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C. A. PORTER, M.D.

(Assistant Professor of Surgery, Harvard Medical School; Surgeon to the Massachusetts General Hospital, Boston, Mass.)

THE PATHOLOGICAL HISTOLOGY OF CHRONIC X-RAY DERMATITIS AND EARLY X-RAY CARCINOMA

S. B. WOLBACH, M.D.

(Director of the Pathological Laboratory, Montreal General Hospital, Montreal)

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THE SURGICAL TREATMENT OF X-RAY CARCINOMA AND OTHER SEVERE X-RAY LESIONS, BASED UPON AN ANALYSIS OF FORTY-SEVEN CASES.*

C. A. PORTER, M.D.

(*Assistant Professor of Surgery, Harvard Medical School; Surgeon to the Massachusetts General Hospital, Boston, Mass.*)

In the Annals of Surgery for November, 1907, I published the account of two cases of severe X-ray lesions; one of possible sarcoma of the finger, the other of an X-ray operator who, since 1896, in addition to the severer forms of dermatitis and ulceration, had developed, between 1902 and 1907, numerous carcinomata, requiring many operations, amputations, excisions, and skin graftings. At the time, I was able to gather the records of ten other cases making, with my own, eleven undoubted X-ray cancers, of which six had been fatal.

Since that time occasional reports of cases have appeared, and three notable papers by E. Schümann [1] in the Beiträge für Klinische Chirurgie, 1907, LXXXIV., Heft 3, page 355; by Karl Lindenborn,[2] in the same journal, 1908, LXXXIX., Heft 2, page 385; and by Dr. Cecil Rowntree [3] of London in the Archives of the Middlesex Hospital, XIII., July, 1908. In all of these papers new cases have been presented, and the etiological relation between X-ray lesions and carcinoma, possibly also sarcoma, has been thoroughly discussed and, in the case of the former at least, definitely proved. In the German literature especially, the subsequent development of cancer upon lupus tissue treated with X-rays has aroused considerable interest; though Steinhans has collected eighty-three cases of carcinoma following lupus, without X-ray treatment, it seems, after a careful perusal of the histories, at least probable that the X-ray had a definite influence upon the subsequent development of the cancer. The cases can be studied in detail in the contributions of Schümann and Lindenborn.

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I propose in this paper to omit all consideration of the lupus cases, and to limit myself, with very few exceptions, to a consideration of the severer lesions which have resulted from the prolonged action of the X-ray upon previously healthy skin, and I should like to emphasize the fact that not only was the skin healthy, but the wearer of it was almost without exception young.

As a result of my former publication, I have had, so far as I know, a unique experience, having operated upon eleven other cases in addition to further operations upon both of the cases previously reported. Thirteen in all: of these three were non-malignant, two beginning carcinoma, six carcinoma, one sarcoma(?), another carcinoma or sarcoma. The distinctions between the phrases precancerous and beginning epithelioma must of course be a matter of opinion, but the clinical histories of other similar cases in this X-ray series seem to show that tissues which presented a precancerous condition or commencing epithelioma at the time of excision would, unless adequately treated, subsequently develop into squamous celled carcinoma. From my experience it seems almost assured that, given lesions of a sufficient duration and severity without adequate treatment, the future development of cancer can be predicted.

Though the harmful results of continuous exposure to the X-rays were unknown to the early workers in this field, it would seem that unwittingly they have given us the best demonstration yet known of the artificial or experimental production of cancer. It is unlikely that old age itself, with its accompanying skin atrophies, even if combined with exposure to such various noxious influences as sea life, raw winds, powerful actinic rays, soot or paraffin, would give such an example of malignant skin degeneration as seems so frequently to result from protracted exposure to the X-ray. When it is remembered that these lesions have been produced in young men at an age when skin cancer is extremely rare, its occurrence is all the more striking.

I have gathered from the literature, and especially through the kindness of physicians whose names will be mentioned

with their personal communications, combined with my own experience, the records of forty-seven cases of severe X-ray lesions. This number in no way represents the actual figures, for there are surely very many cases both of serious damage and also of carcinoma which have not been reported, and are therefore not available. For example, Dr. Pusey of Chicago states:

"I have seen many cases of this kind; certainly more than a score. They are all of one kind and may be briefly characterized in a group. As a result of either an acute or more frequently of a chronic long continued X-ray dermatitis, the skin becomes atrophic, thinned, and harsh, with a number of dilated blood vessels coursing through it and many keratoses forming upon it. These keratoses very frequently become the site of epithelioma. In my judgment, the condition is analogous to senile atrophy of the skin and on the basis of this analogy I prophesied, before the report of any epithelioma in these cases, that epithelioma would develop in them. At the start these X-ray epitheliomata ought theoretically to be very easily handled, just as the superficial epitheliomata beginning in senile keratoses are very easily handled and this has proved true in my experience. In my judgment these epitheliomata should be handled in exactly the same way as epitheliomatous senile keratosis, either by excision or by some other destructive procedure. Many such lesions have been excised upon my advice with good result. Many others that were very superficial I have treated by destruction, usually with carbon dioxide snow. The reason for this sort of procedure is that it does not require the destruction of as much tissue as a thorough excision and sometimes, of course, this is a matter of importance."

Dr. Hyde, in addition to the cases recorded, says that he has seen at least six other patients in a precancerous stage. The experience of these dermatologists is, no doubt, equalled by some in this and other countries, so that the cases reported are by no means an index of the number of persons who are now suffering from early exposures. From France, so far as I am aware, there has been no report of serious X-ray lesions.

Of these forty-seven cases, four of my own were not unusual and are reported simply for record. Four were described as in a precancerous stage or beginning epithelioma; thirty-six were undoubted epidermoid cancer, and two of my own, questionable sarcomata. Had it not been for

the reports of sarcomata by other observers, especially in conjunction with the X-ray treatment of lupus, these two cases would be open to more question. As it now stands, it seems probable that the X-rays may be a factor in the production not only of cancer, but of sarcoma. Of the thirty-six cases of epidermoid cancer, nine have died; a mortality of twenty-five per cent, showing I think quite clearly that these X-ray carcinomata are as malignant, if not more so, than the epithelioiata which ordinarily grow in the skin of older persons, and are, if allowed to advance beyond a certain stage, prone to early metastasis.

In the histories of these cases, the reader will be struck by the period of incubation, if so it may be called, which dates from the occurrence of the original severe lesions, or early unprotected exposures to the rays, during which time characteristic changes have taken place in the skin and underlying tissues, which precede the development of a cancer. This period varies from three to eleven years (Case XXII.), usually from five to seven, and is dependent no doubt upon the number of the exposures and the vulnerability of the individual.

While progressive and characteristic lesions have developed since the dangers of the X-ray were recognized, and some precautions were taken, it is among those who did the earliest work that we have had the greatest number of fatalities and the most severe lesions; and this without regard to the middle age or youth of the individuals. It has seemed that the development of the photographic plates combined with X-ray work has led to earlier and more serious lesions than when X-ray work was done alone. We have, then, quite clearly differentiated from other skin diseases a definite occupation dermatosis which can be diagnosed at a glance, and in the chronic form resembles no other skin affection known to me. The dry thickened skin, without hairs, the telangiectases, the ribbed nails, the keratoses on the backs of the hands in young men are together pathognomonic, and show the results of the specific action of the X-ray; in a more advanced stage,

paronychia, more numerous keratoses, rhagades and ulcerations which alternately heal and break down, until finally there comes, as inevitably as fate, the development of epithelioma at the base of a persistent or inflamed keratosis, or in a chronic ulcer. While the keratoses in no way differ from the usual senile condition, the combination of juvenile keratoses with ulceration of the skin of the dorsum of the hands and fingers seems peculiar to X-ray dermatoses. I have not yet seen an X-ray lesion of the palmar surface of the hands or fingers. Either the thickened skin offers some immunity, or what is more probable, the dorsum, from the position of the hands in work either with the fluoroscope or otherwise, is more exposed. The base of the middle finger seems to be the place most universally affected. This knuckle is obviously most exposed and nearest to the tubes. The thumb, while the nail and the ulnar border is occasionally affected, is to some degree protected in most exposures by the thick palmar skin. The nails suffer relatively early, and the changes are to some degree permanent. An accidental discovery in the case of J. G., Case XVIII., seems to show the value of protection during the early years of work, and the lack of harmful influence to recent exposures with proper precautions. A broad gold ring was worn during the first two years of work on the ring finger of the left hand. This was subsequently removed. The whole dorsum of the hand shows the characteristic changes, while the skin protected by the ring remains to this day perfectly normal. The immunity which even light clothing offers is shown by the rarity or slight degree of dermatitis above the cuffs, and in those parts of the body protected by clothing. It would seem, therefore, in view of this immunity from slight covering, that not the X-ray themselves, but other emanations from the tube are to be held chiefly responsible for the burns and the chronic dermatitis. With these few general remarks, I shall proceed to record the cases, with the pathological reports when available, and to give after each one a brief summary in which any interesting feature will be mentioned.

CASE I. — Miss A. Personal communication from physician. Owing to slight tuberculous disease of the ankle, patient was subjected to vigorous X-ray treatment for a year and a half. Extensive X-ray burn resulted in an intractable deep ulceration 3 x 2 inches in extent, just above the ankle on the inner side of the leg. Pain was extreme. Amputation at point of election, wound healing, but pain in stump persisting a year after operation. No evidences of carcinoma in the ulcer.

Comment: Excision and skin grafting might have been done in this instance but, owing to the tuberculosis of the tarsus, amputation seemed preferable.

CASE II. — Personal. Dr. Wolbach, Case I. F. M.; age 55; was operated upon for adenocarcinoma of the stomach, with partial gastrectomy, Dec. 19, 1905; recovery was perfect. On July 23, 1908, after swallowing bismuth, he was examined for not more than twenty minutes with the fluoroscope, the tube being supposedly at a distance of fifteen inches. In three weeks he reported complaining of severe pain and an area of erythema about the size of a dinner plate, in the middle of the back. This was treated with one per cent. ichthyol wash, but with extreme suffering, the skin broke down, forming an irregular ulcer about three inches by two, which was resistant to all treatment, and steadily increased in size.

Operation under ether, Nov. 18, 1908, Massachusetts General Hospital. In the center of the back, over an area 4½ x 3½ inches, is a superficial ulcer, surrounded by an irregular margin of reddened skin, situated over the last two dorsal and first two lumbar vertebræ. The base of the ulcer is slightly depressed, showing no evidence of granulation tissue, but the surface is covered with firmly adherent fibrin. There are several roundish, moundlike elevations, varying in diameter from a quarter to a half inch. After careful preliminary cleansing, the whole area, with a margin of three-quarters of an inch, was excised down to the underlying muscle. The choice then arose as to a plastic operation or a skin graft; the former was chosen. A flap was made with the base uppermost, extending downward and to the right. This was dissected up and turned over, and sutured without tension to the margins of the wound. Another flap was swung from below into the denuded area; approximation was almost complete. In a few days the wound became infected from a nearby furunculosis and, in spite of vaccines, there occurred some sloughing of the distal part of the flap. Healing took place slowly, but without fever. Superficial necrosis of the surrounding skin is still taking place, and raw surfaces being covered with a characteristic fibrinous membrane. On December 22, the patient was temporarily discharged from the hospital, the depth of the wound granulating healthily, but the skin still undergoing superficial necrosis.

Summary: X-ray burn after long exposure, July 23, 1908. Ulceration began six weeks afterwards, steadily progressing with great pain in spite of treatment. Excision of large ulceration on back on Nov. 18, 1908. Operation brought about immediate and permanent relief from pain, but

subsequent necrosis of the edges of the wound raised the question as to whether the excision had been adequate. Whether the sloughing of the flap was due to infection or to inadequate blood supply, on account of the obliterative endarteritis present, is an open question. There are other instances of the sloughing of flaps where the skin has been for a long time exposed to X-rays. This at least would serve as a warning in the performance of plastic surgery in these cases, and were I to operate again I should simply excise such an ulcer with primary skin grafting. The mounds mentioned on the surface of the ulcer were shown by microscopic examination to be blisters in the deep layers of the epidermis.

Pathological report by Dr. Wolbach. Material consists of Zenker hardened tissue representing a large ulcer about 10 centimeters in diameter surrounded by a border of epidermis 1 to 1½ centimeters in thickness.

Microscopic description: paraffine sections; phosphotungstic and hematein stain.

The portions covered by skin are very similar in appearance to the tissue from the cases of Miss H. and Mr. S., that is, we have the same rarefication of the corium immediately beneath the epidermis. The papillæ are absent, so that the epidermis presents a perfectly smooth under surface. The portion denuded of epithelium shows a slight fibrinous exudate overlying the corium. In a few places there is granulation tissue beneath thick layers of coarse meshed fibrin. The epidermis in places is markedly thinned and the ordinary arrangement of the basal layer is lost. The cells of the epidermis in the thin portions are larger, somewhat vesicular in character and stain less deeply than those of normal epidermis. There is nowhere any evidence of invasion of the corium by epidermis. The deep vessels of the corium show very slight changes. There are many coil glands which are practically normal. Others are atrophic and are surrounded by new formed connective tissue and masses of lymphoid and plasma cells. No hair follicles or sebaceous glands found in the section. Irregular areas and tracts throughout the corium filled with lymphoid and plasma cells are probably spaces once occupied by coil glands and ducts.

In brief, this tissue shows the same processes found in Case VIII. and Case IV., but to a less advanced degree. The characteristic changes of the corium are present. Vessels show very slight thickening of the intima. Epidermis, however, does not show irregular downgrowth suggesting beginning carcinoma.

Case III. — Personal. Dr. Wolbach, Case II. E. R.; 28 years (female); referred to me by Dr. Reeves of Boston. Patient consulted Dr. R. first for ulcerations of elbow and knee on March 18, 1908. X-ray treatment until the end of April at the Emergency Hospital, when they broke down and she went to the Emergency as a patient for three weeks, as ulcers formed on both knee and elbow. Under treatment, the acute dermatitis subsided, but since then the ulcers

have never healed. While at hospital the ulcer diminished on the knee from 5 x 3 inches to 2½ x 1; that on the elbow from 2½ x 1½ to the size of a "quarter." Patient worked for two weeks, and although the ulcerations did not increase in size, the skin surrounding them became irritated. Was again admitted to hospital for three weeks in June; improvement under rest and treatment. Reëntered August 18, where she remained until Nov. 7, 1908, when she was discharged. Daily dressing since then.

Examination Dec. 4, 1908. Over inner aspect of flexure of elbow are characteristic X-ray changes; evidences of old ulceration about 4 x 3 with cicatricial tissue and telangiectases. Just above the inner condyle is an ulceration about size of a dime which is covered with a yellow, fibrinous scab. The skin about it is atrophic; causes pain on motion; no dermatitis. Examination of left leg: dermatitis from middle of thigh to top of boot; a great deal of irritation and itching. There is some edema. On the outer side of the knee over an area 6 x 5 inches the skin is reddened, pigmented and shows scars peripherally to the old healed ulcerations; also telangiectases. Ulceration at present is 2½ x 1 inches; sore and tender to touch. Pain and sensitiveness, however, are less now than during acute inflammation. Patient says boric acid, aristol, corrosive wash, as well as ichthyol all irritated the skin. The edges of the skin show little evidence of healing; there is fibrin at the margin of the growing epithelium. The whole skin of this area is indurated and is two or three times the normal thickness. There is already some tendency to cicatricial contraction, but this is on the outside of the knee, not in the popliteal space. The dermatitis of the rest of the leg can be properly called medicamentosa.

Operation, Jan. 21, 1909, N. E. Baptist Hospital. Since last visit, the patient has been comparatively free from pain, as the dermatitis has subsided, but the ulceration shows no evidence of healing or of growing smaller. Its base is very much indurated. Under ether, thorough excision down to fat, with half-inch margin. After bleeding had stopped raw surface was covered with Thiersch grafts from the left thigh. Protective tissue; firm pressure; splint.

Jan. 28, 1909. First dressing. Little maceration; five-sixths of the grafts have taken, but here and there in the edges, and in one or two places in the center, there have been small hemorrhages with resulting necrosis.

Jan. 30, 1909. Grafts exposed to air and apparently doing well.

Feb. 24, 1909. Almost all of the grafts took, but here and there, one or two small areas subsequently broke down and showed a tendency to spread. It would seem to me as if excision had been inadequate and further operation was advisable. This proves to me quite clearly, in connection with the S. case, that it is hard to gauge how much devitalized tissue should be removed; although my excisions have appeared at the time free enough, I think in general they may have been inadequate.

March 25, 1909. As there had been a previous history of specific disease in this case, I decided to try the effects of internal treatment before

resorting to further grafting. After ten days of mixed treatment and the local application of black wash, the broken-down areas were entirely healed over. It would thus seem as if the original ulcerations, for which the X-rays had been applied, were undoubtedly specific, and that in spite of grafting the disease progressed from a lower level.

April 1, 1909. Patient is entirely free from pain. Grafts are beginning to be mobile; the leg is soundly healed.

For pathological report see Dr. Wolbach's paper under Case II.

CASE IV. — Personal. Dr. Wolbach, Case III. F. H. S.; 40 years; referred to me by Dr. C. J. White Nov. 16, 1908. Treatment with X-rays five years ago, for eczema of both legs, with marked improvement. After subsequent, rather frequent treatments, extending over a period of a year, there developed a rather severe dermatitis which healed slowly with complete desquamation of the superficial layers of the skin from the middle of the thighs downward. Four years ago there appeared on the inner side of the left calf a small ulcer, which from that time has never completely healed. On the right shin there was also an ulcer which took months to heal. Both popliteal spaces showed characteristic telangiectases. There has been no pain. In August, 1908, the ulceration of the left leg began to spread rapidly and refused to yield to any treatment; radium was twice applied. Examination on Nov. 16, 1908, shows about the middle of the left leg an ulceration, 3 x 2¼ inches. The edges are irregular, slightly indurated; in some parts there are islands of growing epidermis, and in others fairly healthy areas of granulation — in still others, there is an unhealthy surface covered with adherent fibrin. The skin is undermined and shows no evidence of repair. Operation was advised and accepted.

Operation under ether, Nov. 19, 1908. Leg was disinfected with extreme care and the whole ulcer excised with a margin of half an inch down to the subcutaneous fat and under the old ulceration to the sheath of the gastrocnemius muscle itself. After bleeding had ceased the wound was again disinfected and moderately thick skin grafts were taken from the left thigh. These were stitched to the edges and wound covered with protective and a firm bandage. On the evening following operation the temperature rose to 101, but he had no pain. At noon on the following day the wound was dressed, the temperature being at that time 100. It was found that infection had taken place, and that the periphery of the grafts had sloughed with some hemorrhagic infiltration into the central portion. In spite of exposure to air, alternating with antiseptic fomentations, all of the grafts separated, except for an irregular area about three-fourths of an inch in diameter, in the very center of the wound. At the end of two weeks the wound became healthy, and granulation was well established. Small Thiersch grafts from another patient were placed on the surface, but in two days all of these except two had likewise sloughed; in the meantime there had been an unusual amount of suppuration of the thigh from which the grafts had originally been removed.

The lower edge of the wound, where the skin was twice the normal thickness, showed no evidence of healing. While infection probably played the chief role in this failure, it seemed to me not unlikely that the tissues both of the thigh and of the leg were less resistant owing to the previous X-ray injuries. On several occasions, small strips of skin were placed upon the wound and covered with crêpe lisse. These grafts with the rapid growth of the original Thiersch graft in the middle allowed the patient to return to his home on Dec. 22, 1908, with the wound four-fifths healed.

Pathological report by Dr. S. B. Wolbach. A large piece of Zenker hardened tissue consisting of an ulcer with surrounding skin. Microscopic examination: Zenker fixation; paraffine sections; phosphotungstic acid-hematein stain.

The tissue is very similar to that from the case of Miss H. The ulcerated surface shows typical granulation tissue springing from a base of rarefied corium. On the surface are small islands of epithelium which present no striking or unusual characteristics. The most striking changes found in the sections are in the corium just beneath the epidermis surrounding the ulcer and in the vessels throughout the sections. The connective tissue cells of the corium just beneath the epidermis are widely separated and of embryonic type in appearance; they are surrounded by very few delicate collagenous fibrils. In this rarefied corium are many large blood vessels lined with a single layer of endothelium. A few of these vessels lie in direct contact with the basal layer of the epidermis, some are completely surrounded by epidermis and a few are filled with fibrin thrombi.

In the deep layers of the corium there is marked thickening of the walls of both arteries and veins. The thickening is due chiefly to an increase in the connective tissue of the intima. The endothelium of some vessels is swollen. There is also an increase of connective tissue in the muscular coats. There are numerous completely obliterated arteries.

The coil glands are nearly completely absent. A few atrophic tubules are found in areas of new formed connective tissue. No hair follicles or sebaceous glands are to be found. The epidermis surrounding the ulcer is slightly thickened. The horny layer is strikingly narrow and in places absent. There are many irregular downgrowths of epidermis into the rarefied corium, but these processes all present an orderly layer of columnal basal cells. At the edge of the ulcer are downgrowths of atypical epithelium, not however more striking than in the case of any chronic ulcer.

There is nowhere any suggestion of malignancy or actual invasion of the corium.

Subsequent history: Feb. 1, 1909. Upon returning to his home, the wound was completely healed in three or four days, but on January 2 the grafts which had been taken from another patient slowly broke down with the formation of blisters, and upon his arrival in Boston had entirely disappeared. The under surface, however, was healthy, and in two days

snips were applied from his arm and covered with crêpe lisse. These grafts rapidly coalesced by January 20, and he was discharged home entirely healed and has so remained until the present time.

CASE V. — Personal. W. H. M. (physician), Lawrence, Mass.; 43 years. Patient's hands have been treated by the X-rays for seven years, for eczema; exposures ten to fifteen minutes — both coil and static machines. Extensive, rather superficial burns of both hands in January, 1906; the skin sloughed off but was replaced. Later exposures in May, 1906, followed by slight dermatitis. Last exposure, Dec. 10, 1906, static machine, five inches, twelve minutes, followed by swelling of hands, and in four days, with small cracks at knuckle of index finger of right hand. Black spots on all sides of the fissure. Continual, though gradually increasing ulceration with no tendency to heal. Pain has been excessive, cutting down his sleep to an average of two hours a night; unrelieved by anything except morphia.

Examination of right hand shows characteristic X-ray lesions, few keratoses and many telangiectases. Over the knuckle of index finger is an ulceration with slightly indurated edges, about 3 x 4 centimeters. On the dorsum of the first phalanx, same finger, is another ulceration about the size of the little finger nail. There are several extremely tender points in both ulcerations. Owing to immobilization of the hand, there is some edema and little flexion of the first and second fingers. (See Plate XXXV., Fig. 1.)

Patient was operated upon by me at the Massachusetts General Hospital May 2, 1907. With a wide margin, both ulcers were thoroughly excised, removing all of the skin down to the tendons, and the dorsal aponeurosis, and the skin grafted in the usual manner. Treated with protective for thirty-six hours, and then exposed to air under a cage. The grafts healed soundly, except for one or two small areas at the edge. Patient was discharged from the hospital in ten days. Pain entirely ceased from the time of operation.

Pathological examination showed no definite carcinoma, but in certain spots the epithelium was clearly in a precancerous stage. The papillary layers were depressed below the surface, mitosis was well marked, and there was slight round cell infiltration.

In August, 1907, for the first time, the slight ulceration at the edge of the graft, near the base of the middle finger, was completely healed. There has been no pain, and flexion in the fingers is rapidly returning. By Jan. 1, 1908, there was final and permanent healing; flexion normal; no pain.

March 11, 1908. Fingers could be flexed normally, the graft was movable on the underlying tissues, and appeared to be the most normal skin on the back of the hand. He still suffers from eczema of other parts of the skin.

Summary: Treatment with X-rays for seven years for eczema of right hand. Extremely painful ulceration at base of first and middle fingers.

Average sleep for past six months, without morphia, only two hours. Deep excision; grafting. Complete freedom from pain. Sore at edge of graft unhealed for several months. Present condition: complete healing; normal motion. Precancerous condition, but no definite epithelioma.

CASE VI. — B. S. B.; X-ray manufacturer; personal communication from Dr. M. M. Johnson, of Hartford, Conn. Patient had severe X-ray burn of back of left hand, and over the middle of the sternum. The skin of the back of the hand was thickened, and cut like leather. There were many small nodules and one large open sore, the result of sloughing. A circular incision was made around the open sore, and the metacarpal bone and the tissues were curetted and thoroughly cleaned. A Wolf graft was taken from the arm and stitched in position. At one time there was indication of sloughing at the border of the transplanted tissue, but eventually the result was perfect. The small nodules were excised and but few have returned. The ulcer over the sternum was excised and closed by granulation. Microscopic examination showed chronic inflammatory tissue, without any trace of epithelioma.

CASE VII. — Personal. Dr. Wolbach, Case VI. W. W. G. (physician), of St. Louis; 42 years. Began using the X-ray in his practice in 1897; a static machine. May, 1900, had an itching dermatitis on the dorsal surface of the left hand; this healed in the course of a few weeks. He next noticed, within a short time, trophic changes about the nails, especially that of the index finger. There was alopecia; the skin became dry and reddened. In December, 1900, infection about index finger caused excruciating pain, and in March, 1901, the nail was removed. In 1903 patient was in Berlin, and at that time had numerous telangiectatic areas on the dorsum of hand and fingers, as well as several keratoses. Owing to persistent ulceration about the matrix of the first finger nail, the finger was amputated through the middle phalanx by Professor Sonnenberg. Since then other ulcerations have developed, the most annoying at the base of the middle finger. This remained open until January, 1905, when it was excised by Dr. Bernays, and a Krause graft implanted; the graft healed well. Following this operation he had but little pain but was frequently annoyed by superficial ulcerations about the fingers. For a year or more, prior to December, 1907, he suffered from a slight ulceration near a keratosis at the base of the ring and little fingers. There was also painful ulceration about the matrix of the little finger nail. On Dec. 22, 1907, Dr. Willard Bartlett operated under ether. The middle finger was amputated, through the second phalanx, several ulcerations at the base of ring and little fingers excised and the skin sutured. An attempt was made to extirpate the matrix of the radial half of the little finger nail. At the same time, Thiersch graft was implanted, after excision of a painful fissure over the distal portion of the proximal phalanx of the ring finger; the Thiersch graft was a success. Except for frequent slight injuries to the dorsal surfaces of the fingers, which healed promptly, the hand

remained practically free from further ulceration until April, 1908, when an ulcer developed beneath a keratosis near the proximal end of the middle phalanx of the ring finger which, like all the other ulcerations, was exceedingly painful at times. The skin about the thumb remained throughout practically free from lesions, except for a horny growth over the inner surface of the proximal phalanx. There had never been serious trophic disturbances of the thumb nail, but the finger nails, in order of severity, from index to little finger, were profoundly affected. The keratotic spots have invariably been the seat of the ulcerations, excepting that on the amputated index finger which arose from retention of some of the nail-producing membrane.

Patient consulted me Aug. 17, 1908. The left hand is typical in appearance; telangiectases are numerous; there are several thickened papules over the base of the thumb; the ends of two fingers have been amputated; the nail of the ring finger is irregular and thickened; the nail of the little finger has in part been removed, but there has been persistent ulceration on the radial side of the matrix which is extremely sensitive. There is an open ulceration, without indurated margins, over the first interphalangeal joint of the ring finger. There is moderate motion in this joint; the last joint is hyperextended and somewhat stiff. On the backs of the other three fingers are areas of keratoses, scar tissue, and occasional petechiæ. At the base of the cleft, between the thumb and first finger, is an ulcerated papule with somewhat indurated edges.

