THE

ANATOMY AND DEVELOPMENT

OF

RODENT ULCER.

A BOYLSTON MEDICAL PRIZE ESSAY FOR 1872.

BY

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NOTE.

By an order adopted in 1826, the Secretary of the Boylston Medical Committee was directed to publish annually the following votes: —

1st. That the Board do not consider themselves as approving the doctrines contained in any of the dissertations to which premiums may be adjudged.

2d. That in case of publication of a successful dissertation, the author be considered as bound to print the above vote in connection therewith.

The cases quoted in the text occurred in the services of Dr. Hodges and Dr. White, at the Massachusetts General Hospital. The accompanying plates were drawn upon stone by Dr. H. P. Quincy, artist to the Massachusetts General Hospital, from the drawings of the author.

2 Park St., July, 1872.

RODENT ULCER.

It is hardly necessary to preface these remarks with the statement that the disease, with which most of us are familiar under the name of Rodent Ulcer, is still but very imperfectly understood by English and American pathologists. The Surgeon, indeed, struck with its strong clinical peculiarities, is impressed with the idea that there is something "cancerous" in its nature, yet looks in vain for a solution of the problem by the Microscopist.

In other countries, the name Rodent Ulcer is almost unknown. The disease is not recognized as a peculiar affection standing by itself, but is classified with other diseases, such as cancer of the skin or chronic inflammatory processes, according to the views of the writer.

A glance at the nomenclature will serve to show the existing confusion. It has been variously termed, cancroid Ulcer, ulcère rongeant, ulcère chancreux du visage, cancroid de la face (Lébert), Rodent cancer (Moore), flache epithelial Krebs

(Billroth and Thiersch), and lastly, the well-known names, Lupus Exedens, and noli me tangere.

It will be seen that many believe it to be a form of cancer; others have been induced by the gross appearances to liken it to lupus, or even chancre, while the older writers placed it under chronic inflammations, an opinion shared by a large number of modern pathologists.

To the practitioner the disease in question is familiar, in its earlier stages, as a small ulcer situated on the upper part of the face, generally near the nose or eye. Its superficial character, its raised and hardened edges, and extremely slow progress, together with the perfectly healthy appearance of the tissues immediately adjoining, serve to distinguish it from any other form of ulcer, occurring in this region. The age of the patient is also characteristic, it being rarely seen in an individual under forty.

The diagnosis is generally not difficult. The patient usually states that it has been preceded in former years by an annoying pimple, covered frequently by a small scab. This may disappear from time to time, but does not remain absent many months. The ulcer, once fairly formed, slowly, but steadily spreads, until, after the lapse it may be of years, the nose, eyelid, or the eye itself is

attacked by the disease. The bones of the face, even, are not spared in the later stages, and frightful deformities result, which have earned for it the significant names given above.

Curiously enough, the lymphatic glands through all this remain untouched. Similar ulcers have been reported as occurring on the breast, and external genital organs, but no very reliable accounts of such cases are to be found. Statistics show that there is very little difference to be observed in regard to sex, though nearly all of the cases which have come under the observation of the writer happen to have been males.

In Holmes' Surgery * the disease is treated of under "ulcers." This writer finds many points in which it resembles lupus, — yet its difference is proved, he says, among other distinctions, by its occurring as generally in the later half of life, as lupus does in the earlier and by its affinity with cancer, and not with struma. The minute anatomy is not spoken of.

Paget † in his article on Rodent Ulcer says: "It has been confounded by many, with different forms of cancer, yet it is distinct from them in structure, as well as in history, and had better be

* Holmes' Surgery, i. 210.

† Paget's Surgical Pathology, edition of 1870.

described by some name, which may not add to the yearly increasing confusion that arises from the use of terms expressing likeness to cancer. . . . Not only is the Rodent Ulcer usually unlike that of cancer in its aspect, rate and mode of progress, but the tissues bounding it, and forming its base and walls, never contain any epithelial, or other cancerous structures: they are infiltrated with only such structures as may be formed in the walls of common chronic ulcers. I have examined, very carefully, six of these ulcers removed by excision, and have never seen, in, or near them, a structure resembling epithelial, or any other form of cancer." Such is the unqualified opinion of one of the most eminent writers in surgical pathology.

We shall see, however, that this opinion is by no means generally accepted, even in England. Yet it is but a confirmation of Hutchinson's views,* whose reports on Rodent Ulcer are among the most elaborate that we have, and which deserve therefore more than a passing notice. They are based on the observations of forty-two cases, which are all given in detail. In case fourteen he gives an account of the microscopical examination; his sections, made with a Valentine's knife, and torn to pieces with needles, "showed on examination none

* Medical Times and Gazette, 1860.

of the elements of epithelial or scirrhus cancer. Its structure consisted of fibroid tissue, in which were imbedded numerous nucleated exudation cells. I may here remark that this sketch may be taken as applying, generally, to all the cases of rodent ulcer, in which I have had an opportunity of using the microscope." In cases fifteen and sixteen it is doubtful, however, whether he has to deal with epithelial cancer, or true rodent. He says: "No doubt the boundary line between these affections, perfectly distinct as they are in most instances, is not an abrupt one. Transitional cases now and then occur and baffle all accurate classification. . . . No decisive evidence was offered by the microscope. There were also some dimly granular, nearly circular corpuscles, like the enlarged free nuclei of young cells of epithelial cancer, but these too, were very scanty and doubtful. I could not satisfy myself as to the existence of any true epithelial particles."

He states again, at the conclusion of his report, that sections of these ulcers show cell structures found only in organizing fibrous tissue. He therefore concludes that although it deserves the name of locally malignant, it should not be called cancer of the skin, as it is liable to be confounded with other forms of cutaneous cancer, epithelial scirrhus,

&c.; essentially different from it, and of a far higher degree of malignancy.

Antagonistic to these views are those of Mr. Moore,* in whose monograph this disease receives the epithet of Rodent Cancer. The microscopical investigations of this observer, as well as those of Hutchinson, can hardly be said to meet the present demands of science. The method chiefly employed was that of picking small fragments to pieces, with needles, but when not combined with the examination of very thin sections, taken in various directions from the fresh or hardened specimens, it can hardly claim to settle a very doubtful point like this. To this somewhat primitive method of investigation may be ascribed "the yearly increasing confusion" which Mr. Paget complains of.

Mr. Moore, in giving an account of his microscopical examinations, says: "The microscopic characters of the solid infiltrating substance which constitutes the disease are not precisely those of any natural texture, yet they do not ordinarily so much deviate from the appearances of cutaneous epithelium, and of granules, as to be entitled to the epithet malignant." Yet he adds, immediately below, "I have found parts of the diseased substance presenting a minute textural composition, precisely

* Moore on Rodent Cancer, 1867.

answering to that of the epithelial form of cancer." These latter appearances he finds only occasionally; more frequently he says it is made up of such innocent, microscopic corpuscles, that it has been likened to chronic ulcer of the leg, or to a perforating ulcer of the stomach. He is obliged, therefore, after all, to fall back on its clinical peculiarities in order to defend his theory of its cancerous nature. He endeavors to explain the exemption of the lymphatic glands, by the slowness of its growth, by the innocent nature of its material, and by its relation to the lymphatic vessels.

The majority of the French and German writers place it among the Epitheliomas. Lébert * divides epithelial cancer of the face into two varieties, viz.: cancer of the lip, and cancer of the rest of the face, and includes Rodent Ulcer with the latter. Thiersch † makes two varieties; the flat, and the deeply infiltrating (tiefgreifende). Ulcers corresponding in description to Rodent are described as flat epithelial cancers. He also quotes Schuh, as giving them this name. Förster ‡ finds in Rodent Ulcer, only the elements of an ordinary granulation tissue. Billroth's § classification of epithelial can-

* Lébert, Traité des Maladies Cancéreuses.

† Thiersch, Epithelial Krebs, 1865.

‡ Förster, Pathologische Anatomie.

§ Billroth, Surgical Pathology.

cer corresponds with that of Thiersch. He takes cancer of the lip as the type of the infiltrating, or more malignant form. This contains both large and small epithelium cells, while the flat epithelial cancer is made up of cylindrical masses of cells which resemble the small round cells of the rete. He formerly described the latter as cicatrizing or contracting epithelial cancer, or scirrhus cutis, to define it more accurately from ordinary epithelial cancer; but now makes no special sub-division of it, and considers it merely as the mildest form of cancer of the skin. He identifies this variety with the Rodent Ulcer of Hutchinson, although his description does not correspond with it fully; for he alludes to cicatrization as one of its peculiarities, and, as we have seen, at one time named it accordingly. Moreover, he says, "There are also cases in which there is no ulceration at all, but only infiltration of the skin with the formation of epidermis crusts, and subsequent cicatricial contraction." Evidently, the flat cancer of the skin is not confined by him to Rodent Ulcer alone.

