor of thickened, rather anuclear collagenous bundles.

9. *Base of First Finger of Right Hand.* (December 23, 1903, Fig. 16.)—This represents scar tissue of considerable thinness. The epidermis consists for the most part of parallel bands of dense nucleated corneous lamellæ with occasional layers of rather amorphous, homogeneous, quasi rete cells containing infrequent round or oval nuclei surrounded by empty spaces. The germinal layer is represented by horizontally lying cells with flattened nuclei.

Even here the epidermis shows an effort toward downward proliferation foretelling future epitheliomatous growth.

The corium shows an absence of papillæ. The subpapillary layer is not as compact as one would suppose and its meshes are strewn with plasma cells, as seen in the photograph (16). There are frequent epitheliomatous cell nests, some solid and normal, others presenting varying degrees of central degeneration. In one (lying nearly centrally in the illustration) there is an outer ring of fair-sized, numerous, darkly-staining nuclei separated by a clear zone (artefact?) from the inner lamellated, flatly-nucleated layers which in their turn envelop an almost homogeneously degenerated centre containing an occasional giant nucleus and scattered nuclear debris and two large cysts partly filled with granulated protoplasm and mononuclear leucocytes.

The base is composed of practically normal fibrous tissue and the deep vessels when present exhibit no marked changes.

10. *Middle Finger of Left Hand.* (December 23, 1903.)—The tissue here is composed of a dense mass of fibrous elements devoid of all epithelial structures and free from vessels. It consists of practically structureless collagen on which lie small, round, solid-staining nuclei, the exact nature of which it is difficult to discern. In the deeper portion of the section the fibrous bundles form a reticulated mesh devoid of nuclei. The whole picture presents an extraordinarily blank mass.

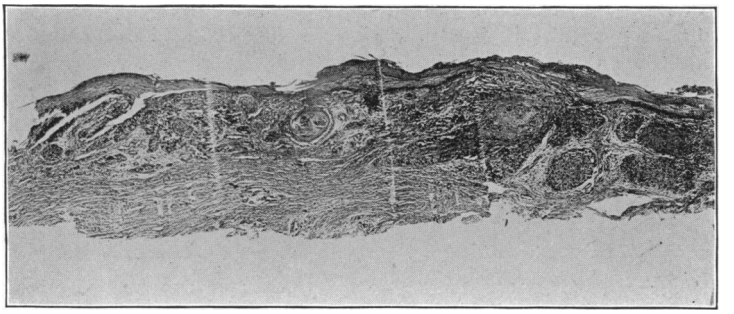
11. *Base of Third Finger of Right Hand.* (December 23, 1903, Fig. 17.)—The photomicrograph, 17, illustrates well the conditions present.

To one side an ulcerated surface of thickened collagenous material supporting numerous, many sized, mononucleated cells and small and large interstices containing erythrocytes with occasional whorls of œdematous and degenerated epithelial cells.

Where the epidermic covering is present the various layers are much altered. The rete shows an irregular base with marked tendency toward downward proliferation. The upper strata are emphatically hypertrophied while their component cells have lost their prickles and tend to coalesce, so that cell boundaries are gone, nuclei are swollen or absent and protoplasm is cloudy. The granular layer is represented for the most part by free kerato-hyalin granules. The stratum corneum is hyperplastic and nucleated. Again a marked picture of acanthosis and parakeratosis. Pigment is conspicuous by its absence.

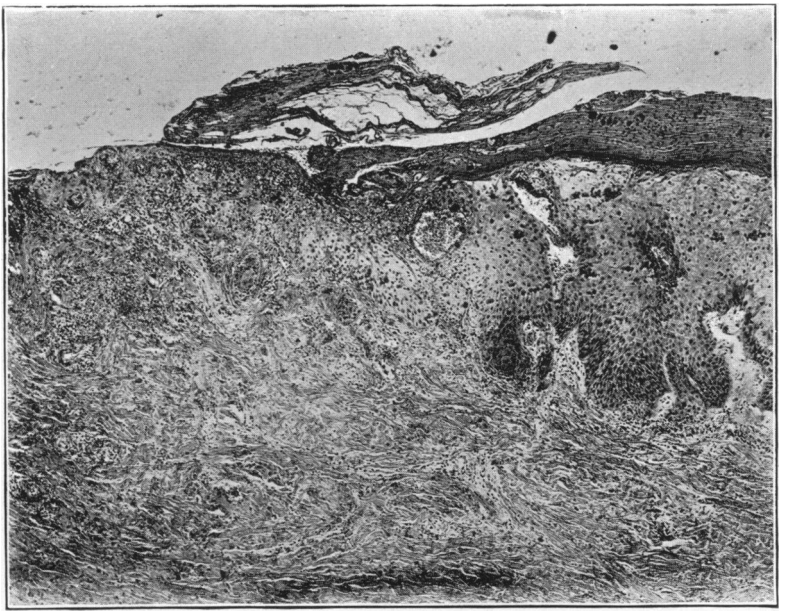
The corium exhibits only occasional papillæ which are filled with