Operation under ether, Aug. 19, 1908. Several small papules were excised; the wound sutured with horse hair. The ulcerated area on the ring finger was carefully excised with a wide margin down to the dorsal aponeurosis; the edges were bevelled as usual; bleeding was profuse. The ulcerated hemorrhagic and keratotic areas on the backs of the other fingers were also excised, as were several keratoses in other parts of the hand. The entire matrix of the little finger was thoroughly removed and a graft applied. Moderately thick grafts were cut from the arm and sutured in position after the bleeding had ceased. Hand was carefully strapped to a well-padded splint, rubber tissue placed in an imbricated fashion over the grafts. Firm pressure with large gauze dressing applied. The operation lasted about two hours and a quarter.

At the end of thirty-six hours the protective was removed, the hand greased with a mixture of benzoated lard, lanolin, and ichthyol. All the grafts, except one on the forefinger, looked well. August 23, grafts looked fairly well; that on fourth finger improving in appearance. Graft on terminal phalanx of little finger dead. Some sloughing of portions of grafts on first and middle fingers. August 26, large part of graft on forefinger is sloughing, and part of that on the middle. Grafts on the ring and little fingers and dorsum have taken well. August 29, grafted areas thoroughly clean and all portions of unattached skin were removed. September 12, all granulating areas are cicatrizing rapidly from the edges. Discharged on Sept. 15, 1908.

Letter from patient, dated Oct. 22, 1908:

"It is just a few days more than a month since I took leave of you, and since that time my hand has shown continuous improvement. The scabs have fallen from index and middle fingers, and the slight cicatrization about these in no way interferes with the free mobility of the joints. There is a certain elasticity about the skin of these two fingers which I have not hitherto felt. The grafts on the other fingers and at the base of ring finger are simply perfect. Even the slight 'V' shaped defect of graft on ring finger has filled in, so that the entire surface is now uniform. There has been no sign of activity in little finger matrix, and this more than two months since the operation, so that I am not anticipating any further trouble at this point. The dorsal surface of the hand, with the exception of one little point, is entirely free from keratoses, and the places where such were shaved are now smooth and pliable cicatrices; indeed, the appearance of the whole hand shows a vitality which I had not dreamed to be possible."

Pathological report by Dr. S. B. Wolbach. The sections show approximately normal epidermis and corium, except in the middle portion where the epidermis is markedly thickened, the corium infiltrated with lymphoid and plasma cells and without papillæ. There is a marked heaping up of the horny layer of the epidermis, and in one place in the center, where the section is tangential to a hair follicle, there is a downgrowth of the epidermis into the infiltrated corium. These processes from the epidermis are atypical in that the columnar regularly arranged basal layer of cells is absent, and because of included collagen fibrils. The corium just beneath the epidermis does not show the rarefication found in many other sections of X-ray keratoses. The hair follicles and glands are practically normal.

Summary: Marked hypertrophy of epidermis with keratosis and beginning invasion of corium by epithelium.

Case VIII. — Personal. Wolbach, Case IV. Plate XXXV., Figs. 2 and 3. Miss H., 40 years, is one of extreme interest from many points of view. In brief, the previous history is as follows: seven years ago, patient was operated upon by Dr. Boothby for a so-called fibroid of the uterus, the operation being an abdominal hysterectomy. She was well for a year, when there formed, to the right of the incision, in the abdominal wall, a slowly growing tumor, which was, however, characteristic of a sarcoma, and pronounced inoperable by Dr. Maurice H. Richardson, by whom she was sent to Dr. W. B. Coley of New York for treatment by toxins. He excised a portion of the growth, and found it to be a fibrosarcoma. At first the growth diminished under toxins, but after ten months it was decided that further treatment was not warrantable as the growth was increasing rapidly. The patient was losing flesh, markedly cachectic, very weak, and complained bitterly of pressure symptoms. I am quoting from the report of this case by Dr. Clarence E. Skinner of New Haven, Conn., to whom she was referred by Dr. Bevan of West

Haven, for roentgenization. At this time, he states that the mass covered ten inches from side to side at the level of the anterior superior spines of the ilia, eight inches vertically in the median line, and about five inches antero-posteriorly. Treatment was begun by him on Jan. 28, 1902, and during the next four months she received forty-six applications. The general condition began to improve at once, but the tumor showed little change. Patient went home for a visit, and upon her return it was noted that the tumor had diminished about one-fifth in size. From June 17 to September 3 she received thirty-one roentgenizations. Her general health continued to improve, and the tumor steadily decreased in size, and at the end of this period she resumed her school teaching.

In brief, then, the patient was under treatment for two years and three months, receiving, however, the majority of her applications during the first eight months. The last treatment was given on May 20, 1904, at which time no trace of the tumor was discoverable at examination by Dr. C. A. Bevan of West Haven, and in July by Dr. W. B. Coley of New York. The patient remained perfectly well until August, 1907, though she had noticed that the skin of the hypogastric region was irregularly mottled and much thicker than normal, especially on the right side. Pain, from which she had been free, began to be severe and ulceration commenced. No treatment seemed of avail, the ulcerative process gradually spreading, undermining the skin, which subsequently necrosed. She lost weight and strength, becoming anemic, and suffered severely from the pain. She was referred to me by Dr. Dennett of Winchester, and I first saw her at the Baptist Hospital on March 7, 1908. Examination at this time showed in the hypogastric region more on the right than on the left, an irregular, undermined ulcer about the size of the palm of one's hand, roughly an equilateral triangle, extending to the right side of the pubis, then nearly to the right iliac spine, the other angle approaching the umbilicus. The base of this ulceration is sloughing in parts; in others presenting poorly vascularized granulation tissue, in which necrosis is advancing rapidly. Several areas in the surrounding skin show characteristic appearances. The irregular undermined ulceration with a firmly adherent fibrinous base is surrounded by a very bright scarlet red areola, which bleeds on the slightest touch. Certain points in the ulceration are exquisitely painful on pressure. There is slight fever. After attempting to cleanse wound with antiseptics for a few days on March 16, the whole ulcerated area, with a margin of about an inch, was excised down to the underlying tissue. This excision left apparently normal fat, except over an area two by three inches to the right of the median line, where extremely firm scar tissue marked the site of the original growth. The skin at the periphery, however, was very tough and three times the normal thickness. The whole wound was thoroughly disinfected with carbolic acid, ninety-five per cent alcohol and salt solution, and an attempt was made by tension sutures to diminish the gaping wound. It was dressed with protective tissue, gauze, and swathe. The tissue was given to Dr.

Wolbach of the Harvard Medical School for examination. His report was as follows:

"The specimen consists of a large, irregularly triangular piece of skin and subcutaneous tissue, its 'base' is 9 centimeters, and the sides are 10 and 11.5 centimeters respectively; it is from 2 to 2.5 centimeters in thickness, except at the central portion where it is .5 to .7 centimeter thick. The skin surface shows a large, irregularly triangular ulcer (5.2 x 7.5 x 8 centimeters) conforming in general to the shape of the specimen. The base of the ulcer is depressed from .2 to .6 centimeter below the rough, irregular, ragged, overhanging, and undermined non-indurated edges which are necrotic, reddish gray in color, and bathed in bright yellow purulent exudation.

"The base of the ulcer is bright red to grayish red in color; it is rough and ragged and is irregularly covered with purulent exudate.

"The lower surface of the specimen consists of bright yellow fat tissue through which is a delicate tracery of grayish-white fibrous tissue. In the central part of this surface of the specimen (the thinner area above referred to) there is an area (3.5 x 4 centimeters) of firm, dense, grayish-white glistening elastic fibrous tissue. On section this fibrous 'disc' is seen to be in places in continuity with the base of the ulcer; in other places it is connected by fine and coarse fibrous strands.

"The margin of skin surrounding the ulcer is from 1 to 3 centimeters in width; it is thicker and firmer than normal skin; it is diffusely reddened with a deep punctate erythema, except for numerous, slightly elevated, rounded, whitened areas (.3 to .6 centimeter in size) which have a distinct nodular, almost 'shotty' feel. On section, these areas are .4 to .6 centimeter in thickness; the surrounding skin is .2 to .3 centimeter thick. The bright punctate appearance in the diffuse erythema of the skin surrounding the ulcer is apparently due to marked injection of very small blood vessels.

"Microscopic examination: I. Disc of fibrous tissue, from deeper tissue of lower portion of tissue, forming floor of ulcer.

"This tissue is dense fibrous tissue poor in cells, composed of bundles which run in all directions. There are numerous small arteries and veins and capillaries, all of which are surrounded by narrow zones of lymphoid and plasma cell infiltration. The amount of elastic tissue is small, and that present is in small masses, usually composed of clumps of thick fibers, most abundant in the neighborhood of the larger vessels.

"II. Section of nodules or elevated areas of skin found at the periphery of ulcer.

"The epidermis for the greater part is markedly thin. There are no hair follicles or glands of any sort. The corium is composed of dense fibrous tissue continuous with the deeper tissues so that its normal relations and appearances are gone. There are no papillæ so that the epidermis lies evenly upon dense white fibrous tissue. The corium immediately beneath the epidermis in places stains very poorly. There is marked diminution of collagen fibrils and there are many connective

tissue cells of embryonic type. There are many large spaces filled with blood and lined by a single layer of endothelium, which on one side may lie directly in contact with the epidermis. The corium is composed of dense fibrous tissue continuous with the subcutaneous tissue so that there is one compact layer between the skin and fat tissue. This fibrous tissue contains areas with excessive amounts of elastic tissue resembling the masses of elastic tissue found in the stroma of carcinomata. In a few places there is a marked downgrowth of epithelium between dilated vessels. A few areas show branching stalks of epithelium with characteristic pearls or onion bodies. There is marked lymphoid and plasma cell infiltration about the epithelial downgrowths. The atypical character of the epithelium, the presence of pearls and many mitoses and the relationship of epithelium to connective tissue in these downgrowths warrant the diagnosis of epidermoid carcinomata.

"The ulcers: All show similar appearances. The floor is usually covered with fibrin and pus, underlying which is granulation tissue. The epidermis at the edges shows slight downgrowths which do not suggest malignancy. The deep connective tissue contains areas of elastic tissue increase like those described above. Completely and partially obliterated arteries are common in the subcutaneous fibrous tissue. The obliteration is caused by a proliferation of intimal connective tissue. A few nerve trunks are found showing increased connective tissue and compressed nerve fibers. The fat tissue below and adjacent to the ulcers show absorption with organization. The newly-formed tissue contains many large, occasionally multinucleated and grotesquely shaped cells, which are derived from connective tissue as shown by the presence of fibroglia fibrils when stained by Mallory's methods."

The operation was followed by marked reaction, pain, temperature of 102, rapid pulse, exhaustion, and at the end of three or four days continuous sloughing of the edges of the wound, involving the skin more than the fat. The wound at first was dressed with dry gauze, but this was soon replaced, on account of pain, by ichthyol lanolin ointment on bandage cloth. By March 15 necrosis stopped temporarily, and granulation was beginning. The constitutional symptoms were distinctly better, though fever in the afternoon still persisted. On March 20, the condition was as follows: the edges of the skin, in the right groin, had ceased sloughing and granulation was fairly well established. On the left, however, necrosis still proceeded involving only the skin, whereas the fat was granulating healthily. There are new areas of necrosis, varying in size from a dime to a split pea in the thickened skin, near the margin of the wound. There is not much discharge, no enlargement of the glands in either groin, and the general condition of the patient is slowly but steadily improving. Her chief complaint is of pain in the right loin, the lightest contact over the old scar causing extreme shooting pains. This cicatrix is covered with an adherent diphtheritic membrane which is extremely tough. If a portion of it be peeled off, bleeding is free. Cultures were made and sent to Dr. Wolbach, and he reported that bacilli,

morphologically similar to diphtheria, were present; inoculation however showed that they were inactive.

April 25: For the past two weeks the wound has been granulating healthily throughout its greater part. The central zone which comprised the old scar is behaving in a most unique fashion. The area, which a month ago was covered by a diphtheritic membrane, is now changed to a smooth, glistening surface, which bleeds on the slightest touch. From the periphery, granulation is slowly stealing in. The skin in the right pubic region is healing soundly, and the epithelium is growing normally over the granulations. Just above the right iliac spine is an irregular dirty fibrin-covered ulcer, about the size of the end of the thumb. The deeper layers of the skin are necrotic. In the central portion, above the umbilicus are a number of similar radiating ulcerations. There are some lymphangitis about the wound. The undermining at the left-hand side of the wound is less marked. From her morning headaches, nervous feelings, and poor pulse, it would seem as if there was continuous, slight infection from the wound, though the temperature is now almost normal. During the summer she lived in a tent, the wound being dressed twice daily. Granulation was slow and epithelium once formed frequently broke down, but over the pubic region, and in the right groin, epidermization continued satisfactorily but slowly and gradually the ulcerations starting in the skin spread, the size of the wound was continually increasing, by their confluence, in all directions. In view, however, of her marked prostration, after her first operation, it seemed better to allow the tissues to slough rather than to remove them. During September her general condition improved very markedly, and with this the central granulating wound took on a more normal appearance. On September 28, I decided upon another operation, at which, under ether, I removed the remaining skin of the anterior abdominal wall, as far out on both sides as the anterior superior spines and upwards to a level of four inches above the umbilicus. At this operation, I only removed the skin, leaving behind as much as possible of the fat tissue. The wound was dressed with protective. Reaction was well marked but was less severe than after the previous operation, and the temperature became normal in ten days.

By Dec. 5, 1908, the patient had gained in general strength and color, and was walking about. Healing has taken place rapidly from the edges, and with the exception of some painful ulcerations in the remaining skin of the left groin the whole wound is granulating for the first time, in a perfectly normal manner. On this date, three long, narrow Thiersch grafts were taken from the arm of a friend, cut into fourteen pieces about three-quarters of an inch square, and scattered over the granulating surface. They were held in position by broad strips of crêpe lisse, covered with protective tissue. After twenty-four hours, salt solution fomentations were applied frequently, and at the end of ten days twelve had healed soundly in position, thus greatly diminishing the denuded area.

Dec. 24, 1908. All of the grafts have grown vigorously during the past week. It seems as if no further grafting would be necessary, as

three-fourths of the huge granulating wound is now covered with apparently healthy epithelium. There is in the left groin, outside the edge of the wound, an irregular, unhealthy ulceration, which is extremely sore and tender. This must be grafted at a later period.

Feb. 24, 1909. After three or four weeks all of the grafts taken from her friend were raised by blisters and slowly disappeared. Two weeks ago the left end of the wound was grafted with snips from her thigh; of nine, eight took and have grown well. In view, however, of the slow progress it seemed to me best to operate this morning, February 23. Accordingly, under gas and ether, the wound was thoroughly cleaned with green soap and water, and the granulations vigorously scrubbed with salt solution, followed by a copious saline irrigation. Moderately thin Thiersch grafts were removed from the right thigh, and the whole wound covered. One could not but be surprised by the copious serous discharge from the whole granulating surface. I have never seen anything like it. Whether this was due to some peculiar condition, or possibly to the irritation of the green soap, I do not know. The grafts were covered with protective, gauze was then placed carefully over the uneven surfaces, and held in place by adhesive plaster. The thigh was covered with protective and bandage. A snug swathe was then evenly fitted over the whole abdomen, making all possible pressure.

April 1, 1909. With a few exceptions, all of the Thiersch grafts took, and, with their continued growth, at present the huge wound is continuously covered with sound, thick, and somewhat movable skin, except for an area on the right hand upper margin, 2 x 3 centimeters. There is no tenderness in the scar, and no pain. Patient has been up and about for three weeks, having been in the hospital thirteen months. Owing to continued flexion of the thighs there is some subluxation of both knee joints, and she walks clumsily and somewhat in a stooping manner, owing to the contraction of the anterior muscles of the body. There is no evidence of recurrence of the sarcoma. Her general condition is excellent.

Summary: This patient, after unsuccessful treatment of ten months with Coley's serum for a fibrosarcoma of the abdominal wall, was entirely cured of this condition by one hundred and thirty-six X-ray treatments, covering a period of two years and three months. She was well for four years, except for some thickening of the skin and telangiectases, when severer and characteristic X-ray lesions developed, not only in the scar of the shrunken tumor, but in the skin over the whole anterior abdomen. In addition to the ulcerations of the skin, which not only refused to heal under all treatment, but steadily increased in depth and area, there were numerous papules of undoubted epidermoid cancer. At the first operation the ulcerated areas of the lower abdomen were thoroughly excised with wide margins, down to the scar of the tumor and the anterior aponeuroses. The operation was followed by marked infection, which was questionably diphtheritic. The wound was extremely sluggish and granulations very slowly formed, covered by unhealthy fibrin. General condition poor. After months of convalescence, granulation gradually

established, and epidermization slowly took place from the pubic and inguinal regions, but the thickened skin ulcerated upward and laterally, with great pain and some fever. Six months after the first operation I decided under ether to remove the remaining thickened skin of the anterior abdominal wall for a distance of four inches above the umbilicus, and laterally to a level with the anterior superior spines. The skin and upper half of the subcutaneous fat alone was removed. The wound was dressed with protective. After two months, the wound at that time granulating healthily, a number of Thiersch grafts were removed from the arm of a friend and applied over the large surface. In three weeks, healing was almost complete, but in two more the apparently healthy grafts began to blister and come away. In three weeks more, patient was etherized and grafts from her own thigh placed in position. These at the present time, thirteen months after the first operation, have grown soundly and the whole wound is healed. This case should serve as a warning not to use Thiersch grafts from other people, unless the condition of the patient contraindicates ether.

Case IX. — M. K. K. (physician); 40 years; X-ray operator, Philadelphia. Began work in 1899. In 1901, hands showed usual early lesions; telangiectases, ribbing of the nails and thickened fissured skin. In 1903 the superficial ulcerations and keratoses shown in the photographs, involving the lower parts of the hands and fingers. By January, 1908, there was general improvement of the dorsum of the hands and fingers of the right hand, but an extensive and suspicious keratosis at the base of the fourth finger. For two years there has been ulceration of the two terminal phalanges of the middle finger of the left hand, and for eighteen months a similar condition over the first phalanx and distal joint of the fourth finger. By December, 1908, the large keratosis on the right hand, under treatment, has almost disappeared, but the ulcerations on the end of the middle finger of the left hand were typically malignant. The ulcerations and a keratosis on the ring finger became infected, and an exuberant growth appeared increasing rapidly in size. On April 4, 1909, the middle finger was amputated at the end of the first phalanx, and the ring finger at the knuckle. There were no glands in the axilla. (Pathological diagnosis: epidermoid carcinoma; Plate XXXV., Figs. 4, 5, 6.)

Case X. — M. N.; 35 years; Swede. Personal communication from Dr. A. D. Bevan of Chicago. In April, 1902, had abscess of obscure nature in left lower quadrant of abdomen. This was opened and found to be fecal and drained. A fecal fistua resulted, which was closed at operation August, 1902. He returned again October, 1902, with symptoms of intestinal obstruction and an exploratory laparotomy was performed and a tumor-like mass found in the descending colon. The operation was purely exploratory. December, 1902, he again had symptoms of obstruction; another operation was performed; some adhesions

between the small intestine and descending colon separated, and a Meckel's diverticulum was found and removed. This apparently had nothing to do with his illness. The tumor-like mass in the colon was of uncertain diagnosis; we regarded it as either carcinoma, syphilis, or tuberculosis. He was given antispecific treatment and was given a large number of X-ray exposures over the mass. This resulted in rather an extensive X-ray burn, which healed slowly. The swelling in the abdomen disappeared and the man made an apparently complete recovery.

October, 1908, he returned to the hospital with several irregular ulcers in the scar of the X-ray burn. It was thought that they were suspicious of carcinoma and a large area about 6 x 6 inches containing the scar of the old X-ray burn and these ulcers were dissected off, and the surface covered with skin grafts. The microscopical sections from the margin of the ulcers show a suspicion of beginning carcinoma. There is proliferation of the epithelial cells with processes extending a moderate depth in the subcutaneous tissue, in several portions of the section, but only at these points is the basement membrane broken. There is some round cell infiltration; nowhere is there a separate island of epithelial cells or epithelial pearls. From the microscopical section I am inclined to regard it as a beginning epithelioma.

Summary: Large number of X-ray exposures for abdominal tumor; extensive burn which healed slowly. Latent period at least five years, when several irregular ulcers developed in the scar. A large area 6 x 6 inches dissected off with successful skin grafting. Pathological report: beginning epithelioma.

Case XI. — Personal. E. W. C.; aged 37 years; admitted to the Massachusetts General Hospital Sept. 3, 1907, with the following history: Shortly after beginning work with the X-rays, ten years ago, patient noticed desquamation and ulcerative areas appearing on the dorsum and knuckles of left hand. He also developed telangiectases of left thigh and lower abdomen. Although he has long since ceased to expose himself, the parts have continued to ulcerate, until some of them have taken on a more deep-seated epitheliomatous character. He has tried all sorts of washes and ointments, exposure to sunlight, arc light, with and without screens, and the so-called luecodescent light. In his case, all of these agents were harmful; the relief reported by some, he explained, as due entirely to the heating effect, for the pain, which prevented sleep, would often yield to treatment for fifteen or twenty minutes, with an electric heating pad.

Examination of left hand shows the usual telangiectases, atrophy of the skin, with numerous keratoses and papules, and several ulcerated areas; two in particular appearing most suspicious — one at the base of the first finger, and another in the cleft between it and the thumb. There were superficial ulcerations with keratoses over the interphalangeal knuckles of the first two fingers, and another rather extensive keratosis at the base of the ring finger.

Under ether, Sept. 4, 1907, all of these areas were excised, the suspicious ones down to the subcutaneous tissues; the others well into the corium. Skin grafts of moderate thickness were applied to the wound, after bleeding had ceased. Protective tissue, just outside the periphery of the grafts, with firm pressure applied by a gauze roller, the hand having previously been immobilized upon a well-padded splint. On the 5th, rubber tissue removed, and grafts exposed to air, covered with ointment. On the 7th, grafts looked finely. On the 8th, grafts were all looking well, except one over the fourth metacarpo-phalangeal joint, which is a little white in the center, where a small necrotic area has developed. On the 9th, all grafts had taken, except the one previously mentioned over the knuckle of the ring finger. Discharged on September 12, eight days after operation.

Pathological examination showed that ulceration at the base of the forefinger was undoubtedly epithelioma. In two other places, a precancerous condition was present; the tissues from other parts showed superficial ulcerations or keratoses.

Quotation from letter dated Sept. 15, 1908 : "For your records, I have to report that all the grafts grew successfully, and most of them have contracted much more than I expected. They are all in splendid condition, except that there is a tendency to the formation of keratoses at some of the margins. It seems to me that this condition, so common in all X-ray hands, nearly always starts from a small abrasion, and that the trauma at the margin of the incision for the skin graft is just the sort of injury which has produced this kind of growth. I have been able to improve the condition very much by having these spots treated with liquid air, after which there is no tendency toward recurrence. There are no signs of metastatic involvement of the epitrochlear or axillary glands."

Summary : Characteristic X-ray hands. For several years, intermittent healing and ulceration; finally persistent ulceration in spite of treatment by various forms of light, in addition to the usual treatment. Eight excisions; all grafts successful. One undoubted carcinoma; two precancerous lesions. All keratoses which formed at margins of graft successfully treated with liquid air. No return of ulcerations or of disease. Satisfactory result.

Case XII. — S. L. (physician), New York. Personal communication in regard to his own case. "Frequent excisions of epitheliomatous areas, which broke down from time to time, has reduced them to a definite number; five on my left hand of very small size. Of course I have absolutely given up the use of the X-ray, and have even had my machine removed from the office. I still find that the left hand resists chemicals very badly. Too strong or too frequent use of bichlorid will give me an eczematous condition, which immediately lights up the spots from which the epitheliomata have been removed."

Case XIII. — C. L. L. (physician). Several years ago developed an

epithelioma of his forefinger, and fearing excision or even amputation, lest metastases result, applied the X-ray very vigorously, with the intention of destroying all malignant cells before operation. He produced a slough which extended to the bone, after which the finger was amputated and healed by primary union. There are a few suspicious areas over the fingers of the same hand; no glandular involvement.

CASE XIV. — Mr. S., New York, radiographer. Amputation of one finger for epithelioma developing in an X-ray lesion. Now well.

CASE XV. — Personal. Wolbach, Case V. Plate XXXVI., Figs. 7 to 11 (inclusive). F. H. S. Patient sent to me by Dr. Percy Brown. First used X-ray apparatus in the spring of 1897; static machine. Received acute dermatitis on back of left hand, which after healing showed characteristic pigmentation. He has had a few attacks of acute processes since then, but not until three years ago did an ulcer form on the back of the left hand between the knuckles of the first and second fingers. This healed up several times and broke down again. Over the backs of the hands in various places keratoses have formed which became black and then spontaneously fell off. Sometimes has scraped them off with pumice stone. Except for the inconvenience of dressing the ulceration he has had practically no pain in his hand since the original dermatitis. For many years he has noticed that the skin on the front of his chest has become thickened; here and there are somewhat more indurated spots; the whole chest is covered with the characteristic venules. For a number of months he has noticed that the pores of the tip of his nose have filled up, occasionally discharging sebaceous matter. For two months and a half he has noticed a warty growth on tip of nose about the size of a pea.

Examination: On the tip of the nose is a warty growth on which a scab has formed of the size before mentioned. This discharges some serum, no pus; is not sore. The chest presents the characteristic appearance of chronic X-ray dermatitis with telangiectases and some pigmentation. There is thickening of the skin in plaques, but no ulceration. The skin of the back of the left hand is thickened in some places, especially over the joints where it is atrophic and cracked. As shown in the photograph, there are about half a dozen keratoses, the skin about them being thickened to twice normal. At the cleft between the first and second fingers is a well-marked induration with a keratosis growing on the distal part. Above this are three open ulcerations, the distal one having slightly raised indurated edges. The proximal one is flat, non-indurated, appearing like smooth granulation tissue. Diagnosis of the distal ulceration probably beginning epithelioma; of the proximal one, simple ulcer.

Operation under ether March 29, 1908. Ulcerated area on back of hand carefully excised with broad margin down to underlying veins, fat and tendon of middle finger. Edge of thickened skin bevelled. Several indurated areas and keratoses were either excised or shaved down to the

deep skin. All of the raw places were skin grafted from the left arm. The growth on the tip of the nose was shaved off deeply. All of the wounds were covered with protective and the hand firmly bandaged on a splint and elevated. No dressing applied to nose.

For purposes of microscopic examination, an indurated superficial ulcerated papule in the cardiac area of the chest was removed by an elliptical incision, and the skin approximated with silkworm gut sutures.

Convalescence: the usual protective dressing remained in position for twenty-four hours, then ointment and cage. Patient discharged in a week.

Pathological examination by Dr. Wolbach.

1. Keratosis from nose. (Plate XXXVI., Fig. 11.)

The epidermis is greatly thickened and irregular and the horny layer is heaped up, forming a thick layer of keratinized cells. The cells of the stratum germinativum are large, vesicular, and present mitoses. In some by high power fields as many as ten mitoses are found. The processes extending into the corium for the most part present an orderly arranged basal layer except in a few places where the epidermis is infiltrated with lymphoid and plasma cells. The corium immediately beneath the epidermis is thinned in places. Some of the smaller vessels are filled with polynuclear leucocytes. There is everywhere extensive infiltration with lymphoid and plasma cells beneath the epidermis. The epidermis on either side of the keratosis is practically normal.

The most striking feature of this tissue is the extraordinary number of mitotic cells in the epithelial processes and the change in the character of the cells from the compact, basic-staining appearance of the normal epidermal cells to the large vesicular neutral-staining cells found in the processes beneath the keratosis.

2. Large ulcer from hand. (Plate XXXVI., Fig. 8.)

The ulcerated surface is practically the exposed surface of a vascular new growth of epithelium, atypical in type and containing many whorls of keratinized cells. This tissue is microscopically a typical epidermoid carcinoma and there is definite evidence of invasion of the corium. The epidermis on each side of the central mass is irregularly thickened in places and thinned in others. The corium immediately beneath the epidermis is rarefied. A few arteries show thickened walls. No sweat glands or hair follicles found in the sections.

