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ACUTE INTERSTITIAL NEPHRITIS.

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PLATES XXXVII AND XXXVIII.

DEFINITION.—An acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependent on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal.

This condition was first described by Biermer (1). He found the kidneys of a child four and a half years old, who died of scarlet fever, greatly swollen, the surface pale, and on microscopical examination showing intense infiltration of the connective tissue with lymphoid cells. He considers the formation of lymphoid tissue here analogous to that found in typhoid fever. The cellular infiltration is more marked in the pyramids than in the cortex. E. Wagner (2) describes a similar case, in which, however, the enlargement of the kidneys was not so marked. The consistency of the tissue was lax, the capsule easily removed, the cortex grayish-yellow, with punctate hæmorrhages. There were accumulations of lymphoid cells in the interstitial tissue most marked in the immediate vicinity of the glomeruli. In a subsequent article (3) he describes the condition under the name of acute lymphomatous nephritis, and considers it one of the four forms of acute Bright's disease. He finds this

form of nephritis most often in scarlet fever, and sometimes in typhoid. The kidneys are greatly enlarged, brittle, the capsule is easily stripped off, the surface is covered with grayish-white elevations which correspond to streaks of cellular infiltration in the cortex. There are accumulations of round cells varying in size in the interstitial tissue. Some of these cells are smaller than leucocytes, others larger. The most acute cases of scarlatinal nephritis are of the lymphomatous form. In three typical cases which Wagner describes there was pharyngeal diphtheria in addition to scarlatina.

Klebs (4) gives a good description of acute interstitial nephritis. The kidneys are enlarged, of lax consistency, the capsule is easily separated, the surface smooth and paler than normal. On section grayish-white nodules, corresponding to fatty degenerated convoluted tubules, are embedded in a rather transparent, gelatinous, grayish background. On microscopic examination the tissue between the tubules is dilated and filled with lymphoid cells. The cells come from the vessels. Letzerich (5) describes a kidney of this character in diphtheria, and regards the cells in the interstitial tissue as fungi. Coats (6), in a case of scarlet fever in an adult, finds the kidneys enlarged and similar in appearance to the leukæmic kidney. The enlargement and pallor of the kidneys are due to infiltration of the cortex with round cells. These are packed between the tubules separating them, but have not destroyed the epithelium. The microscopical appearance closely resembles leukæmia. He afterwards describes the cells in the interstitial tissue as due partly to proliferation of the interstitial cells, partly to emigration of leucocytes. The condition is common around the glomeruli in subacute nephritis.

Kelsch (7) regards acute interstitial nephritis as the typical lesion of the kidney in scarlet fever. He describes the cells as being of an embryonic character, closely packed together and often massed around the glomeruli. Klein (8, 9) found seven cases of well-marked interstitial nephritis in twenty-three cases of scarlet fever which he studied histologically. The interstitial cells are lymphoid in character; they vary in size, the nucleus is round, and two nuclei are often found in a single cell. The infiltration seems to take place first around the large vascular trunks at the base of the pyramids, and from here extends into the cortex. These cells compress the tubules, the epithelium desquamates, and the lymphoid cells enter into the tubules. In these cases albumin is often absent, and there are no symptoms pointing to implication of the kidneys. He thinks that cases which die after the ninth or tenth day of the disease will, as a general rule, show more or less well-marked interstitial changes in the kidneys.

Phisalix (10) takes the ground that acute nephritis accompanying various infectious diseases, such as scarlet fever, is not a parenchymatous, but an interstitial process. In such cases but little change may be found in the parenchyma, while the interstitial tissue is dilated and filled with cells. Weigert (11) does not recognize acute interstitial nephritis as one of the forms of acute Bright's disease. In the acute hæmorrhagic form, he describes, in addition to the hæmorrhages and epithelial degeneration, foci of brightly staining round cells in the interstitial tissue. He does not describe the character of the cells further, and considers the foci to be of an inflammatory character and secondary to the degeneration of the epithelium of the tubules and the destruction of the glomeruli. Waller (12) describes interstitial foci as common in post-scarlatinal nephritis. The cells are due to emigration, fibrous tissue may be formed from them, and a contracted kidney may be the final result of the process. Leyden (13) says that acute nephritis in scarlet fever and diphtheria is of a parenchymatous variety, but foci of small-cell infiltration are frequently found between the tubules and around the glomeruli. Bamberger (14) speaks of interstitial foci as common in the primary form of acute nephritis and in nephritis secondary to other diseases. Dunin (15) regards small-cell infiltration as one of the most characteristic changes in scarlatinal nephritis. The infiltration may affect the entire kidney or be limited to certain areas. These areas are most common close beneath the capsule or around the glomeruli. The epithelial changes may be slight, and there is no relation between epithelial degeneration and the interstitial foci. Fischl (16) finds in scarlet fever dilatation of the adventitia of the small arteries with round-cell infiltration extending from this into the tissue. In the cases of glomerulo-nephritis there is infiltration of the interstitial tissue most marked around those glomeruli which were most affected.

Friedländer (17), in his description of scarlatinal nephritis, describes interstitial septic nephritis as one of the three varieties of scarlatinal nephritis. The kidneys in this are large, lax in consistency, and the markings are obscured; the cortex is of a grayish-red opaque color, with foci of hæmorrhage. The epithelium is but little altered, and the interstitial tissue contains numbers of small round cells. This form of nephritis he finds comparatively rare, occurring only twelve times in 229 cases, and is most apt to be seen in those cases of scarlet fever which are accompanied by diphtheritic septic processes. Cornil and Brault (18) find that acute interstitial nephritis is confined to the acute febrile diseases; they have met with it in scarlet fever and other processes. Nauwerck (19,20) describes in the kidneys, in both scarlet fever and diph-

theria, foci of small-cell infiltration in the labyrinth and about the small and medium-sized veins. The intertubular capillaries may be occluded by cells derived from proliferation of the endothelium. The cells in the interstitial tissue come from emigration, but may be added to by proliferation of the fixed cells. He finds no relation between these interstitial foci and epithelial degeneration.