These quotations selected only from those writers who have made independent investigations serve to show the prevalent opinions.

The majority of English observers, it will be seen, believe in the non-malignant character of the

anatomical changes, yet there is a lurking suspicion in the minds of many that this ulcer is something more than the result of a mere chronic inflammatory process. Those who believe it to be cancer, on the other hand, failing to find the anatomical structures peculiar to that disease, have been compelled to fall back upon its clinical peculiarities to support their theory. As the microscope alone can settle a disputed point like this, they have simply failed in their demonstration.

The elaborate reports and beautiful plates of Thiersch convey a very perfect idea of the minute anatomy of the flat epithelial cancer. In alluding to Rodent Ulcer, however, he does not leave it perfectly clear, whether he considers the two identical.

This glance at the literature of the disease explains readily the prevailing uncertainty in this country, in regard to its true nature.

The following cases are reported with the hope of throwing light on what, to the medical world at large, may fairly be said to be a somewhat obscure point in pathological anatomy: —

REPORT OF CASES.

CASE I. — J. L., æt. 66, presented himself for treatment Feb. 7, 1870. First noticed a "wart" or "wen" on the left side of the upper lip, eight years ago, which was kept continually irritated, by shaving and picking. This was removed by an operation, and in the cicatrix an ulcer formed which has steadily increased in size until a portion of the left ala nasi has been destroyed, and the whole of the upper lip, from the septum nasi, to the angle of the mouth. The disease has also attacked the septum, and the alveolar process. The edges of the ulcer are somewhat elevated, ragged, and covered with brown scabs. There are no enlarged glands in the neighborhood. The patient is made miserable by difficulty in eating, and by a constant escape of saliva. On the 10th the patient was etherized, and a greater part of the disease was removed by the knife, and the whole surface burned with the Galvano-Cautery. The wound healed readily, leaving considerable deformity, for which two plastic operations afterwards were performed. On October 4th of the same year, there had been no return of the disease.

Microscopical examination. — The fragments removed were taken from the elevated borders of the

ulcer chiefly, and when examined in the fresh state by scraping the cut surfaces, or by tearing small fragments with needles, nothing resembling an epithelial cell was seen. The specimen was then hardened in a solution of chromic acid (one part of acid to one hundred parts water), remaining in this solution for a few days, and then preserved in alcohol about sixty per cent in strength. Thin sections made in different directions showed the presence of a large amount of fibrous cicatricial tissue, the bundles of fibres interlacing one another in various directions. There were very few small round cells such as are seen in inflammatory growths. At considerable intervals in this tissue were found small masses of epithelial cells. These cell-masses were narrow and elongated in shape, occasionally sending out small branches, on one side or the other. The cells of which these masses were composed were small in size, and resembled the cells of the rete Malpighii more nearly than those of any other epithelial structure. They were, with difficulty, colored in carmine, and contrasted in this respect with the cells of the rete, which imbibed the coloring matter readily. In the centre, or at one end of these cell clumps, the cells were frequently packed together in concentric layers, forming the well-known epidermic balls. These were,

however, small in size, and not always present. The newly-formed epithelial structures were situated some distance from the epidermis, which was quite narrow, resembling that which usually covers a cicatrix. There was none of the adjoining healthy skin in any of the fragments removed.

Remarks. — The growth appeared, at the first glance, to consist solely of hypertrophied connective tissue, which evidently gave rise to the elevated edges at the border of the ulcer. It was only after a somewhat careful search, that the epithelial disease was discovered.

Case II. — James O., æt. 65, presented himself for treatment Sept. 16, 1870. Thirty-two years ago he first noticed a pimple on the left temple, near the eye. This was generally covered with a scab; it underwent no considerable change until six months ago, when he fell and scratched it. Since then it has gradually increased in size, until now there is an ulcer three-quarters of an inch in diameter, of an oval shape, and with a raised rim about a quarter of an inch in thickness. The surface has a dirty brownish look, and discharges very slightly. The surrounding skin is perfectly healthy. The disease does not seem to penetrate below the cutis vera. The ulcer was carefully dissected out

with the knife, and the edges of the wound brought together with sutures. The wound healed rapidly, and there has been no return of the disease since.

Microscopical examination. — An examination in the fresh state, by picking small fragments apart, showed simply a few connective tissue fibres, and small round or oval cells. The specimen being then hardened in the same manner as described in Case I., a large number of vertical and horizontal sections were made with the razor. These were colored in carmine, and preserved either in Canada balsam or glycerine.

A vertical section showed the surface of the ulcer to be made up of irregularly-shaped masses of epithelial cells, separated by deep clefts. These cells were mostly broken down, and heaped together without order, their nuclei being in but few instances apparent.

The base and edges of the ulcer were composed of a fibrous, vascular, alveolar stroma, containing in its meshes masses of cells. These cells, though small in size, were distinctly epithelial in character. Both vertical and horizontal sections showed the cell masses, nests, or cylinders, as they have variously been termed, to vary considerably in shape. The most frequent arrangement was in elongated, more or less cylindrical-shaped masses, anastomos-

ing with other similar masses, and presenting frequent constrictions. (See Drawing 6.)

At other points, generally near the periphery of the growth, the form was oval. The most marked peculiarity of the cells was their small size, contrasting greatly with the large pavement epithelium cell that is found in cancer of the lower lip. They contained an oval, well defined granular nucleus, which colored readily with carmine, at those points where the structure was not beginning to break down. When the cells were not closely crowded together, their form was either globular, or the borders of the cells were not well defined, the nuclei appearing imbedded in a continuous mass of protoplasm. At certain parts of the edges of these cell structures, the cells resembled cylinder epithelium, reminding one of the shape and arrangement of the epithelium immediately surrounding the papillæ of the skin. Nearly all of the cell-nests contained the epidermic balls, in the immediate neighborhood of which the cells were, of course, more or less flattened out. (Drawing 6.) These balls, however, are by no means as large, nor did they catch the eye as easily as those very striking forms which predominate to such an extent in the large cell epithelial cancers, like cancer of the lip. It may be said of the cells in general,

that they resembled the smaller cells of rete mucosum, more nearly than any other form of epithelium. At the periphery of the new growth, particularly in the parts surrounding rather than those underlying the ulcerated surface, the nests of cells did not have the appearance of epithelium. Here the epidermic balls were wanting, nor was there that regularity in the arrangement of the cells which is characteristic of epithelium. The cells were much smaller than those in the central masses and resembled rather the "indifferent" or "wandering" cells which were seen in numbers in the neighborhood, where they appeared no longer in isolated masses, but infiltrated the tissues.

It was interesting to notice that these peripheral cell-nests were penetrated, almost in every case, by a small vessel which generally ran through the centre of the mass. This central vessel was never seen, on the other hand, in any of the epithelial clusters. (See Drawings, 3, 4.)

The epidermis, as it approached the diseased part, was somewhat thickened, but tapered off to a fine point at the edge of the ulcer. Beneath the rete mucosum of that part of the skin which covered the borders of the ulcer, the small wandering cells were quite numerous. These cells were not collected in nests, but infiltrated the cutis, and

at many points came in direct contact with the cells of the rete. Here the well-defined border which separates the rete from the papillæ, was lost, and the epithelial and connective tissue cells appeared to mingle with one another on the border line.

The hair follicles, which were quite numerous on one side of the ulcer, being probably those of the eyebrow, appeared to be unaltered except in those parts which were actually invaded by the disease; here the hair shaft had disappeared, leaving behind a collapsed tube, lined with cylinder epithelium. These tubes became smaller as the edge of the ulcer was approached, there being no visible alteration in the cell contents, and finally disappeared entirely. The sebaceous and sweat-glands appeared to be unaltered.

The examination of this specimen brings out several points of interest. We find here again epithelial structures, and of the same general character as in Case I., resembling the small cells of the rete. An appearance worthy of notice, as being frequently met with in certain forms of cancer, is seen here at several points, viz.: the fusion of the protoplasm of neighboring cells so as to form one continuous mass, in which the nuclei are imbedded.