3. Keratosis of hand between index and middle fingers.

The same general picture is found here as in the tissue removed from the nose. The rarefication of the corium beneath the surrounding approximately normal epidermis is more striking than in the case of the nose. There is less infiltration beneath the keratosis, and the epithelium shows comparatively few mitoses. No positive evidence of malignancy.

4. Tissue from the chest. (Plate XXXVI., Fig. 10.)

Consists of a semicircular piece of tissue the convex border of which is covered by epidermis. The central portion of the tissue is very similar to that from the ulcer of the hand in that we have a new growth of epidermis

supplied with many blood vessels and having no definite epidermal covering. The projecting stalks of the central mass contain many whorls of keratinized cells, and the relationship to the connective tissue of the corium leaves no doubt that the tissue is that of a new growth, epidermoid carcinoma in type. The corium beneath the surrounding epidermis shows the same rarefication noted in other cases.

General Note: A description of the new growths from the hand and from the chest hardly seems necessary. In both locations the picture is that of typical epidermoid carcinoma. Mitoses are numerous and the masses of epithelium enclose remnants of elastic fibers and collagenous connective tissue. In the corium, immediately beneath the new growth, there is more increase in elastic tissue, otherwise the changes in the deeper tissue are similar to those noted in the cases of H. and S.

April 22, 1908. Patient visited me the day before yesterday. All of the skin grafts have healed and now show the usual increase in vascularity and are raised above the surrounding skin. The large graft on the back of the hand shows a slightly hypertrophic condition, but is beginning to be movable on the underlying tissues. Several areas of keratoses are slowly reforming.

May 30, 1908. The pathological report that the papule excised from the chest was carcinoma came as a complete surprise. This fact was explained to the patient, and on May 29, under cocaine, the scar of the former operation was excised with a wide margin down to the subcutaneous fat; wound closed with sutures.

December, 1908. Present condition: the nose is slightly flattened at the tip and shows a slight scar. Grafted area upon the hand shows no evidence of recurrence of the carcinoma, and is quite freely movable upon the underlying structures. There are several cracks and fissures, as well as keratoses on the various parts of the hand, but nothing suggesting epithelioma. There is no return of the cancer at the site of the excision over the breast.

Summary: Early acute dermatitis in 1897; innumerable exposures of chest for fluoroscopic examination of heart. Characteristic lesions of chest and left hand; ulceration of hand persisted for three years; no pain. Operation: excision of keratosis on tip of nose, of ulceration of hand and keratoses; successful skin graft. Excision of papule on chest for examination, which proved to be undoubted epithelioma. Prognosis doubtful, as the remains of the indurated tissues of chest may develop carcinoma. Very satisfactory graft.

Case XVI. — G. W. D.; 32 years; radiographer and salesman. Patient of Dr. F. E. Pinkham, Providence, R.I. Patient began work in 1896. Had amputation of ring finger of left hand at the Worcester City Hospital in 1905, on account of ulceration and exuberant growth which had been microscopically examined and pronounced to be an epithelioma. He entered the Massachusetts General Hospital April 7, 1908, having noticed, six weeks ago, a hard lump in the axilla which, though slightly tender,

was not painful. In the past three weeks there had been rapid growth of this tumor. No loss of weight.

Examination of left hand: ring finger amputated at the metacarpo phalangeal joint. On the dorsum of back of hand are several small keratotic areas which have been present since 1899. Skin of dorsum of hand is hard and indurated. No enlargement of left epitrochlear gland. In the left axilla is a tumor about the size of a hen's egg, which is slightly elastic and tender, and more or less fixed to the surrounding tissues. No palpable glands above clavicle.

Operation, April 7, 1908. Incision made through center of axilla over the mass, parallel to the lower border of the pectoralis major muscle. Skin dissected back; axillary fascia opened; gland found to be very hard, possibly slightly fluctuating in the center. Incision made into it, specimen given to Drs. Kidner and Wright for examination. Frozen section showed undoubted epithelioma. The center of the gland was softened and about a teaspoonful of pus or epithelial débris escaped. An incision was then made upward from the other, at right angles to the collar bone. The pectoralis major muscle was divided and retracted, and the pectoralis minor divided at its insertion into the coracoid process. By blunt dissection the fascia covering all of the muscles forming the axillary triangle was removed with the inner portion of the pectoralis major, minor, and axillary third of the latissimus dorsi, and some of the subscapularis; bleeding was quite profuse. The long thoracic nerve was preserved, but some of the branches of the subscapular and the latissimus dorsi were cut. A part of the axillary vein in contact with the gland was resected for a distance of two inches, but the collateral branches of the brachial veins, entering above, carried on the circulation adequately. With the arm flexed and brought forward, the nerves, axillary artery and vein were held forward with retractors and with great care, the whole mass of gland-bearing fat was removed well above the clavicle. It was obvious that in order to get good motion in the arm, a plastic would be necessary. The sternal portion of the pectoralis major muscle was therefore freed from its attachment, and brought downward over the axillary vessels and sutured to the insertion of the muscle. A "U" shaped flap of skin was left attached to it, and utilized to close in the axillary opening.

Convalescence: Some infection occurred from the pus in the broken-down gland, accompanied by fever for several days. Several stitches were removed and a portion of the pectoral muscle sloughed, but patient was discharged with a granulating wound May 4, twenty-five days after operation.

Letter dated Dec. 7, 1908: "I thank you very much for your enquiry, and am greatly pleased to report that I am enjoying excellent health. After leaving the hospital, the wound granulated very nicely and closed up beautifully within three weeks. I have now a fairly good use of the arm."

Summary: X-ray work begun in 1896; ring finger amputated in 1905 for an epithelioma of over a year's duration. Patient well until February

1908 (three years) when malignant disease appeared in the axillary glands; epitrochlear not involved. Very radical dissection of axilla; some infection of wound. Sound healing in six weeks; good use of arm. At present well.

Pathological report by Dr. Wolbach. "Microscopic description: methylene blue and eosin; Mallory's connective tissue stain, phosphotungstic-hematein stain. Paraffine sections. Tissue consists of large lymph node infiltrated with new growth consisting of anastomosing stalks of epithelial cells containing many whorls of cornified cells. The whole is supported by a fairly dense connective tissue reticulum. The picture is that of typical rapidly-growing epidermoid carcinoma. Mitoses are extremely numerous."

CASE XVII. — Personal. (Plate XXXVIII., Figs. 22 and 23) H. G.; 48 years. Consulted me first in January, 1908. He had been working since the very beginning in the manufacture of X-ray tubes. The first indication of any trouble appeared in the shape of a red, itching rash, of which he took very little notice, supposing it to be caused by acid fumes. This condition was succeeded, the latter part of 1898, by the appearance of a number of callosities on the back of the hand, which about the spring of 1899 had changed into warty growths, which he tried to remove by pulling them off. The removal was attended by severe pain, and free bleeding, and seemed to cause them to increase in size and multiply. These warts and other scaly areas were removed frequently by means of a live cautery, only to reappear in increased size. His physician used almost every known salve but the only result was to allay the pain somewhat. "No pen can describe the sensitiveness or the pain of these burns." "One peculiarity of my case is that from the frequent examination of my body with the fluoroscope by hundreds of doctors, the skin of my chest became black and hard, like parchment, giving me, however, no inconvenience and never becoming sore; in less than a year, this blackened skin all came off in one piece, leaving the chest clean, without a scar, but of course removing all hair." For seven years, then, there has been ulceration, induration, and keratosis over an area about 3 x 1½ inches on the back of the left hand. This had been treated in various ways, and during the past six months has shown signs of improvement, under a dressing of vaseline, turpentine, and creosote. The backs of both hands show many keratoses, but the usual telangiectases are remarkable for their absence. On the back of both wrists is an area about the size of a pea, which is hard, not sore, ulcerated in the center, with indurated edges, presenting the characteristic appearance of an epithelioma. A similar growth started three months ago on the left forehead. This soon acquired raised and everted edges and was operated upon by a surgeon in Hartford, but in a month had recurred, and was larger than before. It was again excised, but rapidly returned. On examination of the forehead there appeared a growth about the size of a quarter, gangrenous in the center, with palisaded edges. There was induration about it, and the

growth was firmly fixed at the center to the underlying tissues. No glands could be made out in the parotid region or at the angles of the jaw.

Operation Jan. 17, 1908; ether. After thorough disinfection with pure carbolic acid, the growth on the forehead was excised with an ample margin, removing a circle of tissue about two inches in diameter. The incision was carried down to the periosteum, which was removed with the growth. Section of the tumor showed that it involved the periosteum. On this account, the outer table was chiselled away for an area the size of a half dollar, and the inner table was also removed, over an area the size of a quarter, exposing the dura and the mucous membrane lining the frontal sinus. A complicated plastic operation was done, and the wound closed without drainage. The two epitheliomata over the wrists were excised and the skin sutured. Next, with considerable margin, the ulcerated and thickened skin over the back of the hand was removed down to the veins, subcutaneous tissue, and tendons. A rather thick Thiersch graft was applied and sutured in position with firm pressure. The graft grew by primary union, except for a small area at the base of the little finger, which healed within a few weeks. Patient discharged at the end of ten days.

The two discrete epitheliomata from the wrist were lost. The microscopical examination from the skin of the back of the hand by Dr. J. H. Wright was as follows: The surface of the portion of skin removed is covered with crusts, scabs, and discrete and confluent wart-like elevations. After fixation in Zenker's fluid, paraffine sections were prepared from six different places. The lesions found in these may be summarized as follows: "The stratum corneum is very much thicker than normal, and shows cyst-like cavities of varying size containing hyaline material. The stratum germinativum in places is either thicker or thinner than normal, and the interpapillary processes are irregularly variable in size and shape or are wanting. In a few places the cells of this stratum show atrophy with exaggeration of the intercellular spaces and there is infiltration with leucocytes. The cells of this stratum also show some imperfect cornification. In one section two circular masses of cornified epithelium, like the "pearls" of epidermoid carcinoma, are present in interpapillary processes. In another section over a small area, the stratum germinativum is prolonged into small columns of atypical epithelial cells which lie in the superficial portions of the corium. In the corium about the cell masses is some infiltration by cells of the lymphoid series. I am inclined to interpret these appearances as indicating an incipient carcinoma at this point. The corium generally shows an increase of its connective tissue over the normal, and this connective tissue in places is in the condition of hyaline degeneration. The papillæ vary considerably in size and in places contain greatly dilated capillaries. Some papillæ are in a condition of myxomatous degeneration and some others show more or less transformation of the connective tissue into hyaline material. In places, small areas of the corium are infiltrated with cells of the lymphoid series.

Examination of the recurrent tumor on the forehead brings out a difference of opinion between Dr. Wolbach and Dr. Wright.

(See Plate XXXVIII., Fig. 22.) Pathological report by Dr. Wolbach. Tissue from forehead. The sections consist of tumor tissue with adjoining necrotic tissue. No normal tissue in sections, except for a narrow strip of dense fibrous tissue on one edge of a few sections. The microscopic picture is that of invading cells or of cells having proliferated in situ, distending the meshes of connective tissue. There are bands of dense collagen fibrils separated by large, irregularly shaped cells, many in stages of mitosis. That the connective tissue present is not wholly the product of the tumor is shown by the presence of normal nerve bundles. Between the tumor cells and between small groups of cells there is in places only a small amount of collagen fibrils (Mallory connective tissue stain). The tumor cells are very irregular in shape and in size. Many are multinucleated. There is no definite arrangement of cells and in places the appearance suggests that these cells may have arisen in situ by multiplication of preëxisting cells. In other places, the picture is definitely that of a tumor. The nuclei are large, and each contains a large nucleolus. Where numerous nuclei exist in a single large cell, the nucleoli are unusually conspicuous in each nucleus. Mitoses are abundant in all portions of the sections. Multipolar mitoses are common. The smaller tumor cells are round, oval, and spindle-shaped. The larger very irregular in outline and usually have many slender processes. A few tumor cells show delicate fibrils (Mallory fibroglia stain) running parallel to the long diameter. For this reason and because of the arrangement of the tumor and the apparent presence of intercellular collagen fibrils the tumor should be classed as a sarcoma of connective tissue origin.

Pathological report by Dr. J. H. Wright: "In accordance with your request I confirm my verbal report to you made some time ago upon my views as to the nature of the tumor of the forehead in the case of Mr. G. Although the histological character of this tumor is very suggestive of sarcoma, I believe that the essential cells are of epidermal origin, and that the tumor should be regarded as carcinoma originating from the epithelium of the skin of the forehead. I am led to this belief for the following reasons: the situation of the tumor, the presence of fibrillation in some of the cells reminiscent of the fibrils of the cells of the epidermis, and the existence at the periphery of some of the cells of structures strongly resembling the characteristic 'prickles' of the epidermal cells."

Quotation from letter, March 6, 1908: "My hand has healed in good shape and most of the thickened spots on my fingers are disappearing. I can about half shut my hand. My forehead is all right except for some tightness of the skin and absence of normal sensation. The spot, where the growth had been, is tight and does not move."

Examination, Aug. 5, 1908. Sensation has been gradually coming back to forehead, which he can wrinkle almost normally. There is very slight thickening on the inner side of right eyebrow where the flap was reflected. The scars are hardly visible. There is no induration or pain

suggesting any recurrence of the disease. The back of the left hand is entirely healed; the graft is movable over the underlying structures. The backs of the fingers still show keratoses, which he is cutting and paring off. He can flex and extend fingers normally. In every respect a most excellent result.

Summary: Intermittent ulceration of back of left hand for seven years, improving for the past six months; excision down to aponeuroses and tendons; successful skin grafting. Microscopic examination showed commencing epithelioma. The longest case of persistent ulceration, without cancer, in the series. Thrice recurrent growth of forehead, which involved the periosteum; removal of bone down to dura and frontal sinus; complicated plastic operation. Opinions differ as to the nature of the growth; Dr. Wolbach classifying it as a sarcoma; Dr. Wright believes it to be a carcinoma. One year after operation, no evidence of recurrence.

CASE XVIII.—Personal. (Plate XXXVII., Figs. 13, 14, and 15.) J. G.; 34 years; X-ray operator. Patient has suffered for several years from the milder forms of X-ray lesions, atrophy of the sweat glands, eczema, ribbing of the finger nails, telangiectases and keratoses. During the winter he has a great deal of pain and trouble from fissures over the extensor surfaces of the joints. In May, 1906, numerous excoriations and fissures were excised and successfully grafted. On Sept. 15, 1906, there was a recurrence of ulceration near the radial border of the terminal phalanx of the ring finger. 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 applied; sound healing in ten days.

Pathological report by Prof. F. B. Mallory of the Harvard Medical School: "The section shows a small mass of actively proliferating connective tissue cells, covered with epidermis, which is edematous and contains fairly numerous mitotic figures. At one or two points the epidermis is lacking, and a little granulation tissue has formed. In these areas, and beneath the epidermis, is a small amount of infiltration with cells (chiefly lymphocytes) of inflammatory origin. The proliferating connective tissue cells occur diffusely scattered among the bundles of collagen fibrils of the corium. Mitotic cells are numerous and often multiple. Many of the resulting cells are large and often contain large lobulated or multiple nuclei. The lesion is an active, in some ways atypical, proliferation of connective tissue cells."

The finger remained 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. By April 23, 1907, the growth had become decidedly larger and was apparently extending backward into the proximal graft. The terminal joint was accordingly amputated under gas and ether; primary union.

Pathological report by Prof. F. B. Mallory of the Harvard Medical

School (see Plate XXXVII., Fig. 15): "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."

The finger remained well until August, 1908, when on the ulnar side of the same there appeared an induration in the skin which was neither tender nor painful, but gradually grew until it was the size of an old-fashioned three-cent piece. There was no ulceration, the tumor had slight vascularity and was movable to some extent upon the underlying structures. In view of the doubt as to the true pathology of the recurrent growths on this finger, amputation at the interphalangeal joint was performed in November, 1908; primary union.

Pathological report by Prof. F. B. Mallory of Harvard Medical School: "This lesion, like No. 2, is quite definitely outlined. In places at the periphery, however, the cells extend among the bundles of old collagen fibrils of the corium. The tissue is fairly cellular and contains mitotic figures, but they are not so numerous as in lesions 1 and 2, and are rarely atypical. The cells and fibrils are separated by a small amount of fluid (edema). The sections from these lesions show masses of rapidly-proliferating connective tissue cells. In numbers 1 and 2, especially, the cells are often atypical. The mitoses are frequently multiple and large multinucleated cells result from them. All these lesions suggest the possibility of being fibrosarcomata. It seems wisest for the present, however, to regard them as more or less atypical growths of connective tissue cells under conditions not fully understood. If later it should be proved that X-rays cause similar connective tissue growths which give rise to metastases or to evident invasion of other tissues (true fibrosarcomata), these

lesions might be regarded as of a similar nature, but at present such an assumption is not justifiable."

Pathological report by Dr. Wolbach. Amputation of middle phalangeal joint of ring finger, left hand. Beneath the skin of the distal portion on the ulnar side of dorsal surface is a firm, resilient, yellowish, ovoid nodule, .8 x .6 centimeter in diameter. This nodule is completely covered by epidermis and is not attached to the bone or tendon.

Microscopic examination: The nodule is composed of loose cellular connective tissue, the cells of which form bundles and whorls running in all directions. The amount of collagenous intercellular substance is much greater than that in the first specimen removed and examined by Dr. Mallory. The collagenous fibrils are more widely separated than in normal connective tissue, suggesting a slight amount of edema. The cells resemble those of normal connective tissue. The nodule is fairly sharply demarcated from the immediately surrounding practically normal connective tissue of the corium by means of the concentric flattened arrangement of the cells and fibrils of the latter. There is no definite capsule. There is no evidence of invasion. There are numerous mitotic figures throughout the nodule, all of them normal in type. The tissue is supplied with numerous small, thin-walled vessels and capillaries, uniformly distributed. The epidermis covering the nodule consists of a smooth thin layer lying directly upon the tissue described and which presents an unbroken convex surface. The horny layer of this covering epidermis is thin. The stratum germinativum is poorly differentiated; it consists mainly of slightly swollen pale-staining prinkle cells of fairly uniform size. The deepest layer is regularly apposed to the underlying tissue in the manner of normal epidermis. Where the nodule adjoins the normal tissue there is a deep downgrowth of epidermis in the form of slender stalks partially embracing the new tissue. The surrounding epidermis is slightly hypertrophic and shows slight irrelevant changes. A positive diagnosis is not possible in this case, as the same discussion used by Dr. Mallory in his description of the tissue removed applies here. Against the view that the tissue is granulation tissue is the lack of signs of active inflammation, the presence of unbroken epidermis and the absence of a vascular arrangement. Favoring the view that we are dealing with a slowly-growing connective tissue tumor (fibrosarcoma) is the presence of numerous mitoses, and against this view is the lack of evidence of invasion.

Summary: Mild chronic X-ray lesions, numerous skin grafts for keratoses and fissures over knuckles. Primary union. Recurrent growth of the matrix of ring finger nail, left hand; amputation. Occurrence of a fibrous tumor on the ulnar side of stump one year afterwards; amputation through first phalanx. Pathologists differ as to the character of this growth, some believing it to be an unusual form of granulation tissue; others classifying it as a sarcoma.

Case XIX. — Personal. (Plate XXXVII., Figs. 16, 17, 18.) W. J. D. (physician); 32 years. X-ray operator. Began work with a large static

machine in March, 1896; in October of same year a powerful twelve-inch coil was used. In November, 1896, the first severe dermatitis took place. This subsided under treatment, but was followed in April, 1897, by an extremely severe general dermatitis with pain beyond description. All kinds of washes, ointments, and powders were used with orthoform to relieve the pain. My first graft was applied to an ulcer on the tip of the left forefinger on July 10, 1897. On Aug. 13, 1897, fourteen different grafts were applied after excision of as many ulcerated areas. The extreme pain ceased at once and the great majority of the grafts healed soundly. Between this date and 1902 there were seven other similar operations under ether. Most of the grafts were successful, but in spite of several attempts failure was constant over ulcerations on the ends of the ring finger of both hands.

In July, 1902, another attempt at excision and grafting was made; it failed. In October, extremely painful, angry looking ulcers with indurated edges had formed upon the ends of both ring fingers, these were amputated. The report from the pathologist was unmistakable carcinoma. In consequence, on Oct. 31, 1902, both of the ring fingers were amputated at the knuckles. From October, 1902, until June, 1905, a dozen or more operations consisting of partial amputations, excision of growing ulcerations and keratoses were performed. In May, 1905, for the first time in eight years, the patient was free from pain and no dressings had to be worn. In June, the left hand was practically well, but keratoses broke down on the base of the middle finger of the right hand, and there was some ulceration near the matrix of the thumb nail. In November, 1905, an undoubted epithelioma was excised from the base of the third finger of the right hand, and numerous other ulcerations were skin grafted; some of these showed a precancerous stage.

By April, 25, 1907, after ten years of treatment, and twenty-five operations under ether, the condition of the hands was as follows: Left hand: amputation of little finger through the interphalangeal joint; amputation of ring and middle fingers at knuckles; fourth finger shows slight ulceration at its base, and a small ulcer in the middle of the back of the hand; there are numerous keratoses, but no ulcerations. Right hand: the thumb is useful, but its ulnar side is covered with thickened epithelium at the base of which is a small ulceration. For two months there has been ulceration over the joint between the first and second phalanx of the forefinger, with flexion of this joint; this ulceration strongly suggests malignant disease. The middle finger is stiff, the fourth is lacking, as is also the end of the fifth. The hand shows the presence of numerous grafts which have taken, and a few keratoses. The patient was at work at a medical school, and did not submit to an operation until July 5, 1907, at which time it was evident that the forefinger must be amputated, for undoubted epitheliomatous ulcerations were forming in several parts of the dorsum of the finger, notably about the opening into the joint before mentioned. Under ether, the forefinger was amputated at the middle of the first phalanx, a palmar flap of sound skin being reflected backward. Several suspicious areas

were excised in other parts of both hands, and skin grafted. Microscopic examination of the amputated forefinger showed five different areas of carcinoma, which owing to delayed operation had infiltrated deeply the subcutaneous tissues, surrounded the digital nerves on the radial side, and caused the extreme pain (see Plate XXXVII., Fig. 16). The columns of epithelial cells had penetrated to the periosteum. As a result of this examination it was decided on July 15 to amputate higher up. The head of the first metacarpal bone was removed and a large flap reflected onto the dorsum of the hand, thus forming a sound stump for approximation of the thumb.

In September, 1908, after eating lobsters, there occurred a general urticaria and both hands became much swollen and the serous discharge was extreme. The patient was confined to bed for ten days, then very gradually the exudate dried up and there followed desquamation. This, however, did not affect the keratotic areas. There have been one or two injuries to the base of the forefinger of the left hand, and to the base of the middle finger of the right hand, which set up extremely painful and obstinate excoriations. For several months there has been an inflamed warty growth over the stump of the little finger of the left hand.

Examination and operation Dec. 7, 1908 (see Plate XXXVII., Fig. 18). Over the head of the ulna, on the left, are two irritated thickened excoriated areas, which are being continually injured by the cuff Over the center of the hand there is a small, tender, deep ulceration about the size of a split pea. Over the base of the forefinger, and along the ulnar side of the thumb are keratoses cracks and fissures. The left hand was the first operated upon. The warty growth on the little finger was excised down to the aponeurosis and submitted to Dr. Whitney, who reported epithelioma. The question arose as to whether the finger should be amputated at the knuckle or whether more conservative measures were justifiable, owing to the usefulness of this finger. I decided to remove a slightly larger margin down to the aponeurosis, which was then thoroughly cauterized with the Paquelin cautery, The other areas described were deeply shaved, and skin grafted just back of the first interphalangeal joint, and another about the center of the middle phalanx were also excised and grafted. After this operation the remainder of the left hand seemed in good condition. There was, of course, atrophy of the hair, some telangiectases, large areas covered by grafts and cicatricial tissue. The condition of the right hand was as follows: the middle finger is partially flexed and there is hyperextension at the first interphalangeal joint. There is, however, flexion at the knuckle. The worst lesion seems to be excessive hypertrophy and keratosis of the skin, over knuckle of little finger, as shown in the photographs. This spot is frequently subjected to slight trauma. There are similar inflamed and thickened areas on the radial side of the first knuckle, and along the ulnar side of the thumb. The nail of the thumb is deformed and split on the ulnar side of the median line, where granulation tissue and hypertrophied matrix keep up a chronic sore. There exists over the ulnar bone, similar to the left hand, an area of thickened epithelium which is irritated

by the cuff. At the base of the middle finger there are several keratoses. The ulnar half of the thumb nail was removed, and with curette and knife the matrix was thoroughly eradicated. The area over the base of the middle finger was excised down to the cicatricial tissue, exposing a small part of the tendon in the median line. All of the keratoses were shaved off with a knife and grafted. It was quite remarkable at this operation to see the hemostatic action of the grafts. Once placed in position, bleeding quickly diminished, and in a few moments practically ceased. Both hands were placed upon splints, the forearm held in position by adhesive plaster, and the grafts covered with small strips of protective tissue. Two keratoses were excised, one from the forehead and the other from the inner part of the upper eyelid.

Dec. 20, 1908. The large and important graft over the knuckle of the middle finger has healed soundly, as have five other grafted areas on the right hand; grafts upon two small keratotic areas failed. The grafts placed on the left hand, however, have not been so successful, owing to hemorrhages underneath them. Only two out of five have taken. The base of the little finger, which was cauterized, has been extremely painful, and is granulating very slowly.

A more careful pathological report showed epithelioma at the site of the excision on the little finger of the left hand, and commencing epithelioma over the knuckle of the right middle finger. All of the other areas excised were negative.

Jan. 20, 1909. In spite of various sorts of dressing the ulceration after cauterization of the little finger has been persistently and exquisitely sensitive and painful, causing loss of sleep and necessitating opiates and, locally, Schleich's solution. To-day egg membrane was tried, and gave such marked relief that several skin grafts were applied as a dressing, though from the character of the granulations it seemed unlikely that they would grow. The pain was immediately relieved, and much to our surprise part of the grafts "took" and slowly extended downward over the ulcer. Progress ceased, however, by February 10, and in view of the extreme pain and danger of recurrence it seemed as if the attempt to save the finger had been a mistake. It was decided, therefore, that if the next attempt at grafting proved unsuccessful that amputation should be done. On Feb 19, 1909, under ether, the ulceration was thoroughly disinfected and carefully shaved down to a smooth base. Thin grafts were used and held in position by protective strips. Several other areas were excised and similarly treated, the majority of which grew, but at the end of two days infection occurred in the little finger, and all of the grafts came away. Pain, however, has been distinctly less after the last operation and, in a few days, epidermis began to grow from the former grafts and the edges of the wound, so that by March 1, 1909, spontaneous healing was complete.

Summary: Commencing with July 10, 1897, I have operated upon this patient under ether thirty-two times, the operations varying in duration from one hour and a half to three hours. At present there remains of his

left hand two joints of the little finger, the forefinger and thumb; of the right hand, the thumb, the middle finger, barring part of the terminal phalanx, and one and a half phalanges of the little finger. More than half of the skin of the backs of both hands consists of Thiersch grafts. From the initial dermatitis there has been continual, though slight enlargement of the axillary glands, but no evidence of recent increase in size, or any suggestion of metastases. There was undue and dangerous delay in amputating the cancerous forefinger of the right hand. With this exception, epitheliomatous ulcerations have been excised early. For two months it seemed as if the attempt to save the stump of the little finger was a failure, but in spite of the severe pain the patient seemed unwilling to sacrifice it, owing to the damaged forefinger and the fear that with its possible loss in the future the thumb would have nothing to press against in grasping small objects.

The number of different carcinomata in this one case has been over a score. I have no doubt that general metastases would have taken place long ago had it not been for timely excisions and amputations.