FIG. 16.



Section from scar at base of first finger of right hand, December, 1903.

FIG. 17.



Section from tissue at base of third finger of right hand.

highly dilated vessels. The skeleton of the skin is composed of dense, rather anuclear bundles. Deeper vessels when present, show considerable thickening of their walls and constriction of their lumen and are surrounded by plasma and other mononuclear cells.

12. *Base of Little Finger of Left Hand.* (December 23, 1903.)—The process represented here is one of hyperkeratosis. The corium is dense. Vessels are slightly dilated and encompassed by extravasated mononucleated cells. Papillæ are insignificant. The rete is somewhat thickened for this part of the body but otherwise normal. The granular layer is manifestly hyperplastic and consists of five to six rows of large swollen cells with somewhat blunted ends and filled with masses of kerato-hyalin granules. The stratum lucidum is suggested but shows no traces of eleidin. The stratum corneum is conspicuously thickened and composed of layer upon layer of waving horny cells.

13. *Tip of Middle Finger.* (September 19, 1904.)—A very complex and irregular picture. The epidermis is mostly gone, the few surviving vestiges being quite atypical. The corium is totally abnormal and it is difficult to orientate oneself.

The upper layers are filled with dense masses of plasma cells and with sparsely scattered lymphocytes. Small dilated vessels with extraordinarily vesicular nuclei abound choked with red cells and occasional lymphocytes. The supporting fibrous tissue is in places dense, in others delicately reticulated, the intensity of the plasmomata corresponding directly with the density of the collagen. Here and there are small lobules of epithelial cells, occasionally whorls and more rarely branching tubules. All three forms exhibit absence of prickles and presence of highly vesicular cells containing one or two nucleoli and dense chromatin granules. The whorls and the tubules show a tendency toward central hyalin degeneration. When visible through comparative freedom from inflammatory invasions, the fibrous tissue shows a moderate proliferation of its nuclei.

14. *Base of Middle Finger.* (September 19, 1904.)—Great hyperplasia of the rete is the distinguishing feature here. For the most part the change is purely one of overgrowth in the depth of the layer. The cells are normal although somewhat œdematous and there is marked intercellular invasion of leucocytes. Here and there, however, the cellular elements show loss of prickles, vacuolization and tendency towards homogeneity. The stratum granulosum is represented mostly by free lying kerato-hyalin granules with occasional areas of partly developed granular cells. The horny layer is compact but otherwise normal.

The dividing line between epidermis and corium is so indefinite owing to the great overgrowth of the rete and the irregularity of the cut that it is difficult to ascertain the presence or absence of papillæ. There are numerous foci of snared-off epithelial clusters. The corium is dense and interspersed with numerous plasma cells, especially in the subpapillary layer.

15. *Keratosis from Dorsal Base of Middle Finger of Right Hand.*—This region presents an epidermic picture somewhat similar to the last

but here one finds the additional presence of a hyperplastic horny layer containing some nuclear cells. Again, the demarcation between corium and epidermis is well marked and the palisade layer more normal. Papillæ are present and hold dilated vessels—in one instance the whole papillary space is occupied by a vessel whose wide lumen is partially filled with lymphocytes, polynuclear leucocytes, erythrocytes and granular or reticulated fibrin. The corium presents the condition so frequently described in these sections, *i.e.*, dense collagen with dilated vessels and extravasated mononuclear cells.

16. *Tip of Little Finger.* (September 19, 1904.)—Another picture of parakeratosis and acanthosis with absence of papillæ and dense infiltrated corium.