This was shown well in the specimen from which

Drawing 6 was taken. The epithelial structures are more numerous than in the last case, and the branching and anastomosis of the cell-nests more general. The central cell-nests are fairly represented in Drawing 6. The peripheral nests resemble in shape Drawing 3, though here the development has not reached a sufficiently advanced stage to show many epithelial cells. Here we see the central thread of fibres, dividing the alveolus in its long diameter. A still earlier stage is represented in Drawing 4, at a point situated on the extreme borders of the growth. Here the cells resemble the connective tissue cells, and the axis of the alveolus is represented by a delicate blood-vessel. The different stages of development observed in this specimen are well shown in the sections from which the above drawings were taken.

Case III. — Male, æt. 42. Disease began as a pimple on the right ala nasi, eleven years ago. In consequence of scratching it, an ulcer formed which steadily increased in size ; was twice removed by a plaster. Seven years ago it healed, and remained so for nine months, when it reappeared. The disease now occupies the entire ala, and appears as an oval-shaped ulcer, with slightly raised edges.

The adjacent skin and tissues are healthy, and

there are no enlarged glands to be found anywhere. It has increased quite rapidly of late. Patient's general health is excellent. The disease was cleanly cut out with the knife, a small portion of healthy skin being removed at the same time.

Microscopical examination. — The little cake thus removed was cut in halves with a sharp knife, and the surfaces exposed were scraped, and the fragments obtained examined under the microscope. Beside the elements of ordinary connective tissue, one small clump of small globular epithelium cells closely adherent to one another was found.

The specimen was then placed in a one per cent solution of chromic acid, and allowed to remain there two days. Owing to the thinness of the specimen, a too great degree of hardening was obtained. The cells were too much shrunken, in consequence, to show satisfactorily, nor were they clearly brought out by imbibition with carmine ; nevertheless, the examination left no doubt as to the character of the disease.

After allowing the specimen to remain in weak alcohol for a few days, oblique, vertical, and horizontal sections were made with the razor.

Due allowance being made for the imperfect method of hardening, the cells may still be said not to possess so well marked an epithelial character as

in the preceding cases. With low powers, the diseased structures appeared like ordinary granulation tissue ; with three hundred and fifty diameters, however, it was easy to distinguish between the epithelial cells, and the small round cells, which invaded the surrounding stroma. The former were small sized, with large oval nuclei, and nucleoli. Their borders, for the most part, were not easily distinguishable, the protoplasm appearing like one continuous mass, in which the nuclei were imbedded. These cell masses were quite narrow, generally the thickness of two cells, and elongated, and anastomosed freely in all directions with one another, so as to give the appearance of a system of vessels, crowded with epithelial cells. (See Drawing 5 *a*.)

There was, however, no enclosing wall or central cavity. The arrangement was similar to what is seen in the so-called tubular variety of epithelial cancer. This was more apparent in oblique than in vertical or horizontal sections, where there appeared to be no definite order, the cells at some points being crowded together in large masses, at others in long, narrow lines. The epidermic balls were nowhere seen. The separation of the epithelial structures, from the connective tissue stroma, was always apparent in the fully developed portions of the growth.

There was no infiltration of the stroma by them, as was the case with the small, round, indifferent cells. The connective tissue stroma which supported the epithelial cells was not abundant: near the periphery it was so small in amount, that the adjacent cell cylinders seemed almost to run together into one continuous mass. At this point the cells began to lose their epithelial character and arrangement, and soon became undistinguishable from the small round cells which infiltrated the surrounding structures. The epidermis was slightly thickened in the raised border of the ulcer, but tapered off to a fine point at its edge. In the border, the portions of the rete which lie between the papillæ, penetrated the cutis more deeply than usual. They were surrounded by young, round cells, which were quite numerous at this point, and intervened between the old normal epithelium, and that of new formation. (See Drawing 5 *b*.) At this part of the rete, the boundary line between the epithelium and the connective tissue was not preserved, and the cells of the two structures were intermingled for a short distance. In the papillæ of the adjacent healthy skin, it should be said, that the boundary line was well marked.

There were no hair follicles, nor sweat-glands, to be seen. One or two large sebaceous glands were

found under the adjacent healthy skin. The number of blood-vessels was small.

Remarks. — We do not find in this specimen large or well-defined masses of epithelial cells; and yet a careful examination leaves no doubt as to their nature. This is precisely one of those cases which might easily be mistaken for a simple chronic inflammatory process, where proper methods of examination had not been employed. A point of interest in this case was the intermingling of the connective tissue-cells and epithelial structures of the skin, in the neighborhood of the disease. This occurrence, when taken in connection with the fact that at many points the new epithelium was hardly to be distinguished from the young cells adjoining it, would seem to suggest that these young cells were in some way connected with the destruction of the old epithelium, and the formation of the new.

The presence of young, wandering cells, between the cells of the rete, has been observed by both Biesiadecki and Pagenstecker. This was seen in inflammatory processes of the skin, like eczema. (Fig. 34. Rindfleisch, Lehrbuch der Path. gewebelehre.)

Case IV. — Male, æt. 60. First noticed a little black speck, like an acne plug, in the middle of the

forehead, twenty-nine years ago. On endeavoring to squeeze it out with the nail, the spot was irritated and "festered." A scab formed over it, of about the size of a pea, and thus it remained until patient came to this country. The little ulcer then began to spread, until it grew to an inch in diameter. After remaining so for a short time, it began to heal, without special cause, and disappeared. It opened and healed again, several times, until it finally began to increase beyond its former limits. Patient presented himself for treatment, in the summer of 1870. It showed then an irregularly shaped, ulcerated surface, about three inches in diameter; the centre being a little above the level of the eyebrows. It extended downwards on to the nose, and had eaten away a greater portion of the right eyelid, and destroyed the sight in right eye. It had also begun to attack the left eyelid. The edges of the ulcer were raised a line or two above the level of the surrounding skin, which was perfectly healthy. Patient's general condition was excellent.

The disease was partly excised, and partly burned with galvano-cautery, and the ulcer is now apparently in a healthy granulating condition.

Microscopical examination. — The fragments excised came chiefly from the edge of the ulcer. These, when examined, in the fresh state, showed

nothing in addition to the elements of connective tissue. They were then placed for several days in Müller's liquid, and afterwards for two days in a one-half per cent solution of chromic acid, and finally preserved in alcohol. By that means the shrinking of the cells was avoided, and the elements were preserved in a more normal condition.

Sections prepared, as in preceding cases, showed a beautiful network of cells supported in a tolerably vascular connective tissue stroma, to which, owing to the carmine coloring, they came out in strong contrast. (Drawing 2.) The cells were of the same general character as those described in the preceding cases. The nuclei were particularly distinct; round or oval in shape, granular, and frequently containing a nucleolus. The protoplasm of the cells was finely granular, and appeared as one continuous mass at most points. The cells were packed together in spaces somewhat broader than those seen in Case III., but with the same general arrangement. There were no true epidermic balls, except at one point, viz., that represented in the drawing, where there was a concentric arrangement of the cells. In the centre of the circle may be seen one or two cells resembling pavement epithelium in shape (*b*) though hardly more than one third the size. There were but few wandering cells in the

connective tissue stroma, except in the immediate vicinity of the vessels.

In many instances large numbers of white corpuscles could be seen in the cavity of the vessels as well as in the wall of the vessel itself, while immediately surrounding it were a number of amoboid cells of varied shape. (Figs. *c* and *d*.) Unfortunately, little or no skin had been removed with the masses under examination, consequently the relations of the epidermic structure to the disease could not be studied. At one point, however, there appeared to exist a direct communication between the epithelium of the hair follicles, and the epithelial cylinders.

Remarks. — We have in this specimen a type of that structure which is seen in the tubular epithelioma. Although the terms "cell-tubes," and "tubular," have been employed here, it must not be understood that these cell masses form hollow tubes. In none of them was there any central cavity. The absence of this is shown well at *e*. The cells here are seen to form a solid mass. The terms, if used, should be employed to denote the tubelike shape of the cavities in the connective tissue in which the cells lie.

The accompanying drawing, in the upper part, at least, is hardly a fair representative of the epithe-

lial structures of the new growth, for the concentric layers seen at this point were found nowhere else. In this respect, it resembled Case III. rather than Case II., as may be seen by reference to the drawings. The selection was made on account of its resemblance to those forms of epithelioma with which we are more familiar.

The presence of white corpuscles in the vessels of the stroma, and of amoboid cells, evidently in active movement, at the time the part was removed, indicate in this case, also, an activity of the connective tissue structures.