Case XX. — Personal. F. J. B. (physician); 34 years, Baltimore, Md. Began X-ray work in 1900 and suffered at the start from an acute dermatitis. When this subsided, all finger nails, with the exception of those on the thumbs, came off. After six months' rest the dermatitis cleared up, and all of the nails grew again, except that on the right forefinger; this never reformed. In the spring of 1902, after resumption of work with the X-ray, there was no active dermatitis, but keratotic patches formed on the hands with the appearance of the usual telangiectatic areas. Gradually the nails became deformed. Up to this time there was little pain but considerable stiffness in the hands. The keratoses increased up to 1905, when the first ulcer appeared on the dorsum of the left hand and one on the right forefinger at the junction of the second and third phalanges. These ulcerations were excised and numerous keratoses were removed. The ulcer on the right forefinger returned in a few months and remained about the size of a pea. Numerous attempts were made to heal it as it was exceedingly painful, but these were not successful. The keratosis on the base of the right finger returned after excision and has persisted up to the present time, without ulceration. In 1906, ulceration began in a small keratosis which had been present for several years, situated on the external side of the nail of the ring finger of the right hand. This has since gradually increased in size, extending along the outer edge of the nail, and then upwards upon the dorsum of the finger almost to the first interphalangeal joint. The pain in this ulcer for the last nine months has been very intense, so that for many nights no rest could be obtained. In the fall of 1907 the matrix of the right forefinger nail broke down and assumed the character of a sluggish ulcer, exquisitely tender and painful. The whole matrix was destroyed. At present the dorsum of the forefinger, almost to the joint between the first and second phalanges is occupied by a raw, beef red ulceration without induration. This resembles in a striking

degree the ulcerations which occurred on the ring fingers of Case XIX. "The pain is most intense and is best described as a sharp shooting neuralgic pain of the worst character. It lasts two or three seconds and occurs from eight to ten times every minute. When the pain was of this character the ulcer always appeared raw and the granulations very red. Next would come the formation of a slough, when the more intense pain would disappear."

Patient entered the Massachusetts General Hospital on Jan. 19, 1909. Both hands presented typical X-ray dermatoses extending up to the wrists. There were numerous keratoses and a few crusted spots The chief lesions have already been described — the raw ulcerations on the distal phalanx of the first and ring fingers of the right hand. The nail of the middle finger is deformed and there is considerable suppuration about the thin and cracked edges of this nail.

Operation Jan. 20, 1909, under ether. As I feared malignant disease of the forefinger and the ring finger, a small portion from the forefinger ulceration was first removed and given to Dr. Whitney for rapid examination. Though nothing malignant was found, I determined upon amputation of the ends of both of these fingers, owing in part to questionable malignancy, but chiefly because I believed that the grafts, even if successful, would ultimately break down. Accordingly a transverse incision was made down to the bone, through the skin, just below the first interphalangeal joint. The skin was carefully dissected downward, and the bone divided at the middle of the second phalanx; a long palmar flap of healthy tissue being turned backward and sutured in position. This gave a rough resemblance to the crescent of the finger nail. Numerous keratoses and minor ulcerations were deeply shaved from various parts of both hands and skin grafted. All wounds were dressed with protective, and carefully applied pressure held the grafts in firm apposition. There occurred at the site of both amputations a slight degree of infection which delayed healing. By making two parallel incisions at the angle of the nail an attempt was made to extirpate the matrix of the middle finger nail; the pulp of the finger was grafted; of twenty other grafts, eighteen took. The patient was discharged on February 14, with sound union in the amputations and all grafted areas looked well.

On April 1, patient stated that he had been entirely free from pain since leaving the hospital, for the first time in years. About the matrix of the middle finger there is slight suppuration, and from the sides there has been some reformation of soft nail. The grafts are looking very well. After consultation it was decided that this patient should be allowed to continue the use of the X-rays provided he never exposed himself unprotected.

Pathological examination by Dr. Whitney. More careful examination of the tissues removed from this case showed that in both forefinger and ring finger there was undoubted superficial carcinoma; the other areas excised were negative.

CASE XXI. — Personal communication from Dr. L. L. McArthur, of Chicago, Ill. S. C. G. (physician), who combined electrical therapeutics from a static machine with X-ray pictures; he developed his own plates. Chronic dermatitis; ulceration of the terminal phalanges of first and middle finger of left hand; amputation of terminal phalanges. Later, there developed a typical epithelioma on the remains of the left index finger, and numerous keratoses. The finger was amputated and found to be carcinomatous. Keratoses excised and grafted; axilla thoroughly dissected. No glands found to be involved. Patient well one year after.

Summary: Epithelioma of left index finger; amputation; dissection of axilla. No glands involved. At present no evidence of recurrence Prognosis good.

CASE XXII. — Personal communication from Dr. L. L. McArthur, of Chicago, Ill. W., of Chicago; probably the first X-ray burn on record. Eleven hours' exposure within a period of three days. Huge burn extending from the symphysis to the chin, the healing of which required several plastic operations. In July, 1908, having been well in the interim, he was thrown from his pony and injured the cicatrix. The ulcer refused to heal and carcinoma rapidly developed, until an area 10 x 4 inches had become involved. At operation, with a wide margin, the cancerous skin was removed, as well as the anterior sheath of the rectus, part of the rectus muscle, and in parts even its posterior sheath. By undermining the skin laterally, beyond the axillary line, the wound was closed anteriorly, and though infection occurred, healing is now nearly completed, Dec. 11, 1908.

Summary: Severe X-ray burn in 1896, involving the chest and abdomen; plastic operations. Latent period "eleven years;" extensive carcinoma of abdominal wall; radical excision.

CASE XXIII. — Personal communication from Dr. Charles H. Bowen, of Columbus, O. L. M. E (physician); has been doing X-ray work for the last ten years. Nine years ago he developed a dermatitis which gradually increased in severity until ulcers developed. These ulcers were curetted from time to time, and skin grafts were tried, but seemed of no permanent benefit. The grafts would take, but in a few months would break down, and the ulcerations would be as painful as ever. His phalanges were amputated on a number of occasions, until he finally lost three fingers from his left hand and two from the right. Several months ago he developed an ugly ulcer on the back of his left hand, which gradually became an epithelioma. This was curetted on several occasions, but without effect. The remains of the right hand is so painful that it has to be kept continually covered in a layer of cotton in order to avoid the slightest injury. In April, 1908, the left forearm was amputated at the middle. In December, 1908, no evidence of recurrence on the left. The right hand, which had quite a number of very suspicious looking ulcers, has been gradually getting better, under large amounts of iodine,

though not necessarily caused by it. X-ray work and medicine have been given up. There is no evidence of metastases.

Summary: X-ray worker; persistent ulcerations and deep epithelioma necessitating amputation of left forearm at the middle. Persistent ulcerations of right hand required amputation of two fingers. Recently, ulcerations on the back of the hand have improved, while taking iodine and giving up work.

CASE XXIV. — M. W.; X-ray manufacturer; static machines; has suffered for years with the severer grades of dermatitis; recently multiple epitheliomata have developed on the hands and fingers. After several operations there remains on the right hand the thumb and forefinger; on the left hand the thumb, index, and middle fingers — the fourth and little fingers, with their metacarpal bones, have been removed. There are other lesions on the face and back.

CASE XXV. — F. D. A. (physician); radiologist, Rochester, N.Y. Amputation of left hand; X-ray carcinoma; Journal American Medical Association, Dec. 12, 1908. Personal communication from Dr. J. Nevins Hyde and Dr. Ormsby of Chicago; two private patients never reported.

CASE XXVI. — O. R.; severe X-ray lesions after treatment for plantar keratodermia; epithelioma; excisions of soles of both feet; Krause grafting successful.

CASE XXVII. — P. J. S.; epithelioma of back of hand, following X-ray lesions.

CASES XXVIII., XXIX., XXX., XXXI. — Four cases of carcinoma, operated upon by Dr. Sick of Hamburg, abstracted from an article by Dr. E. Schümann in Archiv. für Klinische Chirurgie, 1907, Band 84, page 860.

CASE XXVIII. — X-ray operator; cracks and fissures of fingers and on dorsum of hands, which were excessively painful and did not yield to any conservative treatment. These warty growths of epithelium were finally excised and sutured. Unna examined the specimens and pronounced them as beginning epitheliomata. The tissue was so friable that the sutures did not hold, and it was difficult to make satisfactory sections. The wounds healed by second intention and remained well thereafter.

CASE XXIX. — Patient, X-ray tube maker. Usual pigmentations of the skin of face and arms; typical changes of finger nails. In addition, two prominent keratotic growths on the back of one hand. These were excised and pronounced by Dr. Fraenkel to be epidermoid carcinoma.

CASE XXX. — Young physician; severe lesions on fingers and backs of hands. On the right forefinger a chronic paronychia, and on the back of the hand a small ulceration. Usual treatment without avail. The pain was extreme, often keeping the patient awake all night. Evulsion of the

nail was not beneficial. The terminal phalanx was amputated and the ulcer excised and skin grafted. The graft died, but satisfactory healing took place eventually. Pathological examination showed typical skin cancer.

CASE XXXI. — Man, 32 years, who after three years of X-ray work suffered from severe lesions on both arms, breast, neck, and face. In 1901 there began a slowly growing ulceration of the back of the right hand, which by the middle of 1902 had become a gangrenous epithelioma; glands enlarged at the elbow and in the axilla. Amputation at the shoulder; axillary glands removed, and found full of squamous celled carcinoma. Sound healing. In December, 1904, a typical cancer of the lower lip and another of the angle of the mouth were excised, as was a suspicious lesion on the back of the left hand. In March, 1905, a growth of the cheek was removed, which was pronounced by Unna to be a sarcoma. In September, 1905, excision of the right lower jaw for carcinoma. Recurrence involving the tongue and the adjacent cheek was present in February, 1906. Death soon followed.

CASE XXXII. — Patient operated upon by Professor Trendelenburg. The specimen was carefully studied by Dr. Schümann. Man, 39 years; unusually exposed since 1896 to the X-rays — he used his own hands to test the tubes — four years later, developed a dermatitis of both hands. The skin became rigid, dry, and swollen; the nails brittle with chronic onychia. This condition lasted two years. In 1902 he became worse. On the right hand there developed yellowish, horny growths, particularly over the knuckle of the third finger. In 1906 the removal of this keratosis left behind an ulcer, which in two months grew to the size of a mark piece with indurated edges. The epitrochlear glands were enlarged; the axillary glands not palpable. In February, 1907, the ulcer was radically excised and skin grafted; healing uncomplicated. No mention is made of the treatment of the enlarged epitrochlear glands. Examination of the ulcer showed typical epidermoid cancer.

CASES XXXIII., XXXIV., XXXV., XXXVI., XXXVII. — The following cases occurring in Great Britain are abstracted from a paper by Mr. Foulterton in the Transactions of the Pathological Society, July, 1906, and from personal communication from Dr. Cecil W. Rowntree, and a paper by him, published in the Archives of the Middlesex Hospital, Volume XIII., July, 1908.

CASE XXXIII. — X-ray work in 1897, at the age of 38. In two years, loss of tactile sensation in fingers. In May, 1903, severe dermatitis. Resulting ulcers took four months to heal. Warty bodies next developed on the dorsal aspect of index and second fingers. A similar acute attack in December, 1903. An ulcer on the index finger refused to heal and increased in area and depth; in September, 1904, the finger was amputated. In 1906, a small superficial ulcer on the middle phalanx of the middle finger persisted, and was excised and grafted. Examination of

the ulceration, for which amputation was done, showed a typical epithelioma with cell-nest formation, which invaded the underlying bone. Examination of the ulcer excised in 1906 shows absence of elastic tissue, thickening of the epithelium, early keratinization and plasma cell infiltration; a precancerous condition.

CASE XXXIV. — Man, 60 years; engaged for some years in the manufacture of X-ray tubes. For painful fissure over the last interphalangeal joint of the first finger, excision was performed. Microscopic examination showed early but undoubted squamous cell carcinoma.

CASE XXXV. — Man, 40 years. The third finger showed a glossy appearance of the skin, which was thin and adherent to the underlying structures. The nail had entirely disappeared, except for a small portion at one edge. There were no cracks nor warts, nor any actual ulceration anywhere, but at the base of the finger was an area where the surface epithelium showed a slight irregularity. This finger was amputated at the metacarpo phalangeal joint, and the metacarpal bone subsequently dissected out. Examination of the indurated skin showed the presence of a malignant growth, infiltrating the deeper structures; a typical squamous cell carcinoma, with well-marked cell-nest formation. The axilla was cleaned out, but the enlarged glands showed no evidence of metastases.

CASE XXXVI. — Man, 42 years; engaged for several years in the manufacture of X-ray apparatus. For two years the left hand had been affected, and eighteen months previously a growth had appeared on the middle finger; surgical treatment had been refused. Finally the left middle finger became very greatly enlarged by an irregularly lobed new growth, which was ulcerating on the surface and very foul. There were a number of irregular, pigmented warts; no enlarged glands. The finger was amputated through the proximal end of the shaft of the third metacarpal bone; good recovery. Since this operation in 1905 there has been no evidence of recurrence in the hand, but there are persistent ulcerations upon the chin and over the upper part of the sternum. Microscopic examination of the growth shows that it is composed of small and slender columns of eyelets of squamous cells, irregularly distributed and separated from one another by a well-marked connective tissue stroma, composed of large cells with large nuclei. Mitotic figures are present. "Of special interest in this ulceration is the striking appearance of the connective tissue stroma, the individual cells being of a size and character not usually met with. Their large size and great number produce the appearance as if the small eyelets of epithelial cells were dispersed throughout granulation tissue, and suggesting the view that the connective tissue cells themselves are endowed in these instances with a special activity." None of the cells were found to be multinucleated. An X-ray of the finger removed showed a total disappearance of the bony tissue of the first and second phalanges and suggested further study by the X-rays of such hands. In other instances, also, marked atrophy of the bony tissue was noted, and in one case absorption had

taken place, giving the appearance of a punched-out area in the middle phalanx.

CASE XXXVII. — Man, 38 years; seen in July, 1905. Had been working with the X-rays for six years. On account of trouble with his hand gave up work in 1902. The skin of both hands was thin, glossy, and pigmented; usual telangiectases. On the proximal phalanx of the right middle finger was a growing ulcer about one inch in diameter. There were two other smaller ulcers, which showed no evidence of healing. No enlargement of glands. The finger was amputated with nearly the whole metacarpal bone, and the ulcer over it. The other ulcer was excised and grafted. Patient remained well for a year, when a small ulcer appeared in the scar; this healed, however, eventually. A few months later a scab formed over the scar, which was gradually raised by a prominent growth about the size of half a cherry, which rose dome-like above the skin. This growth was bright red in color; of firm consistency. It was removed, and the resulting wound covered with a Thiersch graft. At present, May, 1908, there is no recurrence. Microscopic section of the original ulcer revealed a keratinization and a squamous cell carcinoma, in which the cell nests are numerous and well developed. Examination of the second growth showed that it consisted entirely of young granulation tissue, which replaced the epidermis and corium for a limited area, the epidermis gradually merging into and disappearing in the granulation tissue. "The cells composing the granulation tissue are unusually large and well developed, and possess large, round, oval nuclei, containing much chromatin and staining deeply; in fact the appearance of these cells are strikingly similar to that of the cells which formed the stroma of the new growth in the previous case. The elastic tissue is disappearing in a narrow zone below the epithelium with moderate plasma cell infiltration.

Summary: Five cases of carcinoma, developing with a long latent period, in cases of chronic X-ray dermatitis. In all but one, early operation. One case neglected, but no involvement found in the axillary glands. In two instances, attention is called to an unusual form of granulation tissue in which the cells are unusually large and contain large, round, or oval nuclei, and stain deeply.

CASE XXXVIII. — H. E. (physician); amputation of arm for epithelioma of hand.

CASE XXXIX. — At Leeds, England; amputation of arm for carcinoma.

Fatal cases, X-ray carcinoma.

CASE XL. — B. (physician), England; X-ray carcinoma of hands; general metastases and death.

CASE XLI. — W. C. E. (physician). Personal communication from Dr. Nevins Hyde of Chicago. X-ray cancer of hand; general metastases and death.

CASE XLII. — W. (physician), Rochester, N.Y. Personal communication from Dr. W. B. Coley of 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 Professor Welch of Johns Hopkins Hospital and found to be undoubted epithelioma. The carcinoma had deeply involved the metacarpal bones of the index and middle fingers. Amputation of right hand above wrist, and thorough excision of ulceration on the left hand, Oct. 10, 1904. Subsequent recurrence in axilla and liver; death.

CASE XLIII. — C. D. 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 Aug. 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.

CASE XLIV. — B. F. (female), of San Francisco, Cal. Personal communication from Dr Childs Macdonald. Patient was a pioneer in X-ray work. In 1903 her hands commenced to show signs of X-ray dermatitis, the nature of which was not understood, and attributed to chemicals used in developing the plates. Patient worked twelve hours a day, without protection. In the early part of 1904 she came for the first time under treatment The fingers of both hands were badly ulcerated; chiefly the tissues over the middle phalanges and the middle joints; all the nails were affected, the surfaces presenting ulcerated, warty condition, the warts assuming the form of necrogenica, healing alternating with ulceration. All the secreting glands and hair follicles were destroyed, so that the skin was hard and dry, and cracked easily. All sorts of treatment of ointments and washes were without permanent benefit. In November, 1904, a wart appeared on the index finger, near the terminal phalanx, which was very raw, and grew with great rapidity. A portion was removed, under cocaine, and submitted to Dr. Rifkogel, who reported a branching papilloma, with a tendency to downward growth, and advised amputation. This the patient refused, so the growth was freely excised and healed healthily. A few weeks afterwards, however, a nodule appeared near the

scar, which pushed up through the epithelium, broke through it and appeared exactly the same as growth No. 1. The glands in the axilla were found somewhat enlarged. Radical operation was again refused, until after Christmas, when axilla was freely opened and the whole space cleared of glands. Pathological examination of these showed undoubted involvement with epidermoid carcinoma. In the course of a week, more nodules appeared just below the acromioclavicular articulation. It was decided that the only chance of recovery lay in amputation at the shoulder. Accordingly on Jan 27, 1905, after preliminary ligation of the subclavian in the third part, the arm and scapula with the clavicle were removed. The patient rallied well from the operation, and the wound healed rapidly, but about the end of April, 1905, a recurrence took place at a point representing the position of the inferior angle of the removed scapula. This was excised and found to be carcinoma. Slowly, and then rapidly, other nodules appeared, until ultimately the whole of the vertical scar, corresponding to the vertebral border of the scapula, became involved. Metastases took place in the pleura and lungs, and the patient died on Aug. 3, 1905.

On reading this history it is obvious that the patient by refusing early radical surgical treatment jeopardized her life, though it is of course possible that metastases had occurred early.

Case XLV. — F. (physician). 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 liquefaction 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.

Case XLVI. — R. V. W. (physician); X-ray machine manufacturer; has used both static and coil machines continuously from their beginning, subjecting himself to countless fluoroscope examinations. His skin, both

front and back, for a number of years, has been covered with characteristic lesions, many of which have recently become epitheliomata. He was operated upon for a carcinoma of the cheek, by the actual cautery, down to the mucous membrane, and a thorough removal of epitheliomatous glands on both sides of the neck. He had also epitheliomata of both hands and some on the back. Patient died in April, 1908, of extensive metastatic carcinoma of the liver.

CASE XLVII. — J. B. Personal communication from Dr. Russell S. Fowler and his house surgeon, Dr. C. H. Criley, of the Brooklyn Hospital, New York. Man, 33 years; a glass worker by occupation, since the age of fourteen. Soon after the discovery of the X-ray, patient became interested in the manufacture of the tubes. His work was chiefly in the testing-room, where he worked over a bench, waist high exposed for one to four hours a day. In 1900 he noticed a few small, warty growths on the fingers, knuckles, and backs of hands. In 1904 patient gave up business on account of general poor health, at which time he noticed a peculiar erythema with a slight tendency toward hard, warty nodules over the face, neck, and anterior trunk, above the waist line. The keratoses were still very small, the largest not more than a quarter of an inch in diameter. He has some on the face removed with the actual cautery and silver nitrate. The growths rapidly recurred and increased in size, becoming soft and slightly ulcerated.

Examination, April 19, 1907. Marked erythema and mottling of the skin of face, trunk, and arms. Many scattered, hard, flat papules. A small cutaneous horn on the forehead and several smaller ones on the chest. Large epithelioma over the metatarso phalangeal joints of index and middle fingers of left hand. Deep ulceration and small ulcerations over some of the joints of the right hand.

Operation: amputation of first and second fingers with heads of metacarpal bones of left hand. Removal of numerous epitheliomata. Patient refused more radical treatment and would only allow curetting of the carcinomata on the right hand.

Nov. 11, 1907. The growths on the right hand had increased in size and fused, but were not deep. Rapid recurrence at site of amputation of fingers of left hand; only curettage was permitted, followed by an unsuccessful attempt at skin grafting.

March 11, 1908. Since last examination, rapid progress of the disease, involving the base of the thumb and the metatarsal bones of the third and fourth fingers; no evidences of glandular enlargement. Amputation at junction of middle and lower thirds of left forearm; amputation healed by primary union. Another curettage of the right hand.

April 20, 1908. Another attempt was made to benefit right hand by curettage and skin grafting; unsuccessful. Discharged on June 14, with cancer slowly spreading on right hand. No evidence of granular enlargement anywhere. By Aug. 8, 1908, however, the general condition had become poor, with marked loss of weight; epitrochlear and axillary lymph

nodes on the left enlarged; no recurrence in stump. Epithelioma of right hand had begun to spread rapidly, and had involved deeply the metacarpo phalangeal areas of the first and second fingers. These fingers were accordingly amputated on August 11, and the wound skin grafted. The left epitrochlear and axillary glands increased very rapidly in size, forming great masses which were extremely painful. On Sept. 25, 1908, interscapulo thoracic amputation was performed, and a small epithelioma-tous ulcer removed in the region of the umbilicus. The amputation wound healed very slowly, showing evidence of recurrence. Patient died Nov. 7, 1908, of general carcinosis.

Pathological report. Glands above clavicle carcinomatous. The lymph nodes in the mediastinum and about the bronchi were enlarged to about the size of a fist. There were nodules in both the parietal and visceral layers of each pleura. Some nodules in both lungs. Nodules also in kidneys and adrenals. Numerous carcinomatous areas in the liver and one in the wall of the stomach.

Summary: In 1897 began work with the X-rays, testing the tubes for several hours a day. First noticed erythema and warty growths in 1900. In 1905, keratoses and warts had formed on both hands, chest, and face. First carcinoma developed and required amputation of two fingers of the left hand in April, 1907; similar growth curetted on right hand. By March, 1908, rapid extension of the disease necessitating amputation of left forearm; curettage of epithelioma on right hand. August, 1908, involvement of epitrochlear and axillary glands. Aug. 11, 1908, amputation of fingers of right hand. Sept. 25, 1908, amputation at shoulder. Death on Nov. 7, 1908; general carcinosis.

On reading this history it is obvious that death was caused by the patient's refusal to subject himself to early and radical operation. The amputation at the shoulder was not performed until after general metastases had taken place.

While on reading the histories of these cases one cannot fail to be struck by the inevitable and progressive evolution of the disease from the milder grades of inflammation to ultimate carcinomatous degeneration, there appear, fortunately, a few exceptions to the general rule, which careful inquiry from my own and other cases have developed; where through the years, in spite of persistent lesions, there has been a gradual improvement in the general condition of the hands, as if the natural reparative power of the skin had begun to assert itself. This is analogous to a few recent cases of improvement in the genital glands, after protracted loss or abeyance of function. The degree to which this return toward normal may develop must depend upon the

presence or absence of continued irritations, and the depth or degree of the original damage to the skin and subcutaneous tissues.

Pain. — The amount of pain which these patients suffer is variable, though usually extreme. From my experience and personal communications from patients I believe that the agony of inflamed X-ray lesions is almost unequalled by any other disease. Its character has been described, and varies with individuals. While morphia has been used in some of the cases, it is really surprising to find how many have borne their pain without resorting to its habitual use. The pain seems to be due, in some instances, to the exposure of irritated nerve endings in a raw ulcer, like the "erethystic" varicose ulcer of the leg, to suppurating nail beds, irritated by small pieces of nail, and, in acute burns, very probably to a definite neuritis. In the more chronic cases I believe that the microscopic sections show quite clearly that the pain is caused by the cicatricial contraction in the thickened corium, compressing the nerves. In one case of mine (XIX.) the nerves were shown to be actually involved in an infiltrating cancer. At another time, the lateral digital nerve of the little finger was exposed at the base of a slowly-healing sore; sensitiveness and pain were intolerable, but ceased as soon as the bare nerve was covered with granulation tissue and skin. Without regard to the particular cause of the pain, in either the acute or chronic cases, adequate excision of the lesions has invariably given immediate relief. In Cases IV. and XV., though differing so far as one could see in no respect from other very painful ulcerations, pain was remarkable for its absence throughout the whole course of the disease. Rupture of the dilated capillaries is of frequent occurrence and always accompanied by extreme, radiating pain, until the extravasation works to the surface, forms a black spot, and is thrown off in the process of desquamation, when the pain ceases. Not infrequently, these minute hemorrhages form the sites of subsequent ulcerations.

Acute infections arising in the fissures or inflamed nail beds, keratoses or ulcerations, or coincident injuries are

responsible for much of the disability associated with such hands, always rendering more painful lesions which were painful enough before.

The palliative treatment of these chronic X-ray lesions must be left in a great measure to the personal experience of the individual. Relief from pain and improvement often take place under remedies which in another patient are most painful and harmful. In general, dry treatment, when it can be borne, combined with protection has seemed to be most beneficial. Maceration should be avoided. Pure benzoinated lard I have found the most valuable ointment; ichthyol combined with lanolin occasionally useful. At times, local anesthetics must be used; preferably a weak solution of cocaine upon two layers of compress cloth. Orthoform I am convinced should never be used, owing to its tendency to produce ulcerations. Of the washes, simple salt solution or aluminum acetate are valuable. If infection is present, citrate of silver (1–6,000) has been very useful in most of my cases. Alumnol (1–200) has proved a most satisfactory antiseptic and astringent. The keratoses may be softened with a solution of caustic soda and shaved down with a sharp knife or pumice stone. If they are scratched off, bleeding is profuse, and ulceration not rare. The actual cautery which several have used, while temporarily destroying the condition, seems to invite recurrence on a larger scale. Sparking with high tension current has been tried by various radiographers with temporary improvement, but no permanent benefit. With the non-surgical methods of destroying keratoses, I have had no personal experience. Dr. Whitehouse of New York prefers liquid air, while Dr. Pusey of Chicago is well satisfied with carbon dioxide snow. Both of these milder methods have the advantage over excision of causing no detention from business, and possibly of acting only upon the abnormal cells, without affecting normal tissues.

After months or years of treatment, or neglect of treatment, carried out with more or less relief upon various lines, the early X-ray worker usually finds that while the general

condition of the hands may have improved somewhat, either certain keratoses recur after removal, or the nail beds are affected, or that after healing and breaking down several times a particular ulceration finally refuses to heal. The lesions are chronic, moderately severe, recurring, eventually persistent. The first question usually asked is, "Should X-ray work be given up?" While it is obvious that to do this would be conservative, I feel personally convinced that no harm results from X-ray work carried out with all modern precautions. It is easy to give this advice, but only in exceptional instances is the advice conscientiously carried out. The second question, "What is the danger of cancer?" Provided ulcerations have not persisted for more than three months, or have not occurred at the site of an inflamed keratosis, I believe it to be slight.