17. *Ulcer on Back of Left Hand.* (October 16, 1904).—A complicated structure. The epidermis is entirely gone and the corium contains many polymorphous epithelial lobules and whorls; superficial dilated vessels blocked with red and with white cells; and innumerable endothelial and mono- and polynuclear elements. The epithelial whorls and lobules consist in the majority of instances of spine-bearing cells and present all stages of degeneration even to cystic spaces containing chromatin granules and reticulated or granular protoplasmatic debris.

The underlying corium is composed of dense fibres with elongated and enlarged nuclei and the deeper vessels are murally thickened.

18. *Keratosis of Right Wrist.* (October 16, 1904.)—Once more conditions now so familiar in this series of sections. Here one finds a hyperplastic rete whose upper layers are œdematous and degenerated; a total absence of granular cells and even independent granules; and an enormously overgrown horny layer bearing nucleated scales and leucocytic crusts.

Papillæ are insignificant. Subpapillary vessels slightly dilated. Collagen delicate in structure and supporting some mononuclear extravasated cells.

Sections from five other excised portions of this same date show pictures presenting the various characteristics which have marked those previously described and need not be detailed again.

19. *Graft Upon Middle Finger of Left Hand.* (October 16, 1904.)—The artificial epidermic covering is to all intents and purposes normal, but in one portion of the section the insidious process has redeveloped and below the rete one finds the now familiar epithelial lobules with central hyaline degeneration.

20. *Keratosis from Forehead.* (December 27, 1904.)—A newly invaded field. This section illustrates almost perfectly the epidermic characteristics of the sole of the normal foot. The rete is somewhat thickened, the cells of the upper transitional layers more or less vesicular and thrown up into jagged summits and depressions into which dovetail layer upon layer of normal horny cells. The corium, however, shows evidences of considerable inflammation. Vessels are dilated and plasmomata are frequent. Sweat and sebaceous glands hitherto not observed in these sections are present in great abundance and exhibit no marked deviation from the normal.

21. *Forehead.* (April 20, 1905.)—The intervening five months have wrought a great change. In the present section ulceration has occured and at the epithelial edge the cells of the upper layers of the rete are flattened and contain peri-nuclear halos or empty nuclear spaces; all semblance of granular cells has vanished; and a thin, parakeratotic horny layer is present. The lower layers of the rete are running riot. They have overcome the normal resistance of the corium and are proliferating enormously into the subjacent structures. Individual cells are often of enormous size and have become amorphous, anuclear swollen masses of protoplasm. In other areas large vesicular nuclei are present with but scant surrounding protoplasm. Cellular invasion is absent.

Farther down in the corium hugely swollen, anuclear bundles of collagen and some veins of extraordinary thickness and jagged, slit-like lumen appear. These unusual collagenous fibres would suggest an incipient colloid degeneration. The sweat glands remain strangely unaffected in the midst of these contiguous pathological structures.

22. *Hand.* (November 8, 1905.)—These sections are cut largely in so horizontal a plane that it would be injudicious to judge of the epithelial changes. There is, nevertheless, marked hyperplasia of the rete with occasional loss of nuclei especially in the germinate zone, general cloudiness of the cells and some intercellular leucocytic invasion. In places all vestiges of normal metamorphosis from rete to horn cells have gone and the free surface of the skin forms a chaotic mass.

The subpapillary layers, which alone are present, show fine reticulation supporting normal vessels and a general plasmomatic infiltration.

23. *Keratosis from the Hand.* (November 8, 1905.)—Here one has an ideal representation of a papillary and verrucous nævus. The rete is cast in individual rounded lobes formed by the fine and widely separated ascending papillæ and in places these lobes strongly suggest the lower rete conformation of molluscum contagiosum. In these lobes the rete is hyperplastic and fairly normal although perinuclear halos are common. The granular cells also exist in great numbers and one can count ten to twelve perfectly developed layers while above, before keratinization has been completed, as many more layers, half granular, half keratinous, appear. Above these increased strata lie row upon row of typical horn cells. Thus far the description has related to the interpapillary lobes but as is the rule in nævous pictures the rete and granular layers surmounting the papillæ do not present these hyperplasias but appear in comparatively normal amounts.

The papillæ are proportionately narrow but project far into the epidermis, in some instances to extraordinary distances. As is customary in this class of nævi the papillary and subpapillary vessels are slightly dilated and accompanied by a moderate number of mononucleated cells which lie between and under the epidermic lobes. The rete is practically normal.