Case V. — The patient was a healthy girl about twenty-five years of age, with a little ulcer about three-eighths of an inch in diameter, on the left side of the nose, within a line or two of the inner canthus of the eye. It was circular, very superficial, had no raised edges, and was covered over with a scab. It had existed only about eight months. It was carefully excised, together with a small rim of healthy skin, and the wound healed rapidly. It is now over a year since the operation, and the patient has not again presented herself for treatment.

The little mass was carefully hardened in chromic acid, and preserved in alcohol.

Microscopical examination. — Thin, vertical, and

horizontal sections were taken, and these showed the disease to be the same tubular form of epithelioma, as Case IV. (See Drawing 1.) There were one or two points, however, worthy of notice. The epithelial cells at the border of the cell-tubes, were, at some points, decidedly columnar in character, such as we find usually surrounding the papillæ. The relation of the disease to the skin could be well studied here. The epidermis was not thickened, and yet was somewhat altered in shape, for the papillæ were but very imperfectly indicated by slight indentations into the rete Malpighii (1). At several points the new cell-tubes came in contact with the epithelium of the rete. Here it was easy to observe a slight difference in the appearance of the two forms. The newly formed cells were somewhat smaller, and their outline was not so sharply marked, as that of the normal epithelial cell; moreover, the nuclei and protoplasm were more granular in the former (*a* and *d*). There were no hair follicles nor sebaceous glands to be seen in the sections examined. The remains of a few sudoriparous glands were found beneath the ulcer, but did not appear to have any connection with the diseased structures. The connective tissue of the skin did not appear to be increased, though

there were a number of wandering cells surrounding the epithelial tubes, near the surface. (*c.*)

Remarks. — It may be objected that the present case is not a fair specimen of Rodent Ulcer, the age of the patient being entirely opposed to such a diagnosis. It is true also that the disease had not been of sufficiently long duration to show that persistency and tendency to spread, which is so characteristic of the disease. It is to be observed, however, that in the preceding cases, as indeed in most cases, the disease dates back for a large number of years before the time when the patient presents himself for treatment.

The possibility that this might be an incipient Rodent Ulcer was the inducement for presenting it, in order that we might have an opportunity of seeing the disease in its very early stages.

If this case can be accepted, it is interesting as proving that the character of the disease does not alter, but is epithelial from the beginning.

Note. — Since the report of this case was taken, the patient has presented herself for a second time with a return of the disease at an interval of about a year. The ulcer was again excised, and showed the same microscopical appearances as those described above.

In addition to these cases, a number of others coming under the writer's own observation might be reported here, did space permit. Suffice it to say that the result of the examination in all cases was the same. All showing that Rodent Ulcer is but a name given to a form of epithelial cancer.

Before alluding to the particular form of epithelial cancer to which these ulcers belong, let us turn our attention for a moment to certain anatomical points of interest brought out by the examination of these cases.

Although they all present a general resemblance to one another, particularly in the small size and uniform appearance of the epithelial cells, and in the absence of an exuberant cell growth, so characteristic in other forms of cancer of the skin, still there are points in which they differ from one another to such a degree, as to deserve notice here.

Perhaps the most striking difference lies in the disposition of the newly-formed cancer cells. In Cases I. and II., the shape of the little cluster of cells may be said to be, in general (Drawing 6), oval, although frequently prolongations connecting one cluster with another give a very irregular contour.

The alveoli, as they may fairly be termed, in

which the cells lie, appear to be spaces intervening between the connective tissue fibres, and the walls of a vessel. We have seen, in Drawing 4, the vessel penetrating the young cell-clusters. As these latter mature, the circulation is probably cut off by the increased pressure around the vessel, and its walls finally disappear, or are seen as a bundle of fibres, penetrating the alveolus for a short distance. (Drawing 3.)

This disposition of the cell-clusters is obviously different from what we find in the last three cases. In these, the cells are contained in an anastomosing system of tubes, and form quite an ornamental network occupying the full thickness of the skin.

The disposition of the spaces reminds one strongly of the now well-known system of plasmatic canals, from which the lymphatic capillaries take their origin. Indeed it is quite possible that the lymphatics, themselves, may have been invaded for a certain distance, though this was a point which could not be demonstrated. There was no epithelial lining to the tubes to be seen, indicating their lymphatic nature. (See Koester. Entwickelung der Carcinome.)

In all cases, then, we find the cells forming in spaces in the connective tissue of the cutis. In one set of cases these spaces surround the vessels of

the skin, whereas in another set, they appear to be perfectly independent of them.

Should it be deemed desirable to base a classification of these cases, on the anatomical arrangement of the cells, we might designate the first class, to which Cases I. and II. would belong, as alveolar, and the second class as tubular.

Another point of difference between these two classes is the almost total absence of any thing resembling an epidermic ball in the tubular variety, while we find them in abundance in the alveolar. This may possibly be due to the want of free communication between the alveoli. The proliferating cells, having no opportunity to spread easily, are crowded together and assume these forms. No such obstacle to their progress is offered by the freely anastomosing tubes. There is, indeed, a slight concentric arrangement in the large cluster represented in Drawing 5, but this was found nowhere else. The form of the epithelial cells is in all cases essentially the same,— slightly oval, except, perhaps, in Case III., where they are rather globular. The cells immediately bordering on the connective tissue-stroma, however, frequently have a shape and arrangement resembling columnar epithelium. The nuclei are round or oval, coarsely granular, frequently con-

taining a nucleus, and always sharply defined, contrasting in both respects with the protoplasm or bodies of the cells, which are finely granular, and frequently run together into an inseparable mass.

The most marked peculiarity of these cells, wherein they differ particularly from those forms of epithelial cancer with which we are most familiar, is their small size. Comparing them with the normal epithelial structures of the skin, we find a resemblance between these cells and the younger cells of the rete Malpighii, sufficiently striking to be deemed worthy of notice.

The connective tissue-structures varied somewhat in quantity in the different cases. It was decidedly less prominent in the tubular forms, than in the alveolar. In Cases IV. and V., the cellular elements of the stroma were much less numerous than in the other cases ; indeed, much less than we ordinarily find in the neighborhood of any morbid growth, and it was interesting to observe, that in these two cases alone was there any apparent connection of the epithelial structures with those of the skin. (See Drawing 1.)

To sum up the result of our analysis of these cases, at this point, we feel justified in arriving at the following conclusions : —

1st. All those cases of Rodent Ulcer examined are forms of epithelial cancer.

2d. They differ from those forms of epithelial cancer, of which cancer of the lower lip is the type, in the small size of the epithelial cells.

3d. These ulcers may be divided histologically into two different groups, according to the arrangement of the cancer-cells; viz., into tubular and alveolar.

Allusion has been made frequently to other forms of cancer of the skin. A word here, therefore, on the classification of cancers of this region may not be amiss.

Paget divides them into superficial, and deep-seated, the former involving the skin itself, the latter forming beneath, and independent of the skin.

Some of the French writers, for example, Lébert, bases this division on the special layer in which the disease originates. Others, as Cornil and Ranvier, adopting a microscopical basis for their classification, although they make no special division of cancers of the skin, speak of a lobulated and tubular form growing in this part of the body; the former representing cancer of the lip, the latter the tubular form already mentioned.

According to Thiersch, Billroth, and others,

there are two varieties of skin cancer, — the flat or superficial, and the deeply infiltrating (tiefgreifende). The flat cancer consists of a shallow layer of epithelial cells, separated from the tissues beneath by a well-defined outline. The deeply infiltrating does not present any such line of demarcation, but penetrates in irregular masses into the deep-seated tissues. This form is rapid in its growth, and infects readily the surrounding structures. The former is, on the contrary, quite slow in growth, and the skin immediately about it appears quite healthy. This variety appears as a flat ulcer with slightly raised edges ; while the deeply infiltrating has an ulcerated surface surrounded by large nodulated masses. There is also a microscopical difference. The flat form is composed of a homeomorphous growth, while the infiltrating has, in addition to these cells, the large flat cell of varying shape and size. The cell growth in this case is polymorphous. We have, in this division into two forms, a classification based both upon a well-marked clinical and microscopical difference, and one which can be applied to all forms of cancer of this region. It would seem to be not only scientific, but eminently practical.

It is easy to recognize in the infiltrating form cancers of the lower lip, penis, vulva, back of hand,

&c. This class indeed includes both the forms mentioned by Paget ; his deeply-seated form being a most excellent example of the large cell, or polymorphous cell form. The flat cancers, on the other hand, are evidently intended to include the Rodent Ulcer. Whether this is the only representative of this class is not definitely stated by German authors. The writer has not found any account of other forms. A certain number of cancers of the cheek have, however, fallen under his observation, which may fairly be placed in this class. Their microscopical appearance corresponds to what he has stated above to be the alveolar form of Rodent Ulcer, while their clinical history is not unlike this disease. They are seen generally as a somewhat superficial, nodular infiltration of the skin, accompanied with little or no ulceration.