The surgical treatment of X-ray lesions. — Acute and sub-acute burns: By this I mean the results of one or at the most a few protracted exposures such as occurred in Case II. The severe symptoms develop from a few hours to a few weeks after the injury, and are accompanied by extreme pain. The area apparently involved gradually shrinks, leaving behind, eventually, evidence of the actual damage done. Depending upon the depth of the lesion there is desquamation, blistering, ulceration, or deeper death of the tissues. In all degrees we have the abundant formation of a very tough and adherent fibrin with great pain upon its removal; this condition is well shown in Case VIII., and is peculiar to X-ray lesions. For a time, at least, the deteriorated tissues seem to be in unstable equilibrium, unable to slough or to repair themselves. Pain is extreme and for its relief the tendency is to perform an early excision, but it is most difficult to determine how much tissue should be excised. While in Case II. immediate relief of the pain followed operation, and the excision at the time seemed adequate, the wound failed to heal and further necrosis occurred in the margins and base of the wound. In general, then, except for the pain, I would advise conservative

treatment of these acute or sub-acute lesions until what would correspond to a " line of demarcation " has been established. Excision with skin grafting should be preferred to plastic operations. If the graft fails to grow owing to continued necrosis, later grafting may be done after the wound has granulated.

Fissures and thin skin over the knuckles. — The treatment, whether conservative or operative, must depend upon the individual experience of the operator and the choice of the patient. If skin grafting is successful, there can be no doubt that the result will be most satisfactory, and to my mind should be advised.

Keratoses. — Until recently, my personal experience led me to believe that simple, uninflamed, non-ulcerating keratoses were benign, but I am now convinced that there are exceptions, and that all keratoses which show a tendency to dip below the level of the surrounding skin should be regarded as suspicious. Microscopical examination of many of those which I have removed showed all stages from a perfectly harmless condition to beginning invasion of the corium. I have had no experience with liquid air or carbon dioxide snow, but have found their removal by operation very satisfactory. If situated upon the dorsum of the hand where the skin is lax, excision and suture is satisfactory. If upon the fingers, especially over the knuckles, excision and skin grafting should be practised. If superficial, excisions well into the corium will be adequate when a thin Thiersch graft can be applied. If primary grafting fails, I am convinced from several observations that thorough removal of the diseased tissue promotes spontaneous healing from the edges. It has been suggested that the irritation of the graft excites the surrounding skin to the formation of thickened epithelium, but it has seemed to me that if recurrence of the keratoses takes place at the margins of the graft that this is more reasonably explained by inadequate

excision. If the keratosis suggests malignancy, the whole thickness of the skin should certainly be removed.

Pachydermia with telangiectasis. — The proper treatment of this condition is extremely difficult to determine. In Case XV., where the whole front of the chest was affected, and in VIII. where the anterior abdominal wall was in a similar condition, with undoubted epithelioma in certain unsuspicious localities, treatment must depend upon the individual indications. In a case like XV. the patient must be watched with care; in one like Case VIII. it soon became obvious that all of the damaged tissues would gradually slough unless removed by operation. The histological examination of such tissue shows that the main arteries are pervious, but that there is both marked endarteritis and endophlebitis, which unless collateral circulation is formed will probably lead to subsequent anemic necrosis.

Paronychia and onychia. — Probably the most painful of the X-ray lesions, and one of the most persistent. If disinfection and dry treatment does not bring about healing in a reasonable length of time, extirpation of the nail is clearly indicated. If healing then does not take place, the whole nail bed, both at the base and on the sides should be destroyed. Owing to the difficulty of distinguishing between nail-forming membrane and the insertion of the extensor tendon into the terminal phalanges, subsequent re-formation of portions of the nail is not uncommon. Amputation with certain cure is often too long delayed in this condition.

Ulcers. — I have learned to dread a slowly developing ulcer, in chronic X-ray lesions, which may or may not be painful; the edges may be slightly raised and a little indurated, or soft and flat. Nothing but the persistence of the lesion really suggests malignancy. In Case XVII., though an intermittent ulceration, never completely healed, had persisted for seven years, only beginning carcinoma was shown by the microscope, while a very malignant tumor, either cancer or

sarcoma on the forehead progressed very rapidly within half a year. I have been informed that ulcerations have been open for years in the same spot in two cases, and then entirely healed. Such variations in the tendency to malignancy must be taken into consideration in advising radical treatment. On the other hand, pain and disability, not the fear of malignancy, is often an indication for operation. Even rapid histological examination may be unreliable, for twice I have found undoubted cancer, after amputation on the clinical evidence, when a small piece microscopically examined was negative.

Treatment of ulcers, benign and malignant. — If an ulceration becomes exquisitely sensitive and painful, raw and beefy red, whether or not the base is indurated, such as occurred in 1902 in Case XIX., and recently in Case XX., early amputation should be done. As a rule amputation at the knuckle of a finger, upon which a carcinomatous ulcer has developed, will be found to be sound and conservative treatment; but when one finds that multiple lesions upon both hands have been treated, and more will probably occur in the future, in view of the possible reparative power of the skin, and the relatively benign character of these epitheliomata, if treated early, it seems, so far as my experience goes, that conservative treatment (by which I mean local excisions or minor amputation) will probably be adequate to control metastases. Although since 1902 Case XIX. has developed very many carcinomata, and twice at least operation has been too long delayed, there is as yet no evidence of increasing glandular enlargement, which surely would have occurred long ago, except for the timely operations. It is not unlikely that this relative immunity may be partially explained by the obliteration of the adjacent lymphatics, which has been induced by the X-rays. It must become a question, finally, as to how close to the wind the patient and surgeon are willing to sail. For example: this same Case XIX. developed an epithelioma on the stump of the little finger. This he did not wish to sacrifice, as the forefinger was maimed, so after thorough excision, down to

the aponeurosis, the actual cautery was thoroughly applied. Healing was most painful and slow, yet at present, six months after operation, there is no evidence of recurrence and the finger is soundly healed. One case has remained well for two years and a half, after thorough dissection of the axilla for cancerous involvement; one of my patients is well a year and a half after a similar operation. In those cases, where there have been many epitheliomata on the hands and fingers, it must be a serious problem as to whether amputation at the wrist, which would practically guarantee a cure, would not be sound surgery; yet I know of no X-ray operator in my experience who would make this deliberate choice.

Skin grafting. — I have been so successful in the treatment of these cases by Thiersch grafting that I personally advise it in all of the more severe X-ray lesions. I have not used Wolff grafts, although some of the Thiersch transplantations have been so thick as to practically amount to the same thing. After two failures in using skin for these grafts from parts to some degree affected, I am convinced that sound skin never subjected to the X-rays has more vitality. Heterogeneous grafts, in the few instances in which I have employed them, have been failures. The disinfection of these cases before operation is a difficult problem, for as open ulcerations invite sepsis in the grafts we would prefer thorough germicidal treatment; but this, if thoroughly carried out, usually results in so much irritation that the subsequent discharge of serum is excessive. I have preferred, therefore, mechanical rubbing with a sponge and salt solution, followed by carbolic acid solution (1–50) for a few moments. If the skin is unbroken, ordinary methods are applicable. A tourniquet should always be used, for bleeding is free and dissections must be delicate when made over the joints, tendons, or aponeuroses. After the removal of the diseased tissues, the tourniquet should be removed, and the hands elevated until bleeding has stopped spontaneously. I have seen little benefit from peroxide, and have never dared to use adrenalin. In some cases the hemostatic

action of grafts quickly placed upon an oozing surface has been remarkable. If possible, excisions should have bevelled edges, and the graft should be cut thick in the middle, thinning out towards the periphery, so that it will accurately fit the wound. Firm pressure must be applied for the first twenty-four hours to prevent oozing and hemorrhage. In order to insure even pressure after operation, and to avoid danger of detachment of the grafts by slight motions of the etherized patient, the hand and fingers must be firmly fixed to a well-padded splint by adhesive plaster before any of the grafts are applied. This is often a painstaking procedure, owing to the various deformities and irregularities in the lengths of the fingers between which gauze must be placed to make them comfortable. The grafts are dressed with small pieces of protective placed in an imbricated fashion, and stuck by blood to the palmar surfaces of the fingers; the protective should be perforated. After sufficient gauze has been placed over the protective to make an elastic dressing, firm pressure should be made directly downwards by series of opened gauze sponges which are tied on the palmar surface of the splint. By this manœuvre, detachment of the grafts is prevented, as I have frequently seen when a roller bandage was used, causing gradual lateral creeping of the grafts. After twenty-four hours the protective should be removed with great care, and if the pain is not too severe the grafts should be exposed to the air in a cage. If such exposure cannot be borne, benzoinated lard is the least macerating ointment which I have found. Blisters are punctured as fast as they are formed. If these punctures scab, and serum accumulates under the graft, dry treatment is contraindicated. At the end of three days the hands are bathed in warm salt solution or citrate of silver; while under water small tabs of skin, etc., may be very readily removed, as in making a wet dissection. In ten days the grafts are soundly healed, when dry treatment with occasional lanolin ointment is all that is necessary. The patient must be kept in bed for four or five days with the hands elevated. If the grafts owing to infection or from lack of blood supply do

not take over the aponeuroses, a subsequent grafting may be done when the wound granulates, provided spontaneous healing does not take place.

SUMMARY.

With the more general recognition of the existence of these X-ray carcinomata, it seems clear that such early conservative treatment as I have outlined will be adequate to prevent metastases, for a careful study of the fatal cases shows that in eight of them inadequate treatment, either in point of time or extent of operation, due almost always to refusal of the patient to submit to the treatment suggested, was the cause of the fatal issue. In the case of Sick, and also of Wagner, coincident development of epithelioma on the face or other parts of the body made adequate surgical treatment more difficult.

[In my former paper I was indebted to Dr. J. H. Wright, Director of the Clinical Laboratory, and to Dr. W. F. Whitney, Pathologist at the Massachusetts General Hospital, for the microscopical reports of my cases. Dr. C. J. White, Dermatologist to the Hospital, made an exhaustive study and report of the numerous sections removed from Case XIX., while both Dr. Wright and Dr. Whitney have examined the material from many of my subsequent cases, and Professor Mallory of the Harvard Medical School has given me his valuable opinion on two cases. Most of the pathological specimens have been sent to Dr. S. Burt Wolbach of the Bender Hygienic Laboratory in Albany, who is making a special study of X-ray lesions and their causative relation to carcinoma. As his contribution will be published in conjunction with this paper, I devote myself chiefly to the clinical side of the subject, leaving to him a more careful description of the pathological lesions found in the less advanced cases, and an estimate of their value in a theoretical attempt to explain the etiology of cancer, or at least the conditions which immediately precede its development.]

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2. Karl Lindenborn. Same journal, 1908, lxxxix, Heft 2, 385.

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DESCRIPTION OF PLATES.

Plate XXXV.

Fig. 1. — Case V. Precancerous ulceration. Dr. W. H. M. Condition before and ten days after operation.

Fig. 2. — Case VIII. Miss H. Huge X-ray ulceration with epitheliomatous nodules, as marked in ink square; after first operation.

Fig. 3. — Miss H. Condition after second operation with outline of extent of excision with subsequent healing.

Fig. 4. — Case IX. M. K. K. 1901; note pachydermia.

Fig. 5. — Same, 1903. Note ribbing of nails, rhagades, and superficial ulcerations.

Fig. 6. — Same, January, 1908. Carcinoma base of ring finger, and over terminal phalanx of middle finger of left hand. Keratosis right hand.

Plate XXXVI.

Fig. 7. — Case XV. F. H. S. Epitheliomatous ulcer back of hand, with numerous keratoses and telangiectases.

Fig. 8. — Same. Low power; carcinoma of hand.

Fig. 9. — Same. Telangiectases of chest with carcinomatous nodule outlined in ink circle.

Fig. 10. — Same. Low power; nodule chest; epidermoid carcinoma.

Fig. 11. — Same. Keratosis nose, high power. Note extraordinary number of mitotic cells.

Fig. 12 — X-ray ulcer leg. Case III.

Plate XXXVII.

Fig. 13. — J. G. Case XVIII. Recurrent growth of finger, pushing through skin graft.

Fig. 14. — Section same case, low power. Note encapsulated growth and small carcinoma on right.

Fig. 15. — High power of same growth. Pathology described by Professor Mallory, under Case XVIII.

Fig. 16. — W. J. D. Case XIX. Condition of hands, June, 1905. Epithelioma base middle finger, right hand.

Fig. 17. — Same case. Condition of hands July, 1907. Epitheliomatous ulceration forefinger. Flexion owing to destruction of extensor tendon over head first phalanx.

Fig. 18. — Same case. Condition November, 1908. Epithelioma base little finger, left hand. Malignant keratosis base middle finger, right hand.

Plate XXXVIII.

Fig. 19. — W. J. D. Case XIX. March, 1909. Present condition after thirty-four operations.

FIG. 20. — X-ray same case, March, 1909, showing no osteoporosis, in spite of long duration of disease.

FIG. 21. — Photomicrograph, Case XIX., showing in center, nerve surrounded by carcinoma, causing intense pain.

FIG. 22. — H. G. Case XVII. Hand one year after operation. Graft is outlined; note thickness of skin, keratoses and characteristic nail changes.

FIG. 23. — Case XVII. Recurrent growth on forehead, low power. Question of sarcoma or carcinoma. See pathological description.

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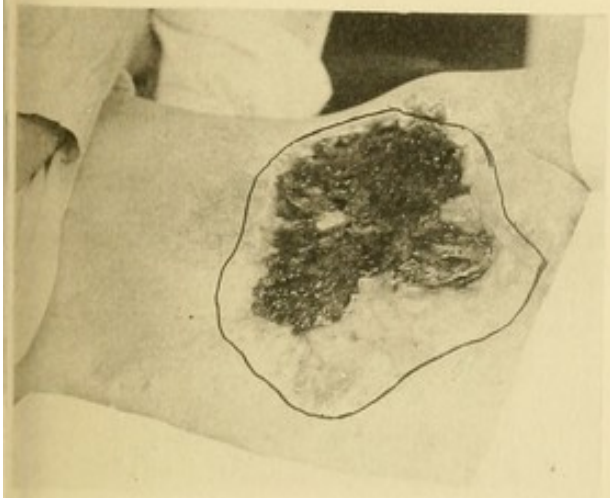

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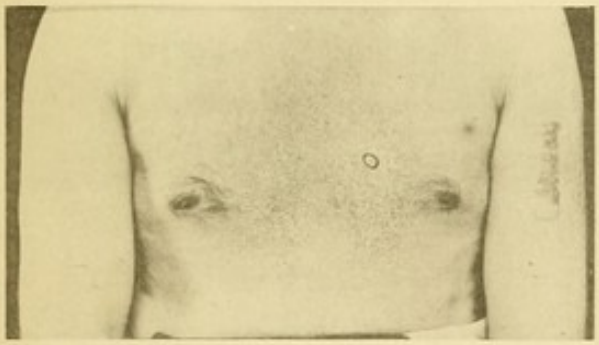

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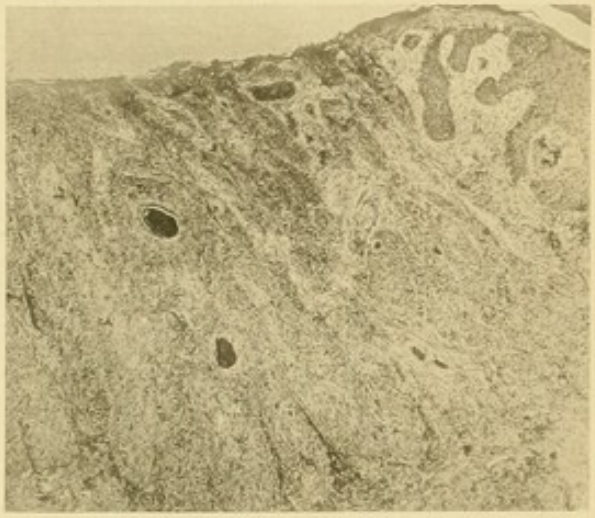

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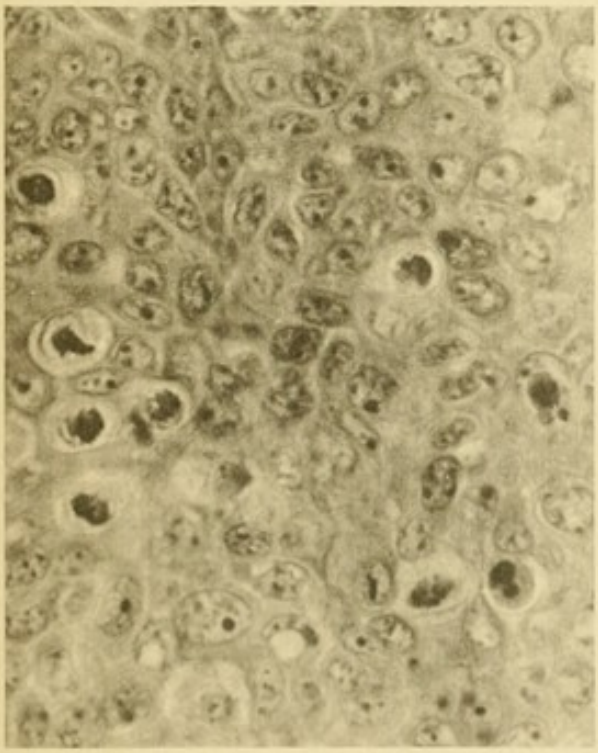

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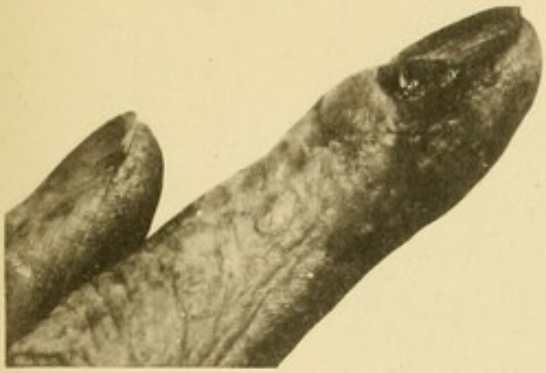

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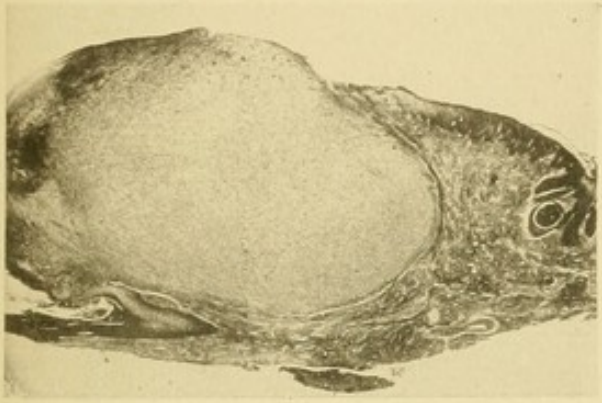

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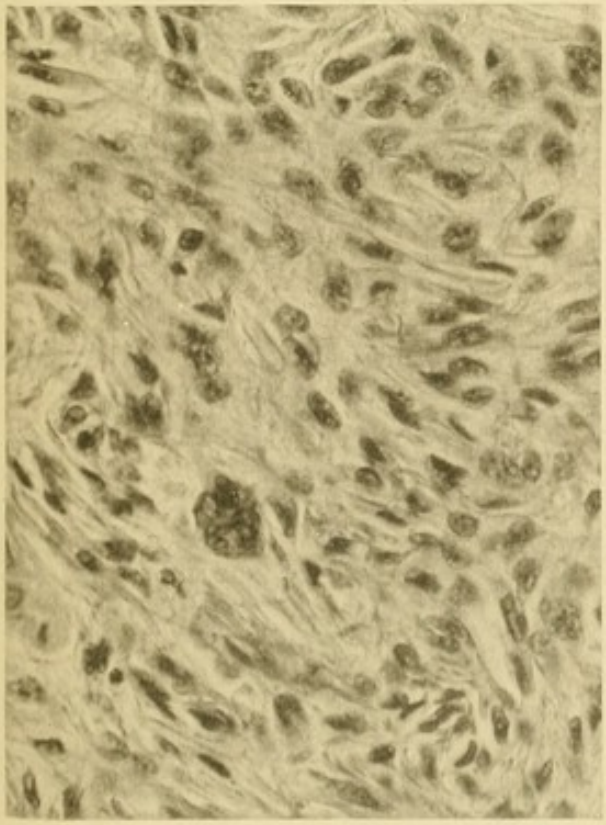

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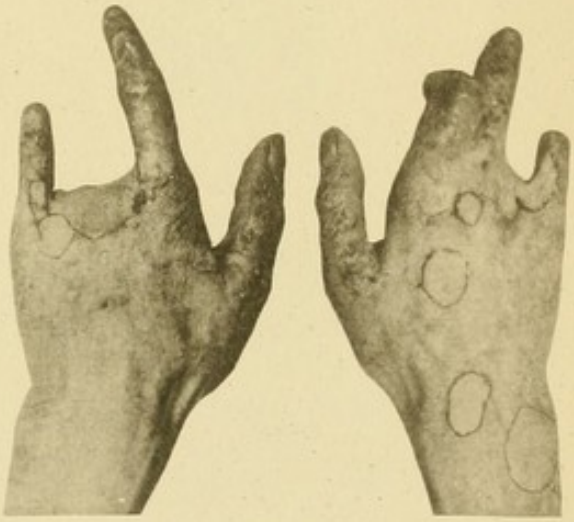

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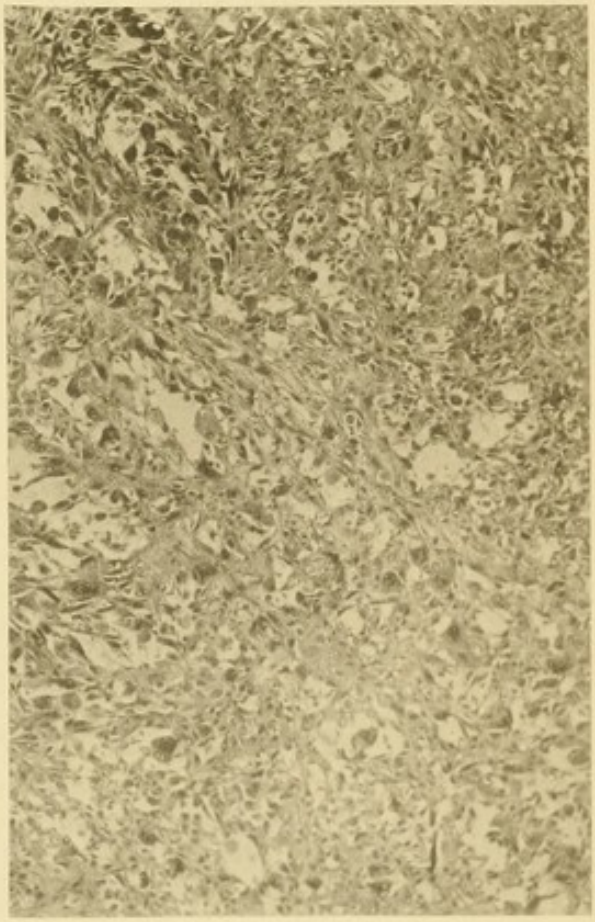

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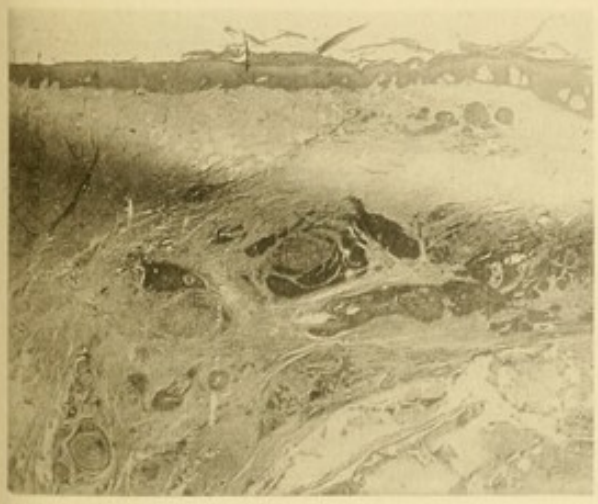

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THE PATHOLOGICAL HISTOLOGY OF CHRONIC X-RAY DERMATITIS AND EARLY X-RAY CARCINOMA.*

S. B. WOLBACH, M.D.

(*Director of the Pathological Laboratory, Montreal General Hospital, Montreal.*)

The development of multiple carcinomata in the skin of patients and operators who have suffered repeated injuries from exposures to the X-rays has occurred so many times that the causal relationship has been generally accepted in all countries. The tumors have made their appearance in each instance reported, several years after the establishment of severe chronic changes in the skin, characterized by great thickening, telangiectases, ulceration, hyperkeratosis, and loss of the epidermal appendages.

The tumors which have developed in the permanently altered skin have been epidermoid carcinomata almost invariably, and microscopically cannot be distinguished from similar carcinomata of ordinary occurrence.

Striking features of the carcinomata following X-ray injuries, already brought forth in numerous publications, are the occurrence in young individuals and the malignant nature of the tumors as shown by the high mortality. The article of Dr. C. A. Porter in this issue describes the clinical features of these cases and presents a summary of those from this country.

The opportunity to make a careful histological study of early X-ray carcinomata and of skin from cases showing varying degrees of the chronic changes which precede the occurrence of these tumors has been a great privilege for which I am indebted to Dr. C. A. Porter. His interest and care has also made it possible to obtain tissues fixed immediately after removal from the patient. In every instance a general anesthetic was employed so that the tissues obtained were not injured by local injections.

All of the material studied for this report was fixed in

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Zenker's fixative, and in every instance immediately after operation. The staining methods employed were the methylene blue and eosine stain, Mallory's phosphotungstic acid hematein, Mallory's connective tissue stain and Verhoeff's elastic tissue stain (all are described in the Pathological Technique of Mallory and Wright, fourth edition).

The descriptions were made chiefly from sections stained by the phosphotungstic acid hematein stain, though the other stains were used for corroborative evidence when necessary. This stain proved to be especially useful in the study of the collagenous fibrils of connective tissue because it brings out differences in staining properties which are not demonstrable by the other methods or any ordinary stain.

As the use of Mallory's phosphotungstic acid hematein stain has not yet become general a brief account of its staining qualities is desirable. Nuclear material and protoplasm are stained blue, collagenous fibrils are stained brownish red. Epidermal, neuroglia, myoglia, and fibroglia fibrils are stained a deep blue. Elastic fibers are stained either a deep purple or purple with a brownish periphery. In the epidermis the superficial layers of cells stain purplish to brownish red. Most cell inclusions stain brownish.

The advantages of this stain in a histological study of skin lesions are:

I. Differential staining of connective tissue.

II. Differences in staining of normal and degenerated collagenous material.

III. The demonstration of fibrils of all sorts and of elastic fibers. The arrangement and development of epidermal fibrils is of importance in the study of altered function of epidermal cells. Myoglia and fibroglia fibrils assist in the identification of smooth muscle and connective tissue cells.

IV. The ease by which products of cell degeneration are recognized when within the cell.

V. The general excellence of the cell pictures, which is largely due to the deep staining of the protoplasm, an especially valuable feature in the study of connective tissue cells in dense fibrous tissue. Eosinophilous cells may be recognized by the presence of deep blue stained granules. Mast cells are not demonstrated, owing to the fixative necessarily employed.

The effects of X-ray exposures upon human and animal tissues have been incompletely determined. Studies from cases similar to those forming the basis for this paper have been few in number, and although the most important of the constant changes have been described, no single observer has had the opportunity of comparing the cases from a series as large as the present one. Many important changes have been overlooked owing to the employment of inferior staining methods.

CASE I. (Case II., Dr. Porter). — R. M., a man aged 55 years was exposed July 23, 1908, for not more than twenty minutes during a fluoroscopic examination. In three weeks a painful area of erythema the size of a dinner plate appeared in the site of the exposure. The edges of the erythema gradually subsided, though the patient continued to have severe pain. The skin broke down and a superficial ulcer 3 x 2 inches resulted, which resisted treatment and steadily increased in size. On Nov. 18, 1908, the whole of the ulcer was excised with a wide margin of surrounding skin.

The material received for examination consisted of tissue hardened in Zenker's fixative, representing a large ulcer about ten centimeters in diameter surrounded by a border of epidermis one to one and a half centimeters in width. The tissue includes the skin and subcutaneous tissues for a depth of one-half to one centimeter.