24. *Ulnar Side of Forefinger.* (November 8, 1905.)—A mild degree of the preceding process, partly purely keratotic and partly slightly papillomatous.

25. *Ulceration of Finger.* (November 8, 1905.)—An intensely interesting picture of multiform and generalized degeneration which has affected practically all the various structures of the skin.

The epidermis is represented by remnants of previous downshoots from the rete which persist as barely recognizable, swollen, amorphous, acid staining protoplasm with occasional vesicular nuclei.

The papillæ of the corium are gone and the subpapillary layer holds numerous moderately dilated vessels within frequent, cloudy vesicular endothelial cells and with swollen lymphocytes, a few pus cells and reticulated fibrin in their channels. Collagen appears as straight, œdematous bundles between which extend chains of oblong plasma cells and more irregularly distributed lymphocytes. These plasma cells are histologically noteworthy for one seldom sees such well defined examples with their eccentrically placed, round nuclei bearing symmetrically arranged peripheral nucleoli.

These rows of alternating plasma cells and swollen collagen are interrupted by frequent vessels whose walls are cloudy and whose nuclei are vesicular and often of great size. Below, there are isolated or grouped masses of wavy or serpentine basic-staining elastic fibres (elacin) which lie between the fibrous bundles or form large, solid areas free from collagen.

26. *Outer Side of Forefinger.* (November 8, 1905.)—Another ulcerated surface disclosing many of the attributes of the previous section but not containing so many interesting histological features.

27. *Back of Right Hand.* (March 16, 1906.)—In this section there are stretches of epidermis and of ulceration. Where the former is present there is some tendency toward hyperplasia of the rete while the stratum granulosum is absent and the stratum corneum is represented by a thin homogeneous mass. Underneath, the corium is normal except for universally dilated vessels surrounded by plasmomata.

Where the epidermis is gone the corium is filled with circular or polymorphous lobules of epithelial cells which show no tendency toward degeneration. Multiple dilated vessels with lumens choked with red cells lie between these epitheliomatous masses and scattered universally throughout the depth of the derma are many mono- or polynucleated inflammatory cells.

28. *First Finger of Left Hand.* (March 16, 1906.)—A pathological condition similar to the last but here the epidermis is intact, exhibiting hyperplasia of the rete and of the horny layer, both of which are infiltrated with many leucocytes usually of the pustular type. Here also evidences of downward proliferation of the rete are visible. Finally there is abundant hæmorrhage everywhere.

29. *Tip of Third Finger.* (March 16, 1906.)—This piece of skin is free from epitheliomatous changes. For long stretches the upper layers of the epidermis are wanting while the corium exhibits in all parts many dilated vessels and multitudinous plasma cells.

30. *Excision.* (November 4, 1906.)—This section, the last in this long series, exhibits undiminished evidences of epithelioma.

The horny layer is practically non-existent, the granular layer is normal. The rete is in places thickened and displays numerous infiltrating leucocytes and at its germinate layer evinces signs of downward-penetrating proclivities. Papillæ are present and bear slightly dilated vessels. The subpapillary layer is delicately reticulated and holds frequent plasmomata and distended vessels containing fibrous meshes and occasional polynuclear leucocytes. Just below this level lies another series of plasma cell masses whose characteristics are strikingly visible and immediately subjacent are extensive areas of epithelial whorls and lobules surrounded by still further plasma cells.

The outer lamellations of these whorls show well differentiated prickle-bearing cells; but within lie degenerated, puffed cells, free from prickles and at times from cell boundaries, containing frequently giant nuclei or no nuclei at all and more mitotic figures than in the previous pathological history of the case. Finally, in the very centre of some of the whorls are found large cysts partially filled with coagulated fibrin, giant nuclei and abundant chromatic remains. Where these cysts appear the epithelial masses are more "pearly" than elsewhere.

This, then, is the detailed description of the pathological side of this discouraging history, and it is distressing to find at the end of this long series a slide exhibiting the most active phases of the disease.

One who has read the histological minutiæ of the case will be struck, presumably, by the manifold varieties of the pathological structures. Almost every known phase of epidermic deviation has been encountered, and the cellular, vascular, and protoplasmic alterations and degenerations have been most varied and interesting. The one striking omission in the case has been the unexpected absence of all pigmentary signs, especially when one remembers how prominent a clinical feature pigmentation is in X-ray dermatitis and its epitheliomatous sequelæ.