They are not quite so sharply separated from the surrounding tissues as is Rodent Ulcer, yet their growth is quite slow, and they are only occasionally accompanied by an infection of the neighboring glands. In addition to these points of resemblance, they have another claim to be placed in the same class with Rodent Ulcer, in an occasional occurrence of the two forms in the same individual.

A case of this kind came lately under the writer's observation. The nodulated epithelial growth oc-

cupied the right cheek, while a Rodent Ulcer had attacked and destroyed the left eye, and a portion of the lids. They were both of long duration, and on neither side were the lymphatic glands affected. The character of the epithelial cells, in the two cases, was similar; but their arrangement was tubular in the ulcer, and alveolar in the nodulated form.

In addition to the forms above enumerated, there are also a certain number of pediculated and warty-like epithelial growths, which frequently remain perfectly superficial, and are composed of the large epithelial cells. Their tendency, however, to change into a more rapidly growing infiltrating form, together with the microscopical character of their cells, would seem to be sufficient ground for classifying them with the large-cell variety. Adopting then the form and appearance of the cancer-cell as a basis for classification, we have a simple means of avoiding the difficulties involved in one based on the situation or accidental external appearances of the growth, and we obtain one which corresponds in the main to an important clinical difference; namely, the degree of malignancy.

We have then to recapitulate two forms of cancer of the skin: —

1st. The large-cell variety, or the infiltrating

form, for which we may select cancer of the lower lip as a type. We find a greater degree of malignancy in this form, both in the more rapid growth and in the liability to an infection of the neighboring lymphatic glands, or of more distant parts.

2d. The small-cell variety, or flat or superficial cancer, the most typical form of which is the Rodent Ulcer. This form is characterized by a slow growth, and is very rarely followed by an infection of distant parts.

We now approach a somewhat more difficult part of our subject; namely, the development of the disease. A study of the growth and development of this new formation gives us naturally a more accurate knowledge of its character, than we should derive merely from an examination of the anatomical structure when fully matured, — the standpoint from which we have thus far considered it. It is obviously quite as necessary to study the disease in its various phases. Moreover, in the earlier stages, the relation between the normal structures and the newly-formed elements is more easily determined. We are consequently enabled to arrive at some conclusions as to the origin of the elements and the route which they take in their further development. Possibly we may find here an explanation of some of the peculiarities of this

form of cancer, particularly the very remarkable immunity of the lymphatic glands.

It must be confessed however, at the very outset, that the origin of the cancer-cell, notwithstanding innumerable investigations, still remains an open and difficult question. We hope, however, to be able to arrive at some conclusions on this point, from a study of the cases above reported, as some of the specimens obtained proved suitable for this purpose. Before doing this, however, it will be necessary to give a brief sketch of the question as it now stands.

It was for a long time supposed by German observers, that cancer was developed from glandular structures ; but Virchow's studies on connective tissue led him to believe that this theory was incorrect, and that it was the connective tissue cells that became the starting point of the disease. We have therefore, according to him, in cancer, a type of the truly heterologous formation ; namely, a formation of cells in a part where those cells, normally, do not exist. This theory was generally adopted, and remained for some time undisputed. Förster, following Virchow's views, found it necessary to separate from epithelioma those growths which he had hitherto considered as originating from the epithelial structures, and called them papilloma, and

destructive glandular tumors. Those only were called epithelioma, which were developed in a stroma entirely independent from pre-existing epithelium. Many other German writers supported this opinion of Virchow, and among them C. O. Weber, Rindfleisch, and others. Observations supporting this view are numerous. C. J. Eberth * describes an epithelioma of the pia mater in which the epithelial cells could have no other than an epithelial origin. Volkman † describes cancer cylinders formed by the proliferation of the nuclei of muscular fibres. Rindfleisch, however, allows a certain participation of the epithelium ; he has observed in the earliest stages of the development of cancer of the skin an inward growth of the depressions of the rete mucosum which lie between the papillæ; also an activity of the cells of the glandular organs of the skin. In explaining his views, however, he says : "I distinguish in epithelium, as in cartilage, a primary and a secondary growth. The first consists in the apposition of younger and smaller cells on the border of the epithelium and the connective tissue. The second is an enlargement and proliferation of the epithelial cells themselves. Through the former the onward growth is produced; and by the

* Virchow, Archiv., xlix. 51.

† Virchow, Archiv., l. 543.

latter the enlargement in the transverse diameter of the epithelial masses."

Remack, on the other hand, had always considered that all epithelial formations were developed from epithelial germs only, as is the case in embryonic development. There we find that the skin, mucous membrane, and the glands, are developed from the horny and intestinal gland membranes only. That which is destined to become connective tissue, the middle germinal membrane, does not mingle with the other two. The process of development goes on separately. He argues that in pathological changes the same separation is maintained, for it is not probable, he says, that pathological processes are governed by other histogenetic laws, than those which apply to normal processes. The development of epithelial cancer, in parts where there exists normally no epithelium, is explained by the straying of an epithelial germ during embryonic life, which, being misplaced, develops its malignancy at a favorable opportunity. Thiersch, one of the most prominent of German writers on epithelial cancer, espoused this theory of Remack, for although, according to Virchow, there is a sufficient amount of connective tissue everywhere for the development of cancer, the fact is, that we find the disease in glandular organs

only. Observations of Kölliker on the teeth sacs, and the formation of the crystalline lens, and the labyrinth, he thinks confirm this view. He cites also the formation of epithelium on open ulcers, considering that it takes its origin from the pre-existing epithelium alone.

Thiersch quotes a number of authorities,—Führer, Hannover, Verneuil, and others,—all of whom are of the same opinion with him in regard to the epithelial origin of the cancer-cells. The structures from which he considers epithelial cancer of the skin to originate are chiefly the sebaceous glands. This he endeavors to show in the plates which accompany his very admirable work on this subject. In some cases, he thinks the epithelial disease takes its origin from the Malpighian layer of the skin, or from the hair follicles ; in others, from the sudoriparous glands. Billroth, also, adopts the Remack theory exclusively ; that is, he does not allow of any mingling of connective tissue and epithelial cells. He formerly thought that the small-cell infiltration of the surrounding stroma played an important part in the development of these growths. He believes now, however, that the epithelial structures of the skin are, from the beginning, the points of departure of the disease. The cutis, he says, is covered by an epithelial layer, from which in the

fœtus ingrowths take place into the subjacent tissue; namely, the hair follicles, sebaceous, and sudoriparous glands. It has been maintained that all these structures may give rise to epithelial growths. Billroth thinks it most easily proved, however, in the case of the rete Malpighii. "The young cells of the rete," to use his own words, "retain at first, during their inward growth, their form and size perfectly. The relation to the cutis, moreover, remains the same, for we find that those cells which are adjacent to the connective tissue retain the same cylindrical form which they have in the papillæ of the cutis." (An example of this appearance is seen in Drawing 1.) As these cell-masses grow inwards, they find their way into the connective tissue spaces, for the tissue here offers the least resistance; and from here into the lymphatic vessels. This activity of the epidermic structures has been maintained lately by Auspitz, in the Archiv für Dermatologie und Syphilis, 1870, in which the development of the skin is described at length. He believes that the papillæ are not to be looked upon as elevations of the cutis, but are formed by depressions in the cutis produced by the actively proliferating epithelial structures above; in other words, that the cutis plays a purely passive part in the process, and is simply moulded into shape by

the more active parts above. His pathological investigations lead him to conclusions which one would infer from the physiology and development of the skin, so far as one is able to study them. Epithelioma, he concludes, represents the type of the hypertrophic ingrowth of the epidermis, into the connective tissue stroma.

Cornil and Ranvier (Manuel d' Histologie pathologique) are of the opinion that epithelioma has its origin in glandular structures or in embryonic cells in their neighborhood, probably belonging to the connective tissue. The epithelial structures, in the latter case, exert a sort of *action de présence*. C. and R. have observed in certain cases changes in the sebaceous and in the sweat glands, which lead them to infer a development from these structures.

Lébert may be said to derive the cancer-cell from the cells of the epidermis.

The investigations of English writers are not of a character to afford us much information on this point. Moore and Bennett have little to say upon the question.