Description, under the microscope, from sections stained with phosphotungstic acid hematein. The most striking lesions, aside from the ulceration, are found in the connective

tissue of the corium and subcutaneous tissues. The corium everywhere, beneath the ulceration and where covered with epidermis, is of great density. Immediately beneath the epidermis, however, it has a delicate structure, and is the seat of an active process. The subcutaneous connective tissue exhibits marked degenerative changes, including deposits of fibrin and reparative processes evidenced by the presence of young connective tissue cells.

The deeper layers of the corium are composed of very dense connective tissue, poor in cells, with thick bundles of deeply-staining collagenous fibrils. The latter are stained a deep red and form bundles many times thicker than occurs in the normal corium. The fibrils are coarse in texture and have a more hyaline refractive appearance than those in normal skin. In places there are bundles in which the collagenous fibrils are fused into homogeneous refractive masses. Elastic fibers are very numerous, they run parallel to the collagenous fibrils, in great numbers at the periphery of bundles, but often imbedded within. The elastic fibers vary greatly in thickness, many can be easily resolved only with the highest oil immersion objective (Zeiss 1.5 mm. apo.). All show a central bluish stained core with a brownish outer zone. The connective tissue cells show no abnormalities.

The corium immediately beneath the epidermis for a considerable depth is of loose texture, contains little collagenous material but many young connective tissue cells. The papillæ are absent. These changes are most marked near the ulceration and gradually diminish in the direction of the periphery of the excised tissue. Still every part of the material examined shows absence of papillæ and rarefication of the collagenous material. The collagenous fibrils in this part of the corium are very delicate and stain less deeply than normal, taking a pale brownish color. The individual fibrils or small bundles of them are widely separated. The tissue is infiltrated with polymorphonuclear leucocytes, lymphoid and plasma cells and eosinophiles. There are numerous large, many processed connective tissue cells

having extraordinarily large nuclei. There are many dilated capillaries in this rarefied corium, made conspicuous by the large endothelial cells lining them. Migrating endothelial cells are easily found, and there are occasional clusters of them surrounding capillaries. A few capillaries are filled with free endothelial cells, occasionally one contains a single giant cell. In places greatly dilated capillaries lie immediately beneath the epidermis. The epidermis is separated from the corium by a basement membrane, usually well defined, but in places composed of an extremely delicate hyaline brownish stained material. In the connective tissue below the corium are large areas containing deposits of fibrin. The collagenous fibrils are faintly stained and in places changed into a hyaline material. Young connective tissue cells are numerous. There are very few polymorphonuclear leucocytes, lymphoid and plasma cells except about the remains of coil glands. The fat lobules show little change. In places the cell walls are wrinkled and there are accumulations of lymphoid and plasma cells between the fat cells and surrounding capillaries.

The epidermis is uniformly thickened. The horny layer is very thin. The layers of prickle cells and granular cells are of increased thickness. In a few places the epidermis is separated from the basement membrane by spaces filled with finely granular material. The layer of basement or cylindrical cells in general is orderly arranged, but in places there are groups of deeply-stained cells which are irregularly arranged upon the basement membrane. These cells are of the prickle cell type, while elsewhere the basement cells are of the normal type. In these atypical groups the cells are often separated by narrow clear spaces. The prickle fibrils, which are stained a deep blue, run vertically at the base into the basement membrane and here, in places, form a delicate blue line by a series of contiguous arches.

The ulcerated surface is covered with a layer of coarse meshed hyaline fibrin. In most places the fibrin lies directly upon degenerated collagenous material, but there are some large areas of granulation tissue.

The smooth muscle in all sections examined shows very marked changes in the walls of vessels and in the arrector pili muscles. In the latter the cells are of increased thickness, and the myoglia fibrils are of unusual size, though this may be due to the fusion of fibrils. Many of the cells are vacuolated, others are filled with a hyaline brownish stained material. In arteries and veins of the subcutaneous tissues the muscle cells show the same changes as in the arrector pili muscles, though there are many atrophic muscle cells which are surrounded by dense collagenous material of which there is a great increase in the media. In some vessels most of the muscle fibers in a given section are swollen, widely separated by connective tissue and all are filled with masses of hyaline brownish stained material.

Besides the thickening of the media above noted, a few arteries and veins show marked thickening of the intima due to an increase of connective tissue and to swelling and vacuolization of the endothelium. Many arteries and veins are normal in appearance. In the arteries showing the above changes the elastic lamina has disappeared and its place is occupied by a thick dense band of hyaline fibrillary material stained brownish and probably collagenous in nature.

Hair bulbs and sebaceous glands are absent in all parts of this specimen. Certain linear areas filled with inflammatory cells and young connective tissue cells undoubtedly represent the sites once occupied by these structures.

Remains of coil glands are found in all sections. The changes are those of simple atrophy — degeneration with infiltration.

CASE II. (Case III., Dr. Porter). — E. R.; female; 30 years. Was treated with the Röntgen rays for ulcerations on outer side of knee and elbow for about one month during March and April of 1908. Healing of the ulcers followed, then rapid breaking down, ulceration, and severe acute dermatitis. From Aug. 18 until Nov. 7, 1908, there was severe pain from the dermatitis and ulcerations. Examination Dec. 4, 1908, showed characteristic X-ray changes

over the inner aspect of the right elbow. The skin was thickened, there were telangiectases and a small ulceration covered with a yellow fibrinous layer. There was marked dermatitis of the left leg from the middle of the thigh to the top of the boot. On the outer side of the knee there was an area six by five inches showing reddened pigmented scars which have healed peripherally, leaving in the center an ulceration three by one inches in extent. Jan. 21, 1901, the ulcer was removed with a surrounding zone of skin one-half inch in diameter.

This tissue was received after hardening in Zenker's fixative. It consisted of an ulcer of the skin three and a half by one and two-tenths centimeters in extent surrounded by a zone of epidermis one to one and a half centimeters in width. The disc of tissue was about one centimeter thick and included the subcutaneous fat.

Description under the microscope. There are the same changes in this specimen that were found in Case I. There are differences of degree, however, that deserve description.

The deeper layers of the corium contain dense collagenous material similar to that in Case I. There are, however, more numerous and larger connective tissue cells throughout. Towards the zone of rarefied corium there is a very cellular layer of connective tissue, the cells of which occur singly or in groups and are separated by wide bands of refractive hyaline collagenous material. The connective tissue cells are large with prominent nuclei and abundant protoplasm having many processes and conspicuous fibroglia fibrils. Elastic fibers are present in extraordinary numbers, in places they run in directions parallel to the connective tissue cells and many are in contact with connective tissue cells.

The connective tissue between the lobules of the subcutaneous fat is dense and similar to that of the corium.

The vessels show much more marked changes than in Case I. There are numerous completely obliterated arteries and all of the vessels in the sections show thickening of the walls with reduction of the caliber of the lumen. The obliteration

and thickening of the walls is due to proliferation of connective tissue in the intima and media and to increased thickness of the smooth muscle fibers. In vessels showing lesser changes, the muscle fibers of the media are large, and widely separated by coarse collagenous fibrils and vacuoles. The location of the vacuoles is difficult to determine. Some of them are within young connective tissue cells, which are increased in number particularly in the adventitia. The smooth muscle fibers are swollen, many contain two to four nuclei. The myoglia fibrils are either normal in appearance or more conspicuous than the normal. Where the process is more advanced, the smooth muscle fibers are surrounded by dense fibrous tissue, the myoglia fibrils cannot be demonstrated and the protoplasm has become homogeneous and hyaline in appearance and takes a brownish blue stain.

The thickening of the intima is due to the presence of a dense yet cellular fibrous tissue. In the arteries the elastic lamina is usually totally absent, its place being indicated by a dense band of collagenous material. Occasionally remains of the elastic lamina are found and in these the elastic tissue is broken up into delicate filaments which stain a deep brownish.

The endothelium is often redundant, the cells are large, cuboidal or elongated in shape and often contain large vacuoles. The above changes are most marked in the arteries. In the veins the media shows less marked changes and the thickening of the walls and diminution of caliber of the lumen is due chiefly to a thick concentric layer of large connective tissue cells, with much or little collagenous intercellular substance in the intima.

The corium just below the epidermis shows more marked rarefication and contains more and larger telangiectases than that in Case I. Many very large blood spaces lie directly in contact with the epidermis, separated only by a narrow border of hyaline-changed collagenous material. Others are surrounded by necrotic tissue and are filled with fibrin.

The many capillaries just beneath the epidermis are lined with large endothelial cells, a few are filled with loose

endothelial cells. In occasional areas capillaries thus occluded are found, about which all of the connective tissue has undergone hyaline change.

The epidermis is uniformly markedly thickened. In general the relations of the different cell strata are the same as in Case I. But there are many places in the tissue where the lowermost layers of cells present differentiated groups and strata of large deeply-stained cells. In places where the basement membrane is not demonstrable there are irregularities of the bottom layer of cells and individual cells are sometimes found in spaces of the corium, though always connected above with the epidermis. Irregular downgrowths between adjacent telangiectases are common, though there is nowhere any evidence of actual invasion or of independent growth, except the doubtful evidence of increased size of the cells and a marked affinity for basic stains. Mitoses are very rare.

Hair bulbs and sebaceous glands are entirely absent. Areas of intense infiltration and active connective tissue multiplication probably represent the former site of these structures. A few atrophic remains of coil glands are found surrounded always by lymphoid and plasma cells.

The ulcerated surface of the tissue is covered for the most part with granulation tissue. In many places dense hyaline fibrous tissue, infiltrated with polymorphonuclear leucocytes, is directly exposed. There is in places slight downgrowth of the epidermis at the edges of the ulcer comparable to that found in cases of chronic ulcer.

CASE III. (Case IV., Dr. Porter). — F. H. S.; male; 40 years. Received Röntgen ray treatment for eczema five years ago. There was marked improvement of the eczema and during that year occasional treatments were given which finally resulted in a severe dermatitis with exfoliation of the skin of both thighs and legs. Four years ago a small ulcer developed on the inner side of the calf and has never healed. Another small ulcer which formed on the thigh healed after a few months. There has been no pain. In August, 1908, the ulceration of the left leg began to spread rapidly, in spite

of various forms of treatment including two applications of radium. Examination on Nov. 10, 1908, showed an irregularly-shaped ulcer three by two and a fourth inches. In the center there were occasional islands of growing epidermis, the rest was covered with fibrinous exudate. The skin was undermined and showed no evidence of repair. The whole was excised on Nov. 19, 1908. The tissue received for examination had been hardened in Zenker's fixative. It included the ulcer and subcutaneous fat with a surrounding margin of skin one centimeter in width.

Examination under the microscope. — The deeper layers of the corium are composed of the same dense tissue found in Cases I. and II. In places there are very many young connective tissue cells with conspicuous fibroglia fibrils in the meshes of hyaline-changed collagenous fibers. Some of these connective tissue cells are surrounded by narrow zones of paler staining normal collagenous fibrils. The picture suggests the proliferation of connective tissue and the deposit of fresh collagenous material in the meshes of degenerated fibrous tissue.

The corium immediately beneath the epidermis shows the changes previously described, *i.e.*, the more delicate structure, presence of young connective tissue cells, dilated blood spaces, absence of papillæ and occasional thrombosed telangiectases in contact with the epidermis.

The ulcerated surfaces show active granulation tissue enclosing masses of hyaline changed collagenous material. The granulation tissue arises from a base of very cellular connective tissue in which the connective tissue cells are imbedded in degenerated collagenous material. The epidermis is markedly thickened. The horny layer is almost lacking. The granular layer is narrow, so that the width of the epidermis is composed chiefly of prickle cells. At the edges of the ulcer are downgrowths of the epidermis into the granulation tissue.

The blood vessels show very marked changes. Many large arteries of the corium and subcutaneous tissue are

completely obliterated. In these sections it can be shown that the characteristic irregularity of the muscle fibers is largely due to the ingrowth from the adventitia of large fibroblasts, the prominent fibrils of which make it difficult to distinguish these cells from smooth muscle cells. The first suspicion that some of the cells of the media, while apparently smooth muscle, were connective cells was awakened by the finding of branched cells with coarse fibrils. Some of these cells are surrounded by considerable collagenous material and these facts together with the presence of occasional mitoses prove the connective tissue origin of these cells. The vacuoles in the media are probably within degenerated smooth muscle cells. Some small veins and arteries have the media completely replaced by dense collagenous material in which atrophic remains of smooth muscle cells can be found. In all partially or completely obliterated arteries the elastic lamina is replaced by a thick convoluted band of dense collagenous material. In a few large vessels the endothelium of the intima is strikingly swollen and redundant and many of the cells contain large clear vacuoles.

The appendages of the skin are absent. Remains of the arrector pili muscles are found consisting of tracts of young connective tissue enclosing degenerated smooth muscle cells.

CASE IV. (Case VIII., Dr. Porter). — Female; 40 years; S. After an abdominal hysterectomy for a tumor of the uterus was treated with the Röntgen rays for a slowly growing tumor of the abdominal wall which appeared one year after operation. She received one hundred and thirty-six treatments between Jan. 28, 1902, and May 20, 1904. She was well for four years, when characteristic Röntgen ray ulcerations developed, involving the whole lower abdomen. There was necrosis and ulceration of the skin with nodules suggesting small carcinomata. On March 7, 1908, the whole area of skin containing ulcers was excised down to the aponeurosis of the abdominal muscles, where a mass of dense tissue was encountered, supposedly the remains of the tumor for which treatment was given.

Description of gross appearances of excised tissue (by Dr. Thomas Ordway). "The specimen consists of a large irregularly triangular piece of skin and subcutaneous tissue. Its base is 9 centimeters and the sides are 10 centimeters and 11.5 centimeters respectively. It is from 2 to 2.5 centimeters thick except in the central part, where it is .5 centimeter to .7 centimeter thick. The skin surface shows a large irregularly triangular ulcer (5.2 centimeters x 7.5 centimeters x 8 centimeters) conforming in general to the shape of the specimen. The base of the ulcer is depressed from .2 centimeter to .6 centimeter below the rough, irregular, ragged, overhanging and undermined, non-indurated edges. The edges are necrotic, reddish-gray in color, and bathed in bright yellow purulent exudation. The base of the ulcer is bright red to grayish red in color; it is rough and ragged and is irregularly covered with purulent exudate.

"The lower surface of the specimen consists of bright yellow fat tissue through which is a delicate tracery of grayish white fibrous tissue. In the central part of this surface of the specimen (the thinner area referred to above) there is an area (3.5 centimeters x 4 centimeters) of firm, dense, grayish white, glistening, elastic fibrous tissue which is found to be, in many places, in continuity with the base of the ulcer, in other places it is connected by fine and coarse fibrous strands.

"The margin of the skin surrounding the ulcer is from 1 to 3 centimeters in width. It is thicker and firmer than normal skin; it is diffusely reddened with a deep punctate erythema except for numerous slightly elevated, rounded, whitened areas (.3 centimeter to .6 centimeter in size) which have a distinct nodular, almost 'shotty,' feel. On section these nodules are .4 centimeter to .6 centimeter in thickness. The surrounding skin is .2 centimeter to .3 centimeter thick. The bright punctate appearance in the diffuse erythema of the skin surrounding the ulcer is apparently due to marked injection of very small blood vessels."

Microscopic examination: I. Disc of fibrous tissue below floor of ulcer. The tissue consists chiefly of dense fibrous tissue, the bundles of which run in all directions. There are groups of bundles where the collagenous fibrils are fused into hyaline masses and regions where the connective tissue is very cellular and edematous in appearance. The latter areas surround thin walled vessels which often are immediately surrounded by fibrin. Many arteries and capillaries are surrounded by masses of lymphoid and plasma cells with occasional eosinophiles. The amount of elastic tissue is small, and that present is in small masses composed of swollen tortuous poorly-staining clumps.

II. Sections of skin surrounding the ulcer. The corium

is composed of dense fibrous tissue rich in elastic fibers and is in general similar to the tissues already described. There is, however, no hyaline change of the collagenous material, and there are no areas containing many young connective tissue cells. The corium immediately beneath the epidermis shows remains of the papillary structure, but shows the same rarefication and other characteristics noted in the other cases. There are numerous large connective tissue cells in this part of the corium with abundant spongy protoplasm and numerous coarse fibrils (Foam cells of Unna). Particularly striking is the occurrence of a layer of homogeneous hyaline changed collagenous material separating the epidermis from the cellular loose connective tissue below. In places this hyaline layer contains migrating polymorphonuclear leucocytes, and occasionally there are groups of a few small, widely separated epidermal cells occupying spaces in this layer, surrounded and infiltrated with leucocytes.

The epidermis is much increased in thickness, chiefly due to the great depth of the prickle cells. Mitotic figures are common in the basement row of cells. Some of the large subcutaneous arteries show eccentric thickenings of the walls.

None of the sections show any trace of hair follicles or glands. An occasional remains of the arrector pili muscles is found in wnich the muscle fibers are small, vacuolated and hyaline degenerated. The fibrils are usually demonstrable.

III. Sections of the elevated areas of skin or nodules found in the skin surrounding the ulcer. The elevation of these areas is due to a great increase in dense fibrous tissue in the corium, which extends down as a continuous layer to the subcutaneous fat. Laterally it gradually merges into the corium of the surrounding skin; there is no line of demarcation. The bundles of collagenous fibers in the nodules and surrounding skin are very dense and hyaline in appearance. The number of elastic fibers is enormously increased. There are no papillæ so that the epidermis lies evenly upon dense hyaline collagenous material or in places upon rarefied connective tissue; in the latter case there is a line of hyaline collagenous material without nuclei immediately beneath the

epidermis. There are numerous telangiectases beneath the epidermis and in the dense corium are large blood spaces lined only with endothelium. The skin surrounding the nodules shows marked rarefication of the upper layer of the corium which contains many large telangiectases, some of them filled with fibrin; most of them are surrounded by zones of hyaline collagenous material continuous with the layer beneath the epidermis.

The epidermis in places is greatly thickened and there are processes extending down between the dilated blood spaces or telangiectases. Some of these processes are thick and branched and contain typical epithelial pearls (Figs. 13 and 14). They are always surrounded by zones of lymphoid and plasma cells and an occasional eosinophilic cell. There are numerous mitoses present in these processes and in the adjacent epidermis.

IV. The ulcer and adjacent skin. The floor of the ulcer consists of granulation tissue covered with fibrin and purulent exudate. In numerous places the ulceration extends nearly to the subcutaneous fat. The granulation tissue includes islands of degenerated collagenous material. In places there is no granulation tissue and degenerated collagenous material, infiltrated with leucocytes, forms the floor of the ulcer.

The corium adjacent to the ulcer shows the changes described in the sections from the other parts of this tissue; hyaline change of the collagenous fibrils, and a diffuse appearance of new connective cells between the collagenous bundles without the formation of granulation tissue. Beneath the epidermis there are the same changes observed in the other sections. Near the edge of the ulcers, however, there are many large telangiectases some of which are filled with fibrin (Figs. 4 and 5). In places the fibrin extends through the walls of the vessel into the surrounding tissue. In a few places where a dilated thrombosed vessel is surrounded by epidermis there are masses of epidermal cells extending into the fibrin (Figs. 8 and 9). These cells form tortuous cords and irregular masses of cells sometimes nearly completely

filling the vessel. In other places compact groups of cells from the epidermis extend for considerable distances into the corium, and the relations of these epidermal processes is such as to make it certain that extension has taken place into and along the course of one of the dilated vessels. These cell processes show epithelial pearls and many mitoses. Occasionally, in such a process a group of epithelial cells is found which stains more deeply than the surrounding cells, and the individual cells show great irregularity in shape with distorted fibrils, many of which are intracellular (Fig. 14). Here and there in the basal layer are groups of epidermal cells which contain large irregular nuclei often with budding processes containing chromatin material. There are also cells containing two or more nuclei. The cells of these groups are closely packed and are, roughly, concentrically arranged, individually the cells are approximately spindle shaped. Numerous mitoses are also found in these small groups of cells and the whole picture suggests that these groups represent isolated, independently-growing portions of the epidermis.

Many large arteries and veins of the subcutaneous tissue and corium are completely obliterated chiefly through the multiplication of connective tissue cells of the intima (Figs. 18, 21, and 22). In some instances the muscle cells of the media are largely replaced by leucocytes and fibroblasts (Fig. 22). In general the obliterated vessels show the same characteristics as those described in preceding cases.

CASE V. (Case XV., Dr. Porter). — Male; 40 years; a maker of Röntgen ray tubes since 1897. Has had several acute attacks of "eczema." The first ulceration commenced in 1905 on the left hand between the knuckles of the first and second fingers. This has healed and broken down several times. At the time of operation, in April, 1908, there were several keratoses and small ulcerations on the hands. On the whole there has been very little pain associated with any of the lesions. The tissues excised were an ulcer from the back of the left hand, measuring about two by one centimeters;

a horny keratosis from between the knuckles of the index and middle fingers of the left hand, a soft wart-like growth from the nose one-half centimeter in diameter capped with a layer of horny epithelium and a piece of tissue from the chest which came from the center of a thickened pigmented area of the skin showing prominent telangiectases (the chest has been frequently exposed to the rays in making fluoroscopic examinations). This piece of tissue from the chest had a scaly surface with minute elevated scar-like areas. The excision included all the tissues of the skin and subcutaneous fat.

Microscopic examination: I. Keratosis from the back of the hand (Fig. 16). The greatly thickened epidermis has long processes extending into the corium. Between the processes of epidermis are papillæ of the corium, usually long and slender, but occasionally short and thick and containing dilated blood spaces filled with fibrin and leucocytes. The collagenous material of the papillæ, as elsewhere in the corium immediately beneath the epidermis, shows the hyaline change and rarefication noted in the other cases. The vessels in the papillæ are of large caliber and many are surrounded by areas of faintly stained collagenous material in which are strands of fibrin and young connective tissue cells. Collections of plasma cells are common in the neighborhood of capillaries and at the tips of the epithelial processes. The cell masses also contain numerous mononuclear eosinophiles and lymphoid cells and occasionally polymorphonuclear leucocytes. The deeper part of the corium is of the dense hyaline type, with great numbers of elastic fibers, already described.

None of the sections include the large vessels of the deep corium and subcutaneous tissues.

The epithelial processes of the epidermis consist of prickle cells with an abrupt change towards the surface into cells of the type of the stratum lucidum (Fig. 19). Cells of the granular layer type are almost entirely absent. The horny layer is very thick and consists of fused elements in which

cell and nuclear outlines can often be distinguished (acanthosis). In places there are spaces in the horny layer containing refractive hyaline transformed cells in which are nuclear remains. The basement layer of cells of the epithelial process is for the greater part regularly arranged and composed of columnar cells. In places the arrangement is irregular, the cells are irregular in shape and widely separated. Such groups are invaded by plasma cells and polymorphonuclear eosinophiles. The epithelial cells show numerous mitoses and in general are small in size and show very prominent prickle fibrils. In places there is growth of epidermis into dilated vessels filled with fibrin which lie in the papillæ or at the base of the keratosis. The epidermis on each side of the keratosis is uniformly thickened and for the most part lies upon a rarefied corium without papillæ. In places there are processes of epidermis extending into the corium, usually around or between telangiectases. The cells of such processes consist of irregularly shaped many processed prickle cells with no definite arrangement. Mitoses are common. These groups of cells are invaded with plasma cells and eosinophile cells and in general present an atypical arrangement and relationship to the surrounding densely infiltrated corium. In addition to such processes there are long stretches of epidermis where the deeper layers consist of similar cells with similar atypical arrangement.

Keratosis from tip of nose (Fig 17). The gross structure is similar to the lesion from the hand. The changes in the corium are also similar. The epidermis is strikingly different because the entire depth of the epithelial processes are composed of a uniform type of cell; large cells with great numbers of mitoses. There are three or four mitoses to every oil immersion field even immediately beneath the layer of horny cells, in some fields there are eight to ten mitoses (Fig. 23). Prickle fibrils can occasionally be demonstrated; usually they are absent. There is a thin layer of horny epithelium which is in many places detached from the active cells below.

At the base of the epithelial processes there are irregular offshoots extending into the corium, always surrounded by densely packed zones of lymphoid and plasma cells and eosinophiles. The epithelial cells composing these offshoots are irregularly arranged, and show absence of or atypical arrangement of prickle fibrils.

In this lesion the picture indicates that differentiation of the epidermal cells into keratohyaline and keratin has ceased and that the whole depth of cells is in active growth with beginning invasion at the base.

Large ulcer from hand. The ulcerated surface is the exposed surface of a vascular new growth of epidermis, atypical in arrangement and containing many mitoses and whorls of keratinized cells. This tissue is microscopically a typical epidermoid carcinoma, and there is invasion of the corium by slender processes of cells on all sides.

The skin on each side of the carcinoma shows the same changes that have been described in the preceding cases, *i.e.*, rarefication of the corium beneath the epidermis, atypical downgrowths of epidermis, vascular changes and hyaline change of the collagenous fibrils in the deep layers of the corium.

Tissue from the chest. This consists of a semi-circular piece of tissue the convex border of which is covered by epidermis, and measures fourteen millimeters long. On each side of the center of the epidermis is an area of new growth very similar to that from the ulcer of the hand. These areas are three to four millimeters long and consist of a vascular new growth of epithelium with whorls of keratinized cells and many mitoses. There is no definite covering of epidermis and the surface is covered with a few small patches of horny epithelium and fibrin. The corium surrounding these two areas is infiltrated in every direction. The whole picture is typical of epidermoid carcinoma. The epidermis between these two areas and outside of them is thick with large processes. The corium and vessels show the same changes that have been described above. In

addition to the two areas of carcinoma there is one small area of marked downgrowth of the epidermis, the processes of which are surrounded by masses of lymphoid and plasma cells (Fig. 15). From one of these processes there is a large mass of cells, containing many mitoses, extending into the corium (Fig. 20). Smaller masses project from two adjacent epidermal processes. All are surrounded by densely packed zones of lymphoid and plasma cells. It is evident that the process here is the beginning of a growth similar to the larger ones in the same piece of tissue. A series of twenty-seven sections through this region excluded the possibility of this appearance being due to a tangential section of a larger growth.

CASE VI. (W. W. G., Case III., Dr. Porter). — Male; 41 years. Began work with the X-rays in 1897. In 1900 he suffered from X-ray dermatitis on the dorsum of the right hand, which after healing left the skin dry and reddened. In 1901 the nail of the index finger was removed because of severe pain. In 1903 the characteristic telangiectases and keratoses developed. Persistent painful ulceration necessitated the amputation of several fingers and numerous areas of skin between the years 1903 and 1908. In August, 1908, the small lesion was excised from which the following description is taken.

The material consisted of a circular piece of skin eight millimeters in diameter. The center is covered with a thick layer of horny epidermis, forming an elevated area five millimeters in diameter.

Microscopic examination. The corium shows marked hyaline change of the collagenous fibrils and a great increase in elastic fibers. There are few connective tissue cells to be found except immediately beneath the epidermis where the corium is less dense in structure and where there are minute foci of necrosis and infiltration. Small arteries show thickening of the intima due to a layer of dense collagenous material between the media and endothelium. There are

a few normal coil glands but many showing atrophy. The very few hair bulbs and shafts which are in the sections are normal.

The corium immediately beneath the epidermis shows traces only of the papillæ in the form of very slight slender elevations extending into the epidermis. These papillæ contain each a single large capillary with prominent endothelium. The epidermis is thick and forms an even layer except where interrupted by the small papillæ. In many places, however, there are large capillaries running high up into the epidermis, surrounded by a thin zone of refractive hyaline collagenous material. The thickness of the epidermis is chiefly due to increase in the prickle cell layer. The stratum lucidum is of increased thickness. The granular layer is not demonstrable. The horny layer is very thick and consists of a fused mass of incompletely keratinized cells in which the nuclei are large and easily visible (acanthosis). In places where the corium contains areas of fragmented collagenous material and masses of lymphoid and plasma cells, there are shallow downgrowths of the epidermis. The cells of these downgrowths extend laterally between bundles of hyaline collagenous material.