Paget agrees with Virchow in the heterologous character of the epithelial formation. He says, — "even that delusive appearance of homology, which exists when the structures like those of epithelium

are formed in the dermal tissues, and therefore near the surface, is lost in nearly all the cases of deep-seated epithelial cancers, and in all the similar affections of the lymphatic glands and internal organs."

"A somewhat novel view has been advanced lately, by Koester and Recklinghausen (Entwickelung der Carcinome). The latter was the first to point to a development from the lymphatics, showing that the epithelial cylinders might be the swollen ends of lymphatic vessels. Recklinghausen supposed the epithelial cancer-cell to originate from the connective tissue, and find its way into the lymphatic vessels through the plasmatic canals, or that a mingling of these cells with the lymphatic epithelium took place. A series of investigations by Koester, made for the purpose of clearing up this point, led him to believe that the cancer-cells actually originated from the lymphatic epithelium. As lymphatic epithelium differs from other forms of epithelium, in originating from the middle germinal membrane, and not from either of the other two membranes, these views would necessarily be antagonistic to those of Thiersch, Billroth, and others already mentioned. They have not, indeed, been very generally received, although it is allowed by many that the lymphatics are frequently the seat

of the disease in certain stages. A case reported by Pagenstecker,* for the purpose of showing the resemblance between the anastomosing cell cylinders and the lymphatics, did not show any activity of the lymphatic epithelium as described by Koester.

A great deal of valuable work bearing upon this point has been done by those who have investigated the reproduction of normal epithelium on wounds, ulcers, &c.

Rindfleisch observes, that the matrix of epithelium is to be found in the subjacent connective tissue, and that the young cells in the deeper layers are derived from that tissue.

This statement is supported by observations of Recklinghausen on the epithelium of the cornea, in which he finds the epithelium developed from the wandering cells.

Biesiadecki (Sitzungsberichte of the Vienna Academy) has shown also that the mucous layer of the skin possesses, beside the epithelial cells, others more like the cells of fibrous tissue, and that these cells originating from the corium (wandering cells of Recklinghausen) penetrate the mucous layer. The youngest cells of the rete are developed from a nucleolated protoplasm belonging to the corium.

* Virchow, Archiv., xlv. 490.

These views he has confirmed by actual observation on the web of a frog's foot, where he has seen the escape of white corpuscles from the vessels, their disposition over a surface deprived of its epithelium, and their gradual metamorphosis into epithelium cells.

An objection may be made to this view, on the ground that in a healing wound epithelium forms only at the edges, and not in the centre, as we should suppose would be the case were the connective tissue alone concerned. Rindfleisch overcomes this by the statement, that a connective tissue-cell can only be converted by coming in actual contact with the pre-existing epithelium. We must believe, he says, in a kind of epithelial infection.

This participation of the two structures in the development of the new cells has been noticed by other observers. Arnold,* who has made a number of carefully prepared experiments for studying the regeneration of epithelium in wounds, finds that the epithelium cells are formed neither from the connective tissue alone, nor from the epithelium alone, but from the former with the influence of the latter. This view has, however, not been confirmed by Wadsworth and Eberth,† who find that the re-

* Virchow, Archiv., xlvi. 168. † Virchow, Archiv., li. 361.

generation in these cases proceeds from the epithelium alone.

This theory of infection reminds one strongly of the *action de présence* alluded to by Cornil and Ranvier, and also to a curious theory advanced by Klebs. This is a participation of two individuals in the production of the new cells, in cases of cancer; the malignant growth being the result of this unlawful intercourse.

We will close this sketch with an observation of Classen,* showing the participation of the white-blood corpuscle, or the wandering cell of Recklinghausen, as it is called when seen in the connective tissue, in the formation of the cancer-cells. The case is one of cancer of the cornea, and the vessels surrounding the cancer-tissue are encompassed by young round cells, which appear to participate in the development of the growth. Similar observations by Hirschfeld are reported in the Jahresbericht for 1870, page 75. He thinks, in certain cases, that cancers are of epithelial origin, though he believes that Thiersch carries his views too far. The different germinal membranes, after all, spring from the same source; namely, the formative cell which has not yet undergone a differentiation; and it is probable that in the developed organism such

* Virchow, Archiv., l. 56.

cells may still exist, which possess the power of becoming either a connective tissue, or an epithelial cell; namely, the white-blood corpuscle.

It will be seen that this question like many others in this branch of science has suffered many fluctuations. The views of Thiersch and others on the epithelial origin of cancer-cells succeeded rapidly to that of Virchow, and gained many adherents, probably on account of their simplicity. They explained satisfactorily the striking resemblance between the new formations and the neighboring epithelial structures. This resemblance it was that gave rise to the term, *tumeurs hetéradéniques*, used by some French writers. We find, moreover, that not only do cancers almost invariably develop in or near some epithelial structure, but also that there is frequently some communication between the two. The observations of Conheim and Recklinghausen, however, on the cells of connective tissue, throwing as they did much light on our knowledge of this structure, have given a new interest to this question. They were rapidly followed by a host of other investigations, among which those of Biesiadecki, reported above, are most satisfactory, showing the regeneration of epithelium from the connective tissue, or white-blood corpuscle.

If this law is true for normal structures, may we

not infer a similar origin for the cancer-cell, particularly when we find that pathological appearances are suggestive of such a change?

We will leave here the literature of this interesting question, and delay no longer to gather what information we may from some of our own cases selected for this purpose.

Cases II. and III. are the most suitable, for in these the whole of the diseased mass, and a portion of the surrounding healthy structures, were obtained for observation. In Case II. we find the diseased tissue, which extends downwards to the subcutaneous cellular tissue, and laterally for a short distance beyond the border of the ulcer, to be made up of masses of cells of new formation, which except at the extreme periphery are enclosed in alveoli of somewhat varying shape, communicating to a certain extent with one another. At the centre of the disease, they have the appearance of epithelial cells, and crowd together, frequently forming epidermic balls. Their general character is not to be mistaken. (Drawing 6.) As we approach the periphery, cells of an epithelial character become fewer in number, and those which predominate here resemble the small round cells which are so frequently found in all morbid growths.

We come finally to alveoli, which are composed

solely of these latter cells. (Drawing 4.) The difference between the two kinds is sufficiently well marked to prevent any mistake arising, on a tolerably careful examination; and yet with only a moderately low power, it might be said to be quite difficult to determine at what particular point the boundary line between the two existed.

One distinguishing feature of those more peripheral alveoli, in which the young indifferent cells exist, was the presence of a vessel running through the centre of the cluster of cells. This at many points was perfectly formed, and contained numbers of blood corpuscles. (Drawing 4, *a*.) It could occasionally be traced to some larger trunk, leaving no doubt as to its nature. At others, this central axis, as it were, was simply a band of fibres, with the appearance of a central cavity. (Drawing 3, *a*.) At still other points, the resemblance to a vessel was less distinct, and yet in all, or very nearly all these alveoli, the central axis appeared to exist in one of these forms. We have already mentioned that in the epithelial clusters this appearance was entirely wanting.

We see then, that in the earliest stages of development of the growth an accumulation of young cells has taken place immediately about some small vessel, and to such an extent as to crowd away the

connective tissue-fibres immediately surrounding its walls for some little distance, in such a manner as to leave a somewhat elongated oval space through the centre of which the vessel runs.

As the disease progresses, we find that these cells no longer maintain their original character, but that here and there, among the mass of cells, cells of an epithelial character are found (Drawing 3, *c*). These grow more numerous as we approach the older portions of the disease, until indeed we find that the epithelial cell has entirely supplanted the young cell. In the mean time our delicate vessel becomes somewhat indistinct in its contours, later is represented by a few fibres merely, while finally no trace of it is found to remain.

The young cells are found however, only in the immediate vicinity of blood-vessels. The cell-clusters give off offshoots, which either communicate with other alveoli, or wedge their way between the fibres of the connective tissue. We find them also in tolerably large numbers in the tissues surrounding the disease, particularly in the papillæ which are in the skin immediately surrounding the ulcer. These cells crowd so closely on the epithelium of the rete mucosum immediately above, as to force their way frequently for some little distance beyond the boundary line, and

between the cells of the rete, the outline of the papillæ at this point becoming somewhat indistinct. Any such intermingling of the cancer-cells with the epithelium of the skin is, on the other hand, seen nowhere.

There are several interesting points brought to light here, bearing upon the question of development. The first of these is the accumulation of the youngest elements of the diseased structures about the walls of blood-vessels.

These elements differ in no way from the small indifferent cell of certain authors, the wandering cell of Recklinghausen, or, if we choose to go one step farther, the white corpuscles of Conheim. May we not here have to deal with cells which have escaped from the cavity of a blood-vessel? The situation and arrangement of these cells is eminently suggestive of such an origin, even if we did not find at certain points vessels whose cavity is filled with white corpuscles. Some of these have penetrated the wall of the vessel, while in the immediate vicinity are to be found cells of precisely similar character, mingled with others of somewhat varying shape, suggesting an amoboid movement at the time of the death of the part. (Drawing 2, *c*.)

Secondly. We find that these cells are collected

in clusters, and not infiltrated, if we may use the term, in the tissues about. These clusters, at first, have a shape corresponding somewhat to the direction which the vessel takes; later, we find offshoots from the main mass existing to such an extent that the different clusters communicate more or less with one another.

The cells lie evidently in channels in the connective tissue, and are not interspersed between the individual fibres.

Thirdly. There is free contact at certain points between these cells and the pre-existing epithelium, and lastly, we find that in these young cell-clusters the first traces of the new epithelial or cancer-cell are discovered.

In Case III. we have a very different arrangement of the cancer-cells. Here, they fill very narrow tubes, which anastomose much more freely with one another, than the alveoli of Case II. We find the so-called tubular form of epithelial cancer. The cancer-cells are to be found only in the central portions of the diseased structure, while at the periphery we find again only young indifferent cells. These latter are not arranged in clusters, as in Case II., but infiltrate the connective tissue. The corium and papillæ are crowded with them, and they penetrate, as in the former case, between the cells

of the rete. As we approach the central parts, a certain arrangement of the cells in rows is discernible, while at the same time a gradual change in the appearance of the cells takes place, until we come upon the tubular arrangement and epithelial character, already described.

At no point was any communication to be found between the cancer-cells and the normal epithelium of the part, although a careful examination was made with this object in view. It seems justifiable, therefore, to conclude from the data afforded by these observations that, in some instances at least, the cancer-cells are in no way connected during their development with the previously existing epithelial structures, and that we are to seek for their origin rather among the young cells of new formation, which are present in large numbers, and with which the cancer-cells appear to come in intimate relation. Indeed, we are able to observe in both these cases such a gradual change in the character of the cells, from the earliest pathological change to the fully developed diseased structure, as to leave hardly any room for doubt upon this point.

The next question which naturally arises, is, the origin of these young cells: are they produced by a proliferation of any of the normal elements of the

part, or are they, as we have already suggested, in any way connected with the corpuscles of the blood? It is not probable that the epithelium takes any part in their formation, for although we have seen an intermingling of these young cells with those of the rete, there is nowhere any appearance which suggests a proliferation of the epithelial cells of this part. On the contrary, we find simply an atrophy, and destruction of the epithelial structures, keeping pace with the advance of the disease. To what extent the so-called fixed cells of the connective tissue of the part were implicated in the process, it was impossible to say, as there was no evidence bearing upon this point afforded by the specimens examined. It was quite evident, however, that the vascular system was in some way connected with the early history of the disease. The masses of young cells, which are arranged in clusters around the walls of blood-vessels, and the frequent accumulation of white corpuscles within, together with the other data given in Case II., render it extremely probable that the parent cells of the future cancer are derived in part at least from the white corpuscles of the blood.

We have alluded several times to the accumulation of the young cells in the papillæ of the skin and their frequent contact with the epithelial cells

of the rete. Observations similar to this, as we have seen, have been made by Biesiadecki in the study of the process of regeneration of epithelium, and the development of the epithelium of the rete. When, in addition to this, we find the cancer-cells resembling strongly the epithelium of the part, it seems quite possible to believe in a certain influence exerted by the normal epithelium on the new cells; the *action de présence* of the French writers. Or it may be that the cancer-cell is the result of a sort of infection or impregnation of these young cells, by the same elements. Such a theory would allow, at the most, only of an indirect participation of the epithelium in the formation of the new cancer-cells.

That the lymphatic spaces of the connective tissue of the skin are the seat of the new formation, is shown quite satisfactorily in Case II. in the earliest stages of development, and in the anatomical arrangement of the cancer-cells in all the specimens examined. The so-called perivascular lymph-spaces are distended by the young cells which accumulate about the vessels in the manner already described. From this point, the young wandering cells appear to penetrate the lymphatic network of the skin, where, collecting in clusters of varying shape, the eventual development into cancer-cells takes place. The anatomical arrangement of the newly-formed

cells, as seen in the different stages of development, speaks strongly for this supposition. By peculiar methods of preparation, Köster has been able to demonstrate this point in a large number of epithelial cancers, both of the large and small cell variety. An actual invasion of the lymphatic vessels by the disease, as observed by Köster, does not appear to have existed in these cases, except perhaps to a very limited extent. This immunity of the lymphatic vessels is further shown by the superficial character of the disease, and an entire absence of any infection of the neighboring glands.

We have based our conclusions on the mode of development thus far, on Cases II. and III. It is necessary, however, to mention that both in Cases IV. and V., a communication with the epithelium of the rete Malpighii was found to exist; a fact which would seem to controvert the opinion that the cancer-cells are derived from the connective tissue elements alone, and accord at least a certain participation to the epithelial structures.

As we have said before, these cases were ill suited for an investigation for this purpose, the limits of the disease, and the surrounding healthy parts, not being obtained for examination. It was not possible, therefore, to decide to what extent the connective tissue participated in the development.

At certain points, indeed, an accumulation of white corpuscles was seen within the blood-vessels, and occasionally the penetration through the wall, and the accumulation about the vessels, were also observed, showing at least a certain activity of these elements. This communication with the epithelium of the rete, moreover, was found only at one or two points, although a careful search was made for the purpose (see Drawing 1); nor did there appear to be any proliferation of the cells of this layer, as one would expect to find were an active ingrowth taking place into the parts below. The direct participation then of the epithelium in the formation of the new growth, although suggested by appearances found at certain points, did not seem to admit of satisfactory proof, while, on the other hand, the connective tissue showed in all cases signs of a more or less active participation in the process.

In summing up then the result of these observations, we find that in certain cases, —

1. The formation of the cancer-cells is preceded by an escape of the white blood corpuscles through the walls of the vessels, and an accumulation of similar cells in the adjoining lymphatic canals.

2. That this is followed by an apparent transformation of these cells into cells resembling strongly the epithelium of the rete Malpighii.

3. That the epithelium of the parts affected does not appear to take an active part in the process, but may exert a certain influence on the character of the formation taking place.

4. That the cancer-cells lie in the lymphatic spaces of the connective tissue, and do not invade, to any appreciable extent, the lymphatic vessels.

Do these observations afford us an explanation of the very striking peculiarity of the disease, its purely local character, and the immunity both of distant organs and the neighboring glands? Few of the writers, already quoted, endeavor to account for this. Mr. Moore offers as an explanation, the shrinking of the lymphatic vessels and an obstruction to the lymph stream by a growth of connective tissue about them, so that the elements find no outlet to the lymphatic glands. No such alteration of the lymphatics was observed in any of these cases, and the growth of the connective tissue was found to be exceedingly variable: at times the amount seen was quite considerable, as in Case I.; at others it had disappeared almost entirely.

On what does the malignant character of any new formation depend? Chiefly, on the quantity and activity of its cellular elements, on the amount of juices, either inter or intra cellular, which it may contain, or on its richness in blood-vessels.

In these cases we find that the presence of a large number of blood-vessels was not a prominent feature. There did not seem to be that local increase of the vascular supply that one would expect to find in cases of epithelial cancer. The nutrition of the newly formed elements must therefore suffer accordingly. In fact, the dry character of the ulcerated surface is considered one of the most characteristic clinical features of the disease.

The cells can never accumulate in large masses, owing to their low formative power, and the early retrograde changes which they undergo. The latter is due chiefly to the delicate nature of the cells and their imperfect nutrition. They are essentially a short-lived race, the retrograde changes following very closely upon the formative. In this peculiarity of the cells, we find an explanation of the ulcerative character of the disease.

The cancer-cells, when once formed, appear to possess little power to multiply themselves by further proliferation. The masses of cancer-cells certainly do not show any signs of such activity. We find no evidences of an active cell proliferation, and consequently no active outgrowth into the neighboring tissue. Contrast these conditions with what is found in the large-cell variety of epithelial cancer. There the cells are nourished by a rich

net-work of blood-vessels, and when once formed undergo a rapid proliferation, enabling them to penetrate deeply into the tissues about. The retrograde changes do not appear until a late stage of the disease, when the excessive growth cuts off the vascular supply to the more central parts, and a consequent degeneration of the cells follows.