In addition to the above cases, sections prepared at the Massachusetts General Hospital of a case reported by Dr. C. A. Porter (Annals of Surgery, November, 1907) have been studied (Case XIX., Dr. Porter's paper, this issue). The sections were described for the above report by Dr. C. J. White, who paid particular attention to changes in the epidermis.

The series of sections include thirty lesions removed in eight or nine different operations.

All of the changes described in detail from the tissues of the six cases reported above have been found in the tissues from this one individual. This man, according to Dr. Porter and corroborated by the sections, had ten different epidermoid carcinomata removed in five years.

This case, therefore, furnishes strong evidence that the

changes described in the epidermis are progressive and develop into carcinomata.

SUMMARY OF THE HISTOLOGICAL CHANGES.

The changes that have been found in the cases described can be summarized best under separate headings as follows: connective tissue, smooth muscle, blood vessels, and epidermis with its appendages

1. *Changes in the connective tissue of the corium and subcutaneous tissue.* — The most conspicuous of the constant changes in the corium are the rarefication immediately beneath the epidermis and the great density of the connective tissue deeper down (Figs. 1 to 6). The loose textured connective tissue immediately below the epidermis is best interpreted as imperfect repair of degenerated connective tissue due at first to the direct action of the X-rays. The imperfect repair and subsequent degenerations are due most probably to the vascular lesions. The presence of degenerated hyaline collagenous material throughout the depth of the corium must be a direct effect of the rays. That this modified collagenous material represents inert or dead tissue, if such a term may be used in speaking of intercellular substance, is proved not only by the physical appearance and staining reactions, but also by the presence of young connective tissue cells surrounded by normal appearing collagenous fibrils between the masses of this dense collagenous material (Figs. 10 and 11). Further proof is furnished by the finding of isolated masses of similar material, identical in appearance and staining, in the granulation tissue below the ulcerations. This diffuse aseptic necrosis of connective tissue and resulting diffuse proliferation of connective tissue cells is probably directly responsible for the obliteration of blood and lymph vessels. Repeated exposures to the X-rays is in this way accountable for the production of successive deposits of collagenous material, and this is the only satisfactory explanation of the great density of the deep corium. Areas of fibrin in tissues many months after the last exposure to the rays prove that the lesions are slowly progressive. The

marked increase of elastic tissue almost constantly found is difficult to account for. That a new formation occurs, may be proved by the association of delicate elastic fibers with new connective tissue cells. Coarse fibrils present may represent remains from successive crops of connective tissue which have undergone degeneration. The presence of many degenerated fibers suggests this explanation. The question needs more elaborate study for its solution than the scope of this paper will permit.

Many of the connective tissue cells in the rarefied corium are of extraordinary size with large processed nuclei (Fig. 7). Many have numerous small nuclei each containing a particle of chromatin. These cells may be distinguished from endothelial cells by the presence of fibroglia fibrils. Apparently they do not form collagenous material. With the methylene blue and eosin stain the protoplasm stains a deep blue. A few are vacuolated. Similar large cells are found in the fat lobules of the subcutaneous tissue, where the fat is undergoing resorption. The interpretation is that these cells are the result of proliferation under conditions of poor nutrition. As they are found only where there is multiplication of connective tissue cells, they must represent imperfect growth and differentiation.

2. *Changes in the smooth muscle.* — The large size of the arrector pili muscle and the thickness of the nuclei of arteries has led some authors (Unna and Wyss) to speak of the condition as one of smooth muscle hypertrophy. In the present study degenerative changes were always present and the large size of the smooth muscle cells is due to vacuolization (noted by numerous authors) and distension of the cell with hyaline material, the latter easily demonstrable by the phosphotungstic acid hematein stain. In cases of long duration only atrophic remains of the arrector pili muscles were found, showing that the changes noted are unquestionably degenerative. This degeneration of smooth muscle will be considered again in connection with vessel changes.

3. *Changes in the vessels.* — The study of lymphatics in skin, which is the seat of chronic changes, presents

extraordinary difficulties when attempted by the methods employed in this study. The unquestionable obliteration of blood capillaries and the extreme difficulty of demonstrating lymphatics in the tissues studied makes the assumption warrantable that there also has been obliteration of lymphatics.

The changes in blood vessels on the other hand are easily demonstrable. The telangiectases apparently develop from preëxisting capillaries, those of the papillæ of the corium (Figs. 2, 3, 4, and 5). Various stages of dilatation of these capillaries can be seen in connection with other changes, in lesions of varying intensities from different cases. The mechanism of their formation cannot be discovered through histological examination, though obliterative changes in the larger vessels and in the deeper anastomosing capillaries must play a part. Another factor to be taken into consideration is possible traction upon the capillary walls exerted by contracting connective tissue. New collagenous material is frequently laid down between the meshes of older degenerated fibrous tissue and undoubtedly must undergo some contraction before the dense stage is reached. Thrombosis of these telangiectases is common and is usually associated with necrosis of the tissue immediately surrounding as well as of the lining endothelium. Obliteration of capillaries by proliferation of endothelium is a fairly constant finding in most of the cases studied.

The obliterative changes in the veins and arteries are manifested chiefly in a great increase of connective tissue beneath the endothelium and in marked thickening of the media. In the arteries there is disappearance of the elastic lamina and a substitution of a thick, irregular band of hyaline collagenous material. The thickened intima is composed of connective tissue with much collagenous intercellular substance. The endothelium is often composed of swollen and vacuolated cells which occasionally form tufts of cells projecting into the lumen.

The thickening of the media is due to an increase of connective tissue. By means of the stains employed it is possible to demonstrate large fibroblasts and abundant collagenous

material between the smooth muscle cells. The latter show varying degrees of atrophy and degeneration — hyaline change and vacuolization (Figs. 17, 21, and 22).

The finding of mitotic connective tissue cells in one case (No. III.) four years after the last exposure illustrates the extreme slowness of this process, as well as its progressive character. In advanced cases of obliterative endarteritis the media is wholly replaced by connective tissue with many large branching fibroblasts. In all of the cases studied obliterative changes have been found in some of the vessels, though normal vessels are usually also present.

4. *Changes in the epidermis.* — Except over foci of acute degeneration of the corium, hypertrophy of the epidermis is a constant finding. The hypertrophy in most cases is in the form of a fairly uniform thickening of the epidermis. In other cases there are local more marked hypertrophies taking the form of keratoses and downgrowths (Figs. 13, 14, 15, 16, and 17). In nearly every case there are numerous areas where the proliferation of epidermis seems unquestionably to be due to disappearance of connective tissue in the corium which has not the power to repair itself (Figs. 12, 4, and 5). The downgrowth of epidermis is analogous to the growth of the corneal epithelium following an incised wound of the cornea, or even gaping wounds of the cornea such as may be made by plowing beneath the corneal epithelium with a sharp triangular-shaped needle (Glover's needle).

Extensive downgrowths of epidermis are found, in several cases, having all of the characteristics of carcinoma with and without evidence of invasion. The cases showing metastatic growths have not been included in this report. Growth of epidermis into thrombosed telangiectases is unusual and must be interpreted as indicative of increased powers of growth (Figs. 8 and 9). Generally the epithelial downgrowths are surrounded by zones of dense infiltration with lymphoid and plasma cells, eosinophiles and polymorphonuclear leucocytes. The epidermis where there is evidence of greatest proliferation of the basal layers has a thin horny layer, as if the

whole capacity of the epithelium was taxed to preserve its continuity (Fig. 2).

In general the increased thickness of the epidermis and the production of wart-like growths or keratoses and downgrowths is best explained as the result of constant active proliferation called for by the constant production of small defects in the underlying corium. In Case V. the ulcer from the hand shows undoubted signs of malignancy.

Complete absence of hair follicles, sebaceous and coil glands is the rule in cases of long duration. In less marked cases atrophic glandular structures were found. In no case was there evidence of proliferation of any of the skin appendages. Coil glands were often found in regions where there was total absence of hair follicles and sebaceous glands.

In the description of cases minute cell changes have been omitted. The finding in the epidermis of cells with extraordinarily large nuclei with evidences of direct division into several smaller nuclei was of frequent occurrence. Such cells are most often in small downgrowths or in compact masses of cells inserted in the basal layers. This change and others such as irregularity in size, greater affinity for basic stains and confused arrangement of prickle fibrils have been regarded as concomitant with proliferative and degenerative changes. Possibly the finding of such changes in downgrowths and isolated masses of cells has a slight value as evidence of altered function and increased proliferative power.

Discussion. — All of the cases of this series present only late effects of single or repeated X-ray exposures; and it is therefore beyond the scope of this paper to give a complete account of the effects of X-rays upon human skin. The chronic changes described were necessarily preceded by acute changes, which were the immediate result of the X-ray exposures. No complete investigation of the acute changes has as yet been made. As many of the changes described in this paper have been previously described, a short review of the most important papers is included.

Gassmann (Archiv. f. Dermat. u. Syphilis, 1904, Heft I.) described the vessel changes produced in rabbits. He exposed rabbits until ulcers of one month's duration had been produced and found the following changes in the arteries: The muscularis showed a sieve-like meshwork due to vacuolization. The intima was thickened and broken up, the elastica was fragmented and the endothelium was thickened and in places heaped up two or three cells deep. He claims to have demonstrated obliteration of lymphatics through excessive proliferation of endothelium.

Linser (Fortschritte auf dem Gebiete der Röntgenstrahlen No. 8, 1904–5) excised human skin at varying intervals while the patient was receiving treatment for lupus. At the end of four days there were vessels occluded by thrombi. The endothelium was absent in places and in other places swollen and projecting into the lumen. The media was "broken up" and "fissured." There was slight perivascular infiltration with "round cells." At eight days thrombosed vessels were most numerous and the perivascular infiltration was most marked. At sixteen days there was beginning thickening of the intima. The breaking up of the media and invasion by leucocytes was at its maximum. At twenty days there was marked thickening of the intima due to pure connective tissue without elastic fibers. Many vessels were completely obliterated. At the end of thirty days the "inflammatory changes" were absent. The arteries showed typical thickening of the intima with newly formed elastic fibers, giving to the vessels a shrunken, irregular form with polyp-like projections into the lumen. Linser concludes that the epithelium is not primarily affected even after severe exposure. The only changes that he found was an increase of pigment in the Malpighian layer. The hairs and glands remained normal.

Unna (Fortschritte auf dem Gebiete der Röntgenstrahlen No. 8, 1904–5) reported a study of four cases of chronic X-ray dermatitis. He emphasized the latent period, which varied from a few months to two or three years, and in view of the experimental work already done upon animals stated

that the etiology of the lesions was unquestionable. The origin of the telangiectasis is discussed at length. Unna says that a deep obliterating endophlebitis would explain the production of the telangiectasis, but that this has not been proved. The arterial obliteration does not explain it. Unna agrees with Baer and Linser (Münch. Med. Wochenschr. No. 23, 1904) in believing that the blood transforms the X-rays into a form of energy that is injurious to the vessel walls. This he says is supported by the fact that tissues rich in blood as granulation tissue, either exposed or covered by epithelium, is more affected by the X-rays than is normal tissue.

The microscopic appearance of the tissues is given in great detail. Great stress is laid upon the density of the connective tissue of the cutis, which is attributed to degenerative changes following edema. In one case he describes atypical growth of epithelium at the edge of an ulcer, which he believed to be a beginning carcinoma. He did not find changes in the larger vessels of the deep cutis and hypoderm. As a possible cause of the telangiectasis he suggests tension of the smooth muscle bundles called into play by the general atrophy of connective tissue and by the disappearance of intercellular substance between the muscle cells. The keratoses are manifestations of the atrophy of the epidermis, analogous to those occurring in senile changes, sailor's carcinoma, and xeroderma pigmentosum. In retrospection he says that the effects of the X-rays are not limited to the vessels, but affect all parts of the skin, and that there is no indication of an especial susceptibility of the epidermis. The epidermis becomes markedly cornified, in part hypertrophic and predisposed to cancer, in part atrophic. The appendages atrophy, first of all the hair follicles and sebaceous glands. In the cutis there is a marked chronic interstitial edema which loosens and rarefies the collagen and leads to atrophy of the elastic fibers. The smooth muscle alone becomes thickened. Unna emphasizes the difficulty of obtaining good sections because of the great density of the cutis.

Schümann's (Archiv. f. Klin. Chirurg. Berlin, 1907,

LXXXIV., Heft 3) description of cases differs from that of Unna's only in the statement that there was proliferation of the sweat glands producing tortuous solid chains of cells. He states that the chronic X-ray dermatitis predisposes to carcinoma and points out similarities between it and other conditions followed by carcinoma such as xeroderma pigmentosum, senile changes, and Unna's carcinoma of sailors.

Wyss (Beiträge z. klin. Chir. Tübingen, 1906, XLIV.) argues for the connection between vessel changes and the origin of carcinoma and says that he is the first to insist upon this point. Following Ribbert's ideas that connective tissue changes precede carcinoma of the skin, and bring about isolation of epithelial cells, he comes to the following conclusions: That the carcinoma cell is one isolated from the rest of the body through the gradual withdrawal of nutrition owing to successive obliteration of vessels; that the cells thus gradually acquire greater capacity for securing nutrition and finally become capable of living at the expense of other cells. He claims that similar vascular changes precede many kinds of carcinomata associated with peculiar practises or occupations.

In a subsequent paper upon the origin of carcinoma (Deutsch. Archiv. f. Chirurgie, Leipzig, XCIII., Heft 6), Wyss offers the evidence furnished by the X-ray carcinomata and the results of a study of fifty early carcinomata in support of Ribbert's theories. In all cases he insists that vascular changes are primary.

Lindenhorn (Beiträge zur klin. Chir. Tübingen, LIX., Heft 2) has collected twenty-nine cases of X-ray tumors, most of them carcinoma and very malignant. The two cases which he adds were in lupus patients treated with the X-rays. The vessel changes described by him were limited to the media. In general he corroborates the work of Wyss and others, but states that the condition is essentially that of premature senescence.

Porter and White (Annals of Surgery, November, 1907) contribute the only important paper on the subject from this country. The histological changes are described without

attempt at a summary. Particular attention is paid to the fine changes in the epidermis. Obliterative changes of large veins and arteries are noted as well as obliteration of capillaries by proliferation of the endothelium. Very excellent objective descriptions are given of the keratoses and epithelial hypertrophies and of the telangiectases. Several typical epidermoid carcinomata are described as such, in the case presented by Porter.

GENERAL SUMMARY.

The value of this study of cases here reported is largely dependent upon the wide range of time represented after receipt of the injuries and in the varying amounts of exposure to the X-rays received in the different cases. A sequence of changes can be seen which previous studies have not brought out. The immediate effects of the X-rays, of course, are not included, but the early changes can be inferred from the nature of the chronic changes and the possibilities agree with the results obtained by Linser upon human skin and by others upon animals.

The most important fact brought out in the present study is that after sufficient injury has been done complete repair does not take place. There are in every case active processes going on, and when we consider that some of the cases had received the last exposure two to four years before excision, this fact becomes of great importance. Not only are degenerative and reparative changes constantly taking place in the corium, but the occurrence of progressive vascular lesions is proved by the findings in the media of arteries of young fibroblasts and, in one instance, mitosis of connective tissue cells.

All the changes primarily produced by the X-rays are probably degenerative in character. Normal repair is impossible after a certain amount of injury has been done because of the vascular changes. Thus there is constant degeneration of the tissue in foci and constant efforts at repair. The non-vascular rarefied corium beneath the

epidermis is an example of imperfect repair. The finding of necrotic foci here and deeper in the corium, many months and even years after the last X-ray exposure, is conclusive proof of the vascular origin of the degenerations. If the focus of degeneration is small, ulceration does not occur. The continuity of the epidermis is preserved through downward proliferation, and thus a deeper stratum of connective tissue is reached better able to maintain nutrition. That proliferative changes in the epidermis are constantly going on in these cases is proved by the character of the cells of the basal layers and the presence of many mitoses. In many instances the growth into such foci of degeneration has been observed, and even into thrombosed telangiectases. Other evidences of impaired nutrition of the skin are the atrophy of the glands and the absorption of fat tissue and replacement by connective tissue.

The large size of the arrector pili muscles is not due to hypertrophy, but to swelling of the cell and fusion of the myoglia fibrils. In cases of greatest duration these muscles are entirely replaced by connective tissue. The same degenerative changes in the smooth muscle of the media of vessels account for the vacuolization and later the replacement of muscle tissue by connective tissue.

The obliteration of small vessels and capillaries probably takes place slowly and continuously owing to the swelling of collagenous material and proliferation of connective tissue. Endothelial proliferation is possibly a primary cause of capillary obliteration. It would also occur in capillaries occluded from other causes. Excessive infiltration of the corium by lymphoid and plasma cells undoubtedly, as Wyss suggests, helps to interfere with nutrition of epithelium by pressure upon capillaries.

Epithelial proliferation is a constant finding over foci of degeneration in the corium. Ulceration occurs only if the degenerated area is too large to be bridged over by the epidermis. It is probable that long continued proliferative processes are responsible for the hypertrophy of the epidermis. Downgrowth of epidermis takes place to fill small

gaps in the corium. This property of downgrowth to fill gaps in the epidermis as well as the growth of epidermis into thrombosed telangiectases must be taken as evidence of increased vitality of the epidermis. Some downgrowths, of a size discoverable only with the microscope, show all of the characteristics of epidermoid carcinoma including the presence of whorls of cornified cells and evidence of invasion between bundles of connective tissue. There are larger epithelial downgrowths which are apparently limited in their growth. The depth seems to be determined by the reaching of viable connective tissue. In the same case all degrees of epithelial hypertrophies, downgrowths, and keratoses may occur, and also growths which are histologically carcinoma and which grow slowly and invade normal tissues. Although this series does not include cases in which metastases have occurred, such cases are too well known to admit of any doubt as to the malignancy of the slowly growing invasive tumors such as are described in Case V.

The evolution of X-ray carcinoma from the smaller lesions, scaly patches, and keratoses has been constantly observed in the clinical study of reported cases so that there can be no doubt that the smaller epithelial growths described in this paper are the starting points of the malignant growths and especially is this true in those cases where similar lesions had already developed into ulcerations which microscopically were unquestionable carcinomata. This evidence is of course wholly clinical, but the observers of these cases have been for the greater part prominent physicians who often were caring for their colleagues. Because the subjects of these experimental carcinomata have been men instead of animals and the observers not laboratory workers does not invalidate the evidence. And this evidence is overwhelming that the carcinomata are produced by changes following severe X-ray exposures. As Wyss has already insisted, the X-ray carcinoma is the first experimental carcinoma.

What then gives rise to the carcinoma? Is it the direct action of the X-rays upon the epithelium or is it the result

of changes produced in the deeper tissues? All the evidence advanced by Unna and by Wyss and that found in the present study of cases proves that the epidermis is the least susceptible of the tissues of the skin to direct injury by the X-rays. Even if this were not the case the long "latent" period elapsing between the last exposure to the rays and the appearance of proliferative changes in the skin could not be accounted for except by assuming that the repeated action of the rays excites proliferative powers which remain dormant for months to years. But we do know that during this "latent" period the epidermis is subject to changed conditions involving marked alterations in the character of the connective tissue supporting it and presumable marked changes in the nutrition of the cells. And also that constant proliferative changes are necessitated on the part of the epidermis in order to preserve its integrity. We must then conclude that the factors responsible for the acquisition of great powers to proliferate and eventually the properties of malignancy, are those furnished by the changes in blood supply and in the connective tissue. This theory is supported very completely by the microscopic appearances, especially in those instances where we find evidence of active proliferation of epidermis but incomplete or no differentiation into horny epithelium. The finding of growth of epidermis into fibrin thrombi and into areas of dense bloodless collagenous material seems to be evidence of increased powers of proliferation. Such reasoning as the above, based as it is upon microscopical findings and upon observed gross changes in the living, leads to the conclusion that a slow augmentation of the growth power is achieved (attended with a loss of differentiation) that finally results in the ability of the epithelial cells to derive their sustenance at the expense of other living tissues. The fact that the "virulence" or growth power of mouse tumors may be increased by successive transplantations helps to make the idea acceptable that a similar change may occur in normal human epithelium. There must be conditions however which call for, as does the chronic X-ray dermatitis, a continuous series of

proliferative processes, which in a sense are auto-inoculations extending over years.

That connective tissue changes precede and lead to the development of malignant epithelial growths is essentially the theory of Ribbert as propounded in his second Beiträge zur Enstehung der Geschwülste. It is essentially the conclusion reached by Goebel (Zeitschr. f. Krebsforschung, Bd. III., Heft 3) in his study of bladder tumors associated with Bitharzia disease. It is the conclusion reached by Wyss in his study of X-ray carcinoma and of early carcinoma in general. But none of these observers has described the mechanism leading to the repeated proliferation of the epidermis. Neither have they furnished microscopic evidence of the various histological changes assumed to take place, and the idea conveyed is that the acquisition of malignant power takes place suddenly.

The acquisition of malignant powers is completed during years of active proliferation accompanied by progressive impairment of nutrition. This much we have microscopic evidence for, and the hypothesis that the former is a direct sequence of the latter seems justifiable.

Finally it is not far removed from von Hansenmann's hypothesis of tumor origin, that of anaplasia wherein the power of growth is attributed to reversion to the stage of proliferative function at the expense of that of differentiation. The only difference between this and the theory suggested above is, that in the latter this power is assumed to be acquired through changed environment.

The apparent demonstration of the origin of the multiple carcinomata of chronic X-ray dermatitis in primary connective tissue changes and the attending disturbances of physical and nutritive conditions does not speak for the acceptance of the old ideas of trauma and irritation as causes for the origin of carcinoma. In the case of X-ray carcinoma we are dealing with injuries incapable of complete repair and therefore progressive in character.

Other peculiar forms of injury associated with carcinoma, such as those occurring in aniline workers and workers in the

various products of combustion and distillation of coal, those associated with certain diseases, as syphilis (leukoplakia) and lupus, the Kangri carcinoma of the natives of Kashimir and "horn core" cancer of cattle in India, deserve the most careful study to see if the antecedent processes are similar to those in X-ray cases. There is an apparent analogy in the instances of cancer associated with lupus and syphilis in that in these diseases there are continuous connective tissue changes taking place for years.

Considering the present great activity in cancer research it seems strange that more attention has not been given to this field of work and it is the earnest hope of the writer that this paper may stimulate investigation and experimental work along these lines.

[The writer is greatly indebted to Professor Councilman for the privilege of using the photomicrographic apparatus of the Pathological Department of the Harvard Medical School, where these photographs were made.]

DESCRIPTION OF PLATES.

PLATE XXXIX.

FIG. 1. — Case V. Second operation. Skin from chest showing a recent focus of degeneration in the corium beneath the epidermis. Epidermis remains intact.

FIG. 2. — From Case IV. shows rarefication of the corium immediately beneath the epidermis. The lower strata of cells in the epidermis are large and are stained deeply with the basic stain. The horny layer is imperfect. Rapid multiplication of the epidermis is evidenced by the finding of many mitoses. The large capillaries are probably the precursors of telangiectases.

FIG. 3. — Higher power of Fig. 2 showing the character of the basal layers of epidermal cells and the structure of the corium.

FIGS 4 and 5. — From Case IV. These photographs show many large telangiectases and extreme rarefication of the corium beneath the epidermis. Fibrinous thrombi are forming in several of the telangiectasis. The downgrowth of epidermis in the rarefied corium is well shown. This condition is always accompanied by endarteritis and endophlebitis.

PLATE XL.

FIG. 6. — From Case IV. High power showing structure of rarefied corium and a connective tissue cell in mitosis.

FIG. 7. — From Case IV. Connective tissue cell from rarefied corium. Atypical cells of this type and cells in mitoses are abundant in the corium

beneath the epidermis and furnish evidence of the continuous change which is reparative in nature and secondary to obliteration of vessels.

FIG. 8. — Case IV. Low power photograph of epidermis growing into thrombosed telangiectases.

FIG. 9. — High power detail of Fig. 8.

FIG. 10. — Case I. shows hyaline change of collagenous material with absence of connective tissue cells.

FIG. 11. — Case I. Hyaline degenerated collagenous material in the neighborhood of vessels showing invasion by connective tissue cells and deposit of new collagenous material between the masses of the old.

PLATE XLI.

FIG. 12. — From Case IV. High power photograph of epidermis growing into rarefied corium. At this point the corium is represented by a delicate homogeneous material without cells. The epidermis dips down at this point. The large size and deep staining of the cells is shown. There is a single mitosis.

FIG. 13. — Case IV. High power view of epidermal processes extending into rarefied corium. The process on the left shows a whorl of keratinized cells. At the tip of the process there is marked lymphoid and plasma cell infiltration and the epithelial cells are large and irregular with many mitoses.

FIG. 14. — Case IV. Epidermal process extending into rarefied corium. Evidence of independent growth shown by the arrangement of cells and production of epithelial whorls. In the bar connecting the two larger masses is a nest of cells with atypical arrangement suggesting independent growth.

FIG. 15. — Case V. From chest. Epidermal process extending into corium and having the characteristics of the larger growths which were frankly malignant in character.

FIG. 16. — Case V. Keratosis from back of hand showing activity of cells at the base, but also the presence of the different layers of the epidermis with dense horny layer.

FIG. 17. — Case V. Keratosis from tip of nose showing absence of differentiation. The whole thickness of the epidermal process is composed of large cells of a uniform type. There are many mitoses.

PLATE XLII.

FIG. 18. — Case III. Obliterated artery from the deep corium showing separation of muscle cells by connective tissue. The lumen is filled by connective tissue.

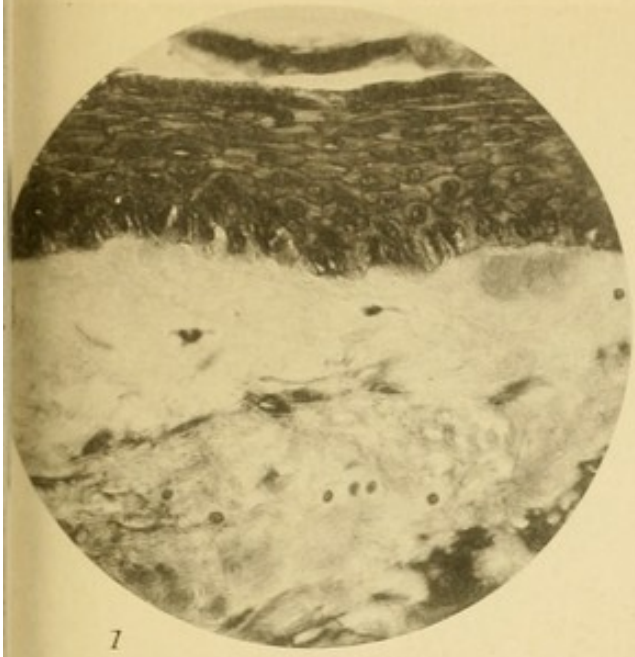
FIG. 19. — High power view of Fig. 16.

FIG. 20. — High power detail from Fig. 15 showing invasion of epidermis into the corium.

FIG. 21. — Low power photograph of an obliterated artery from Case III.

FIG. 22. — Obliterated artery from Case V. At this stage the muscle fibers have disappeared and there is marked infiltration.

FIG. 23. — High power detail of Fig. 17 showing large number of mitoses.