In Rodent Ulcer, the cells rarely extend a line or two below the surface of the ulcer, and beyond its edges. The lymphatic vessels, as we have seen, are invaded at the most to a very limited extent, while in other forms of cancer the cells penetrate freely into the lymphatic net-work about them, and by repeated multiplication are enabled to continue their progress until conditions are arrived at most favorable for the infection of the adjacent glands.

The low formative power of the elements, the absence of power to multiply themselves to any extent, when once formed, and their extremely short-lived character, seem to afford the most satisfactory explanation of the inability of the disease to affect distant parts.

These peculiarities combine to make Rodent Ulcer the type of the mildest form of cancer with which we have to deal.

EXPLANATION OF DRAWINGS.*

Drawing 1.

Vertical section from ulcer of Case V.

a—Epithelial cancer-cells.

b—Connective tissue-stroma.

c—Papillæ containing indifferent cells.

d—Epithelium of rete.

Drawing 2.

Section from a fragment removed from edge of ulcer of Case IV.

a—Branching mass of cancer-cells.

b—Large cells, around which there is a concentric arrangement of cells.

c—Connective tissue-stroma, filled with cells, which have evidently been in active movement.

d—Vessel filled with white blood corpuscles. One or two red corpuscles are also to be seen.

Drawing 3.

Clump of young indifferent cells at periphery of same section.

a a—Central fibres, showing situation of blood-vessel.

b—Indifferent cells.

c—Cancer-cells, forming among preceding.

d—Stroma.

* The power used for these drawings was Hartnack's 9 immersion lens, with 2 eye piece. 1, 2, and 5 have been reduced to one-half the size of the original drawing.

Drawing 4.

Clump of cells seen at deepest point of the disease, in same case. The central vessel is here still preserved.

a a—A blood-vessel, in which the blood corpuscles are distinctly seen.

b—Young cells.

c—Stroma.

d—Branch from blood-vessel, *a*.

Drawing 5.

Vertical section from ulcer described in Case III.

a—Anastomosing tubes of cancer-cells.

b—Young cells occupying papillæ, and upper part of corium.

c—Epithelium of rete Malpighii.

d—Papillæ.

e—Point where the indifferent cells become continuous with cancer-cells.

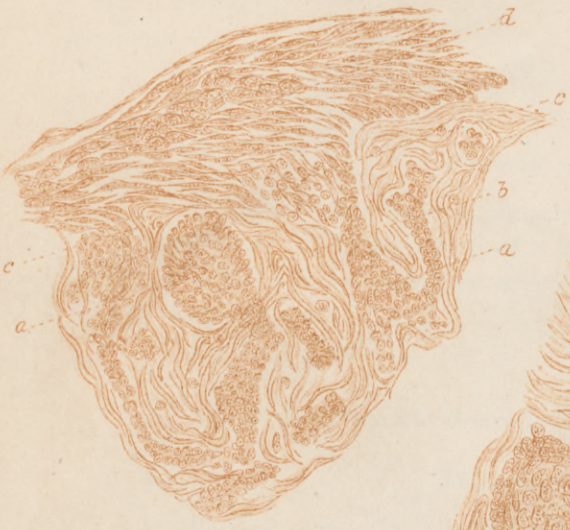
Drawing 6.

Clump of cancer-cells in vertical cut, taken from specimens of Case II. The cells are near the centre of the diseased mass.

a—Epidermic balls.

b—Stroma.

1.



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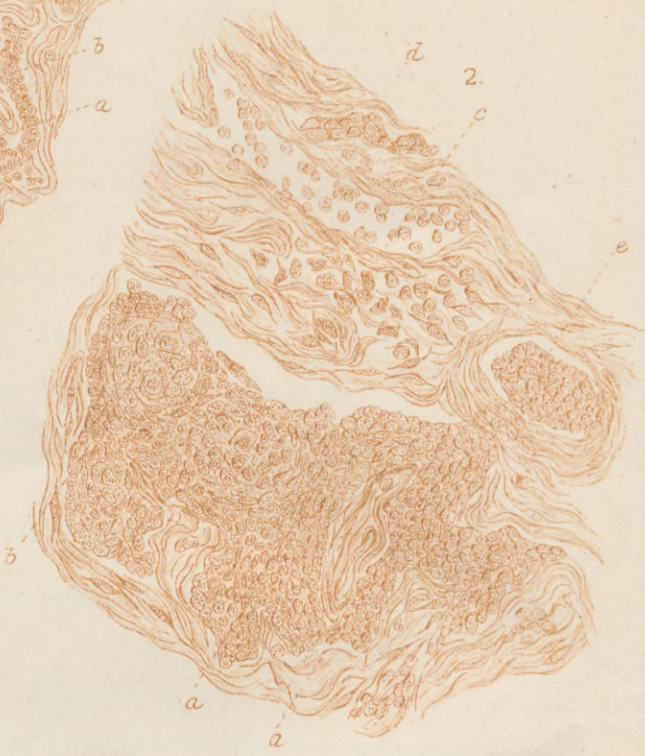
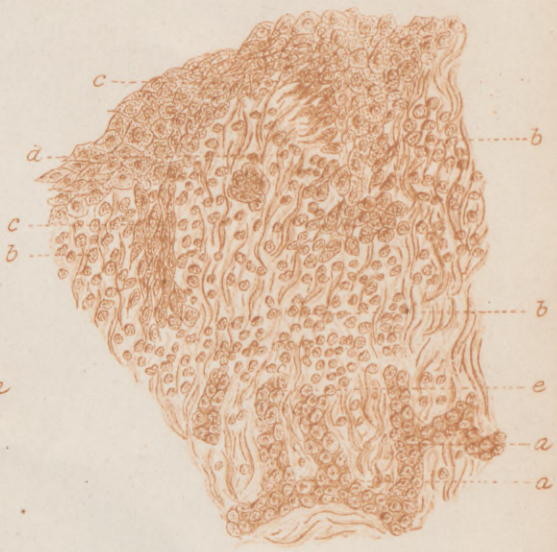


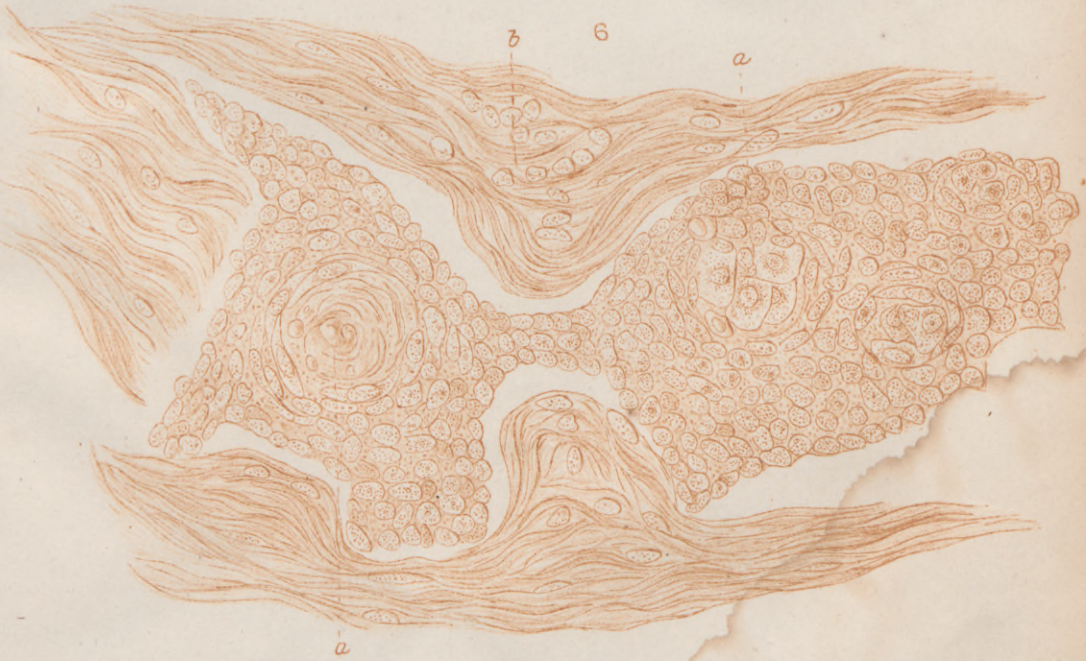
3.

4

5.



6



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