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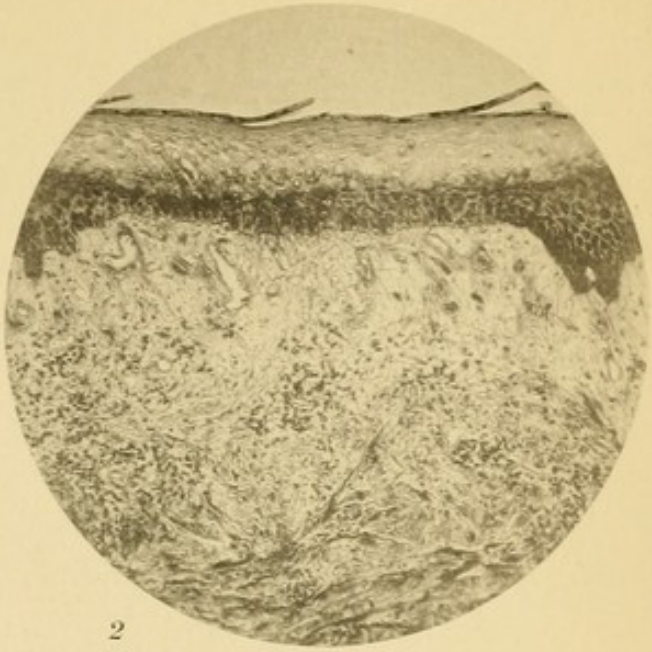

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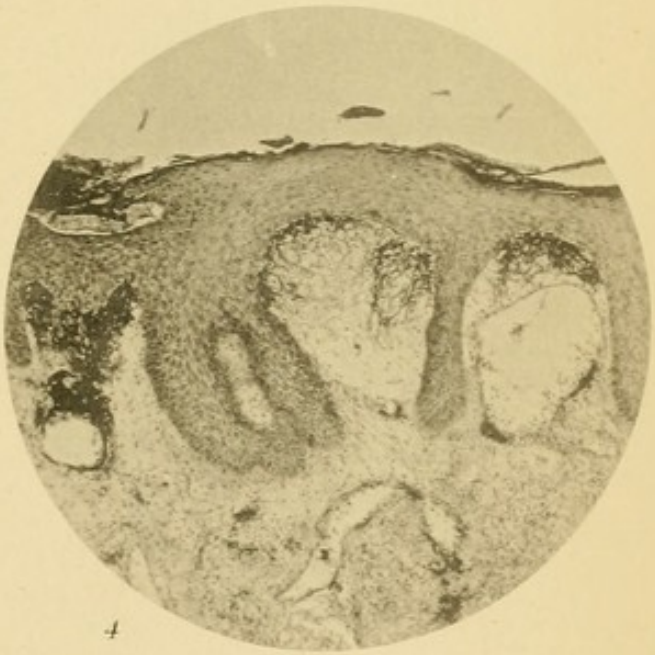

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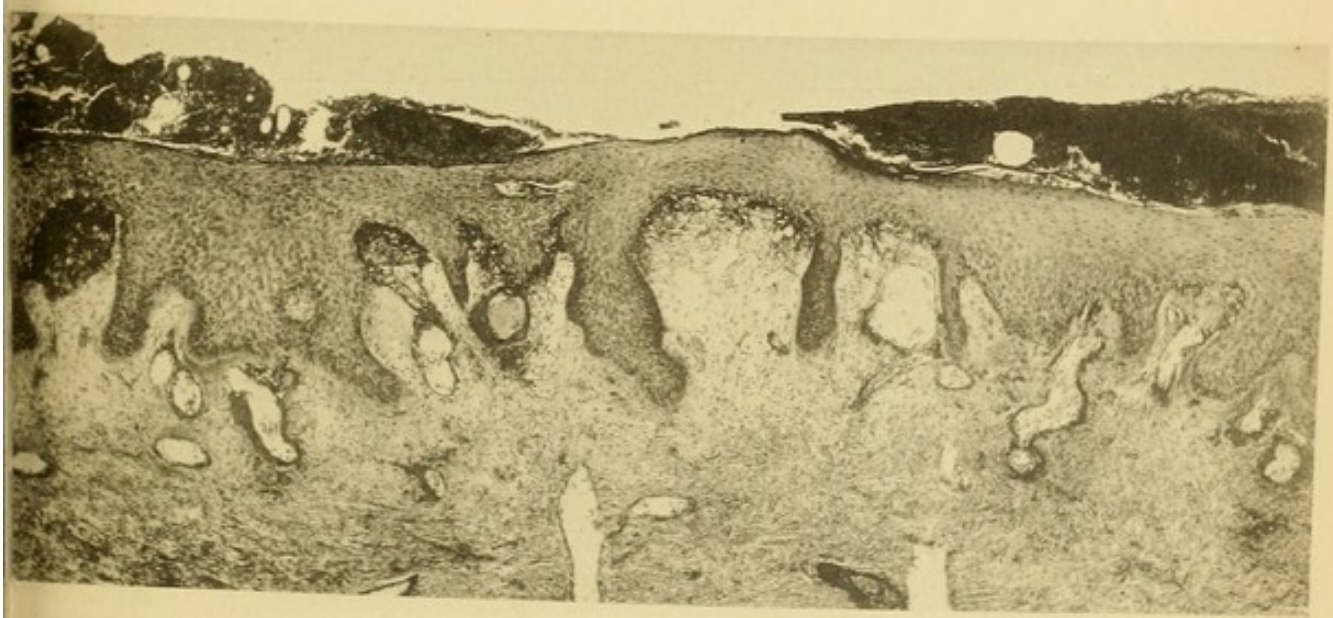

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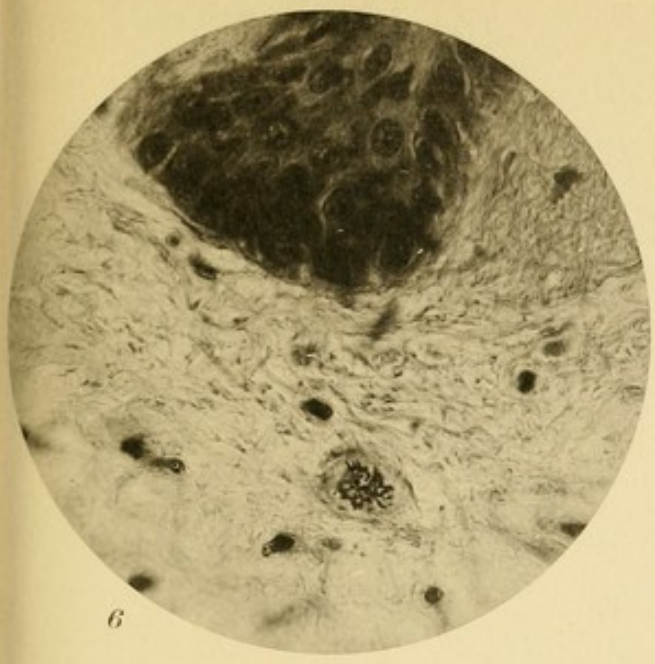
Wolbach.

Chronic X ray dermatitis.



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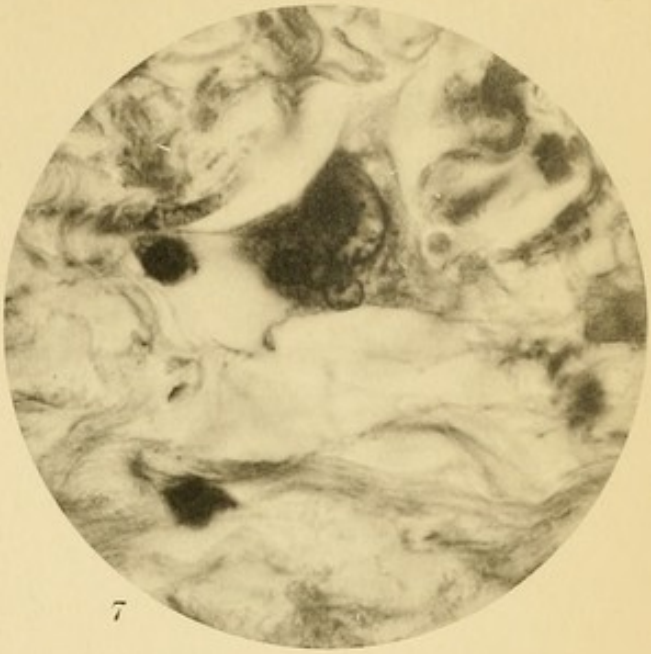

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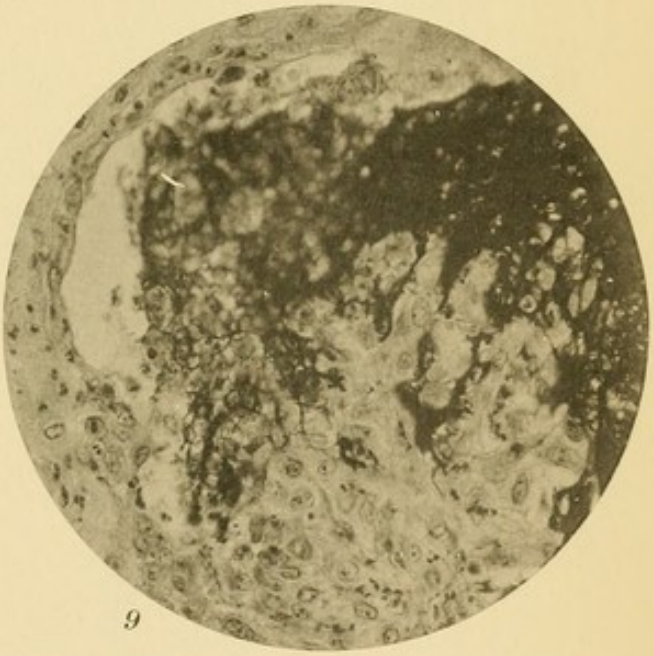

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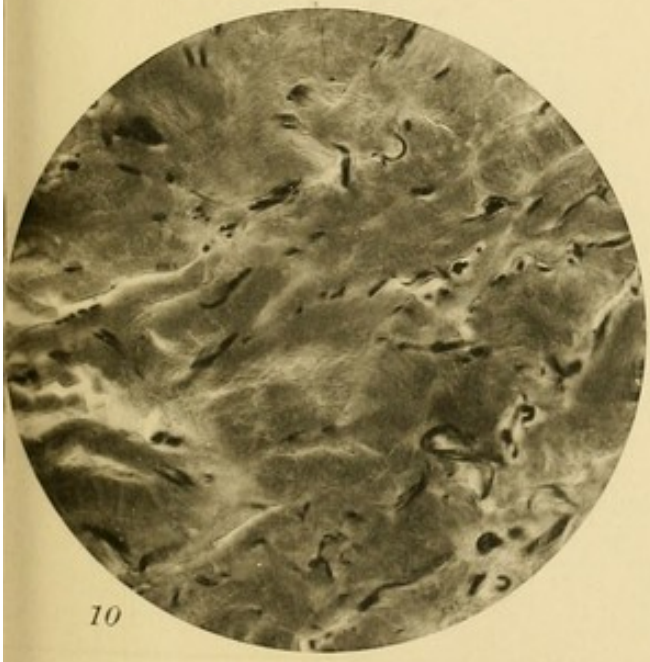

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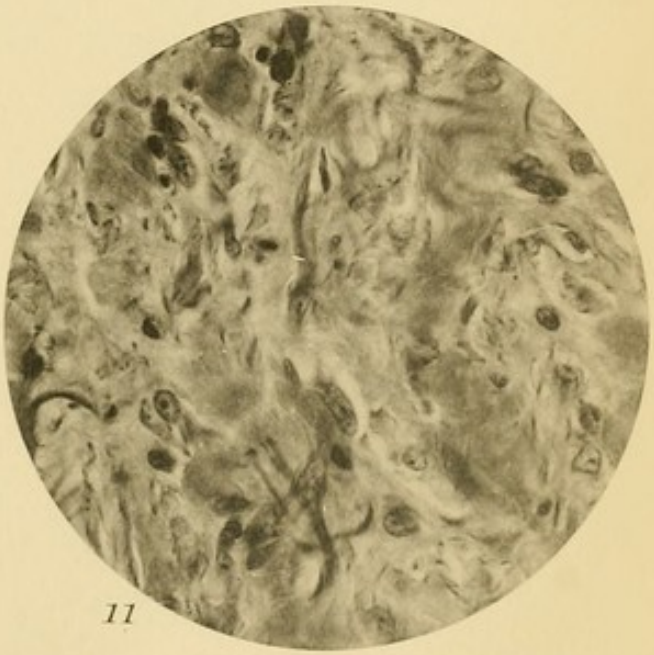

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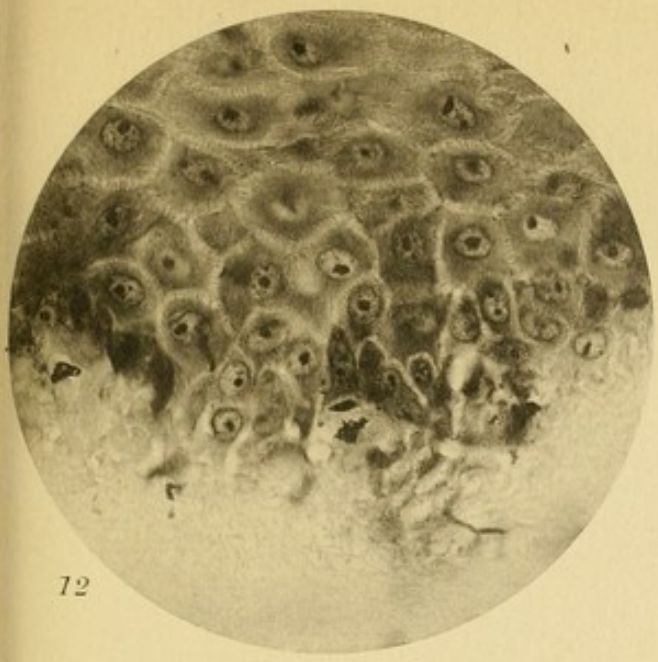

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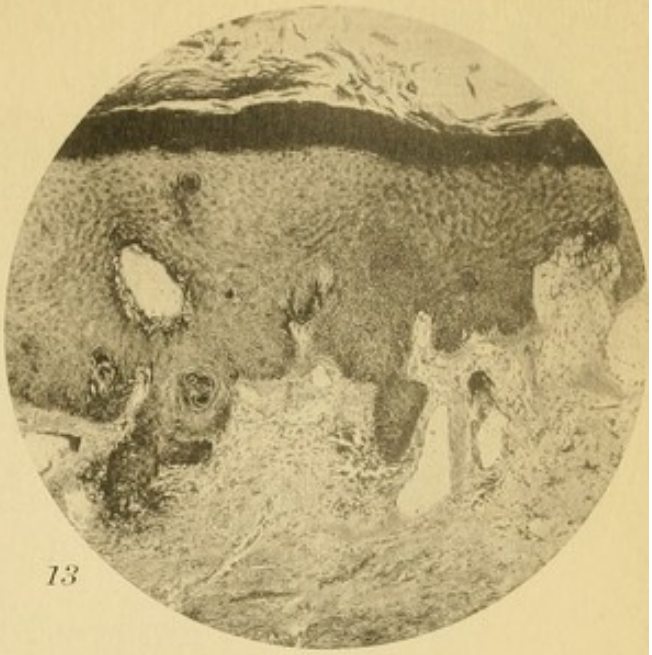

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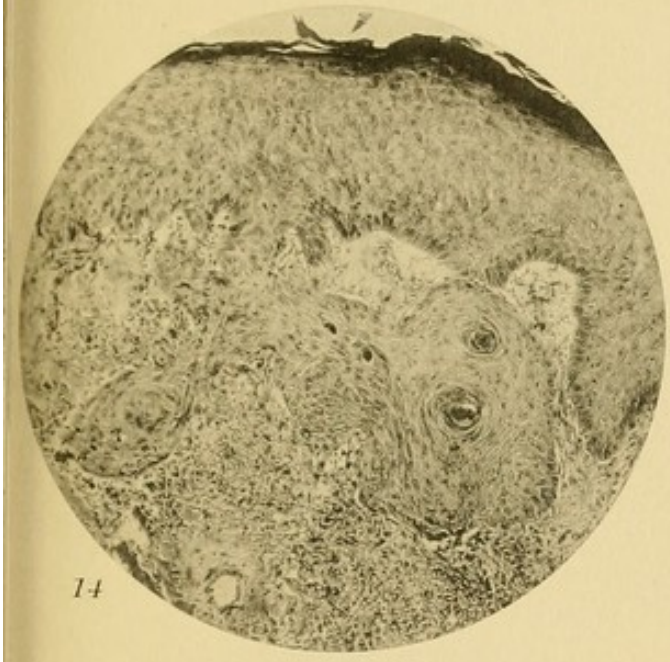

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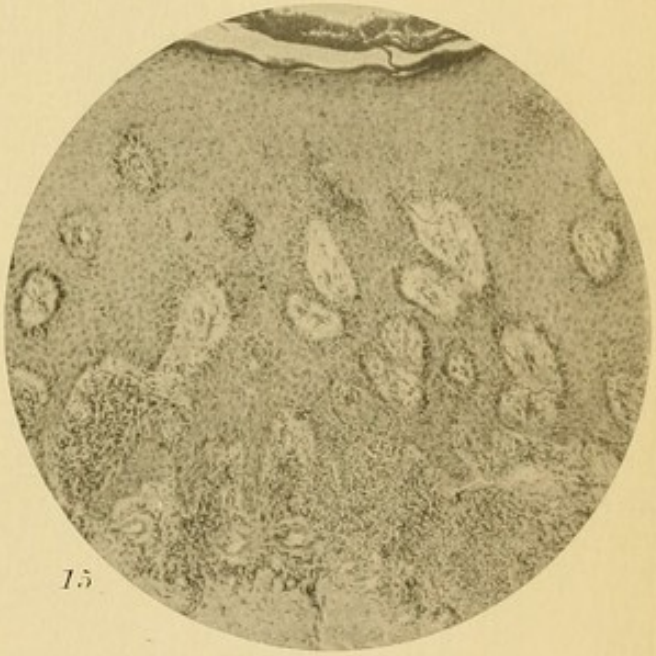

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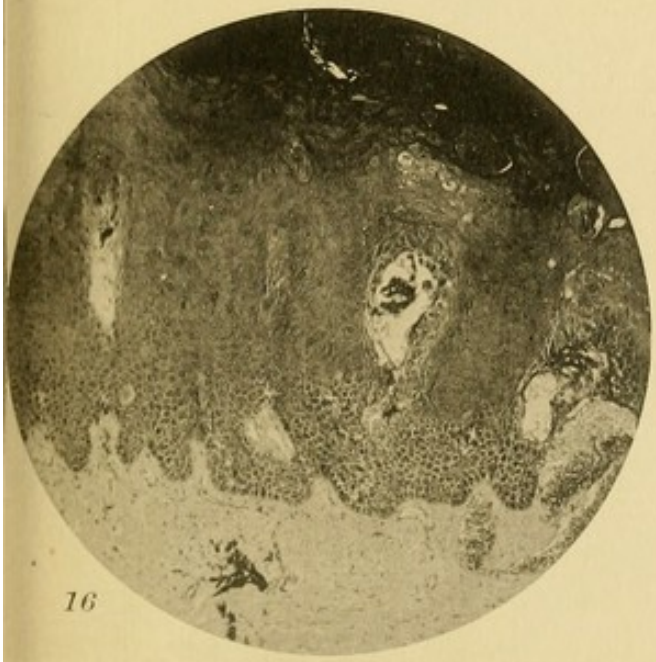

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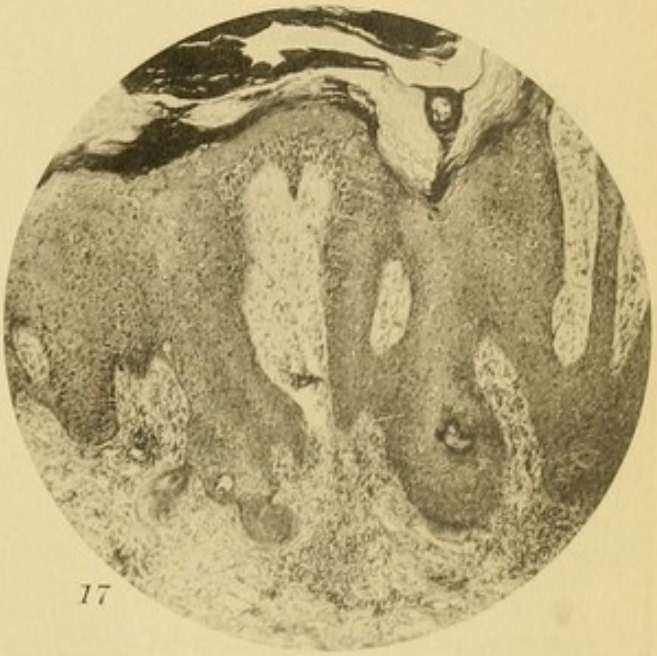

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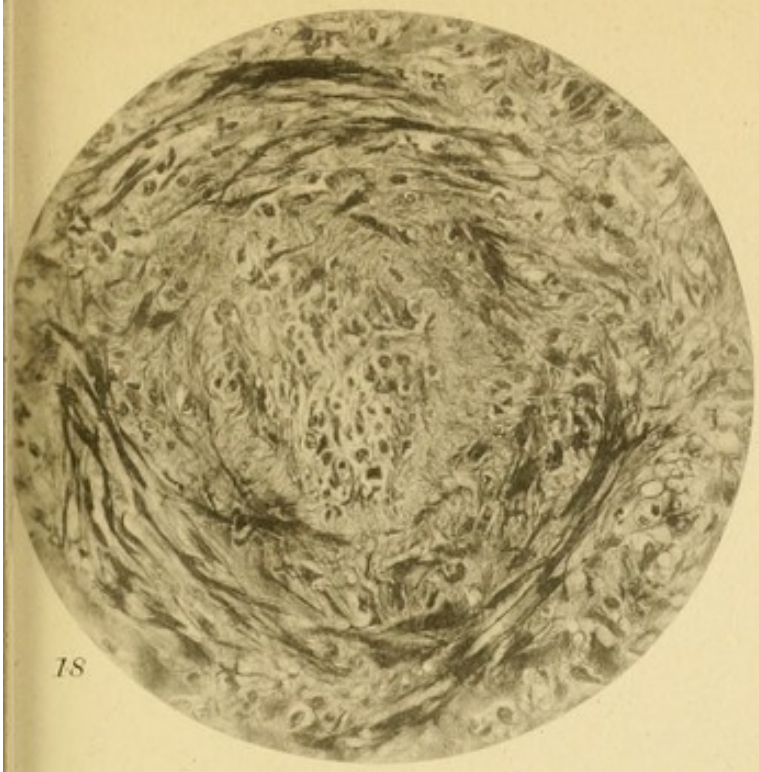
Wolbach.

Chronic X ray dermatitis.



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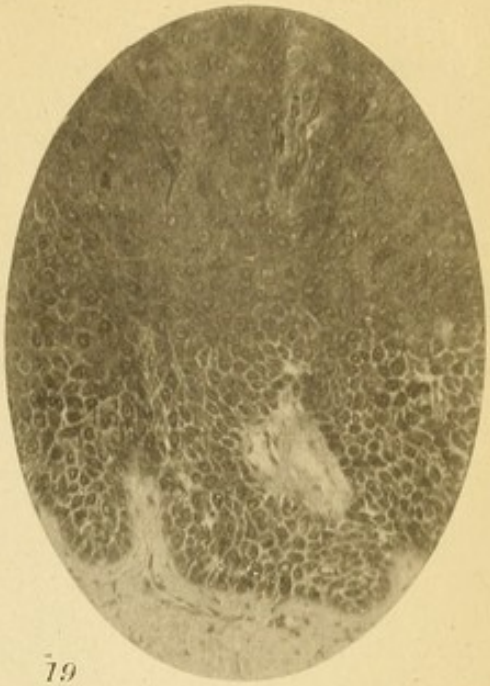

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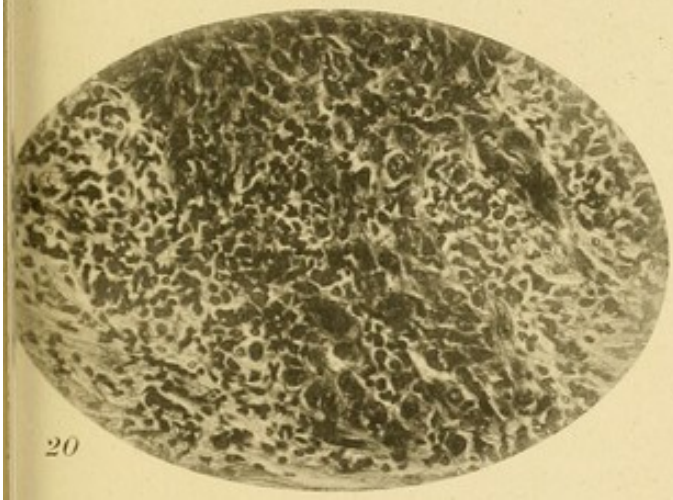

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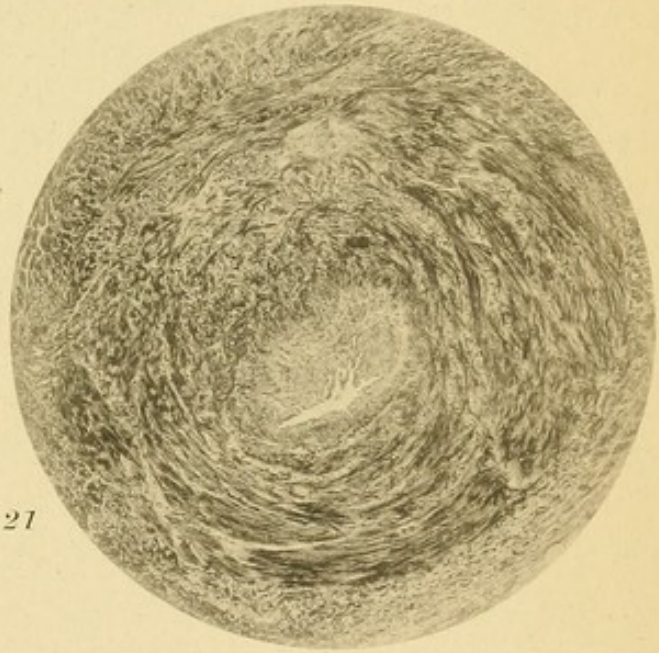

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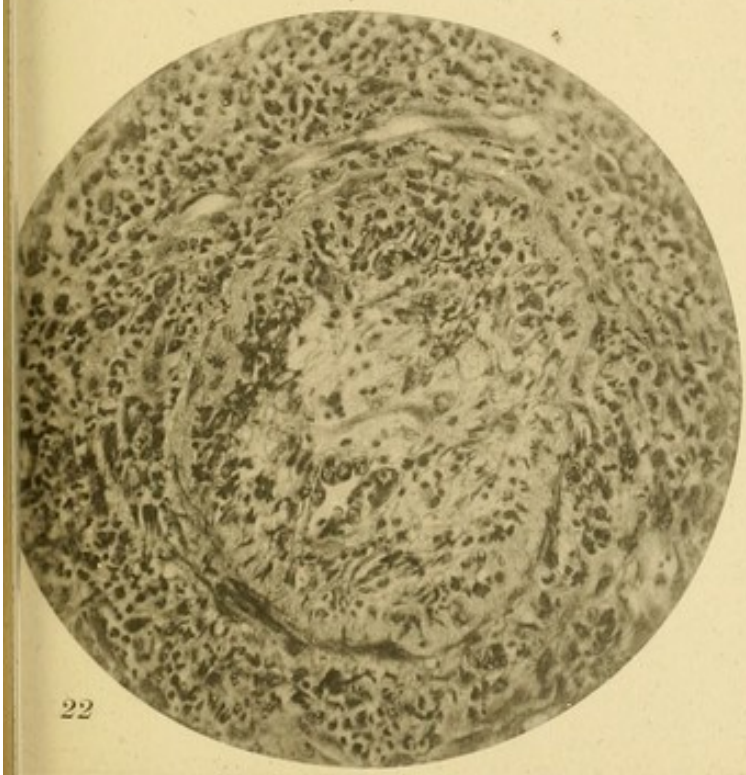

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