Langhans (21) has never found a case similar to Wagner's lymphomatous kidney in scarlet fever, but has seen a slight degree of cellular infiltration in the walls of the small veins and around the glomeruli. Crooke (22) finds distention of the capillaries in the interstitial tissue by lymphoid cells and cells derived from proliferation of the endothelium of the vessels. In many cases foci of interstitial infiltration are found both in the labryinth and close beneath the capsule. Litten (23) says that, apart from fatty degeneration and hæmorrhage, the most common lesion found in the kidney in scarlet fever is the inflammatory round-cell infiltration of the interstitial tissue. Foci of this, consisting of closely packed leucocytes, are scattered through the entire kidney, varying in extent with the intensity of the process.

Oertel (24) in his work on diphtheria describes foci of round-celled infiltration both beneath the capsule and in all parts of the tissue. Cellular infiltration is also seen in the walls of the veins and arteries. There is no connection between the accumulations of cells and desquamation of the epithelium.

Sörenson (25) gives the clinical history and the pathological anatomy of a number of cases of scarlatinal nephritis, and among them of three cases in which the interstitial lesions were well marked. In some of these cases there is a whitish opaque rim around the bases of the pyramids, with streaks extending from this into the cortex. V. Kahlden (26) gives a good description of interstitial nephritis in scarlet fever. He finds the cells in the interstitial tissue of unequal size, some smaller, some larger than leucocytes. In a case of diphtheria he finds numbers of cells in the vessels of the tissue between the cortex and the pyramids. These cells are round, in many cases twice as large as a leucocyte; the protoplasm is homogeneous and transparent. The nuclei are round or sometimes indented, and two nuclei are sometimes seen in a single cell. These cells are more frequently found in the arteries than in the veins. Baginsky and Stamm (27) find in the kidneys of scarlet fever patients who die in the first week of the disease more or less extensive interstitial infiltration with round cells. These cells are either collected into masses simulating lymph nodules or are diffused over the entire cortex.

Bernhard and Felsenthal (28) find in diphtheria, along with degenera-

tion in the epithelium, which they consider the principal change, foci of interstitial infiltration beneath the capsule around the glomeruli and in the upper portion of the pyramids. The veins are dilated and contain numbers of leucocytes. Aufrecht (29) gives the clinical history and pathological anatomy of three cases of scarlatinal nephritis which differ from the ordinary form in their early appearance and intensity. In all three cases there are masses of round cells, chiefly about the glomeruli. The changes in the parenchyma he considers independent of the interstitial lesions. Burmeister (30) describes interstitial foci in the kidneys of rabbits which were produced by the injection of chromate of ammonium into the circulation. There is no especial change in the epithelium of the tubules in the interstitial foci. He found similar interstitial foci around the glomeruli in a case of glomerulo-nephritis in a tuberculous subject. Morse (44) produced similar foci of cellular infiltration of the interstitial tissue of the kidney by injecting filtered cultures of staphylococcus aureus into the circulation of rabbits. Turner (31) makes two varieties of nephritis in scarlet fever, the glomerular and the interstitial hæmorrhagic. In the glomerular type interstitial changes are often seen. Rosenstein (32) says the large interstitial kidney, described by Friedländer, is rare in scarlet fever, although even in cases of short duration, with albuminuria from the beginning, there is evidence of interstitial proliferation with focal accumulations of cells around the vessels.

Summing up these descriptions, I find that acute interstitial lesions of the kidneys have been considered as common in scarlet fever, and are regarded by some authors as constituting the most frequent pathological alteration of the kidneys in this disease. This has also been described in diphtheria and in other infectious diseases. The cellular infiltration of the interstitial tissue may be general throughout the kidney, with more intense foci in the cortex. In these cases the kidney is greatly enlarged, in some cases twice the normal size; it is of a lax consistence, and on section is grayish and opaque. In other cases the infiltration appears as circumscribed foci either immediately beneath the capsule or around the glomeruli or at the bases of the pyramids. The cells in the interstitial tissue are almost universally described as lymphocytes, in several cases their large size and the presence of two nuclei in a single cell are mentioned. Cell accumulations have also been described around the large vessels and infiltrating their walls. Von Kahlden describes in one case accumulations of large cells

in the vessels in the pyramids. The cells have been generally considered as coming from the vessels by emigration. Almost all observers state that there does not seem to be any relation between foci of interstitial cellular infiltration and epithelial degeneration. There is general agreement that in scarlet fever the interstitial form of nephritis is most often found when the nephritis develops early in the disease, and is most common in the so-called septic cases. Many of the cases in which the most typical interstitial lesions were found are described as having also diphtheritic pharyngitis. No evidence has been given by cultures that in these cases there was mixed infection with diphtheria.

The text-books on pathology do not devote much space to this condition. Most of the authors do not recognize acute interstitial nephritis as a special type of the disease. Others speak of foci of interstitial cellular infiltration as occurring frequently in acute and chronic nephritis. In many cases the cells in the interstitial tissue are regarded as pus-cells and the condition is confounded with acute suppurative nephritis. Ziegler (33) has a very good description of the minor degrees of the process. In speaking of inflammatory œdema of the kidney he says, " the changes in the vascular stroma may take the form of circumscribed cellular infiltrations of the interlobular and circum-glomerular tissue, a condition of acute disseminated interstitial nephritis. The cellular infiltration makes its appearance in the neighborhood of the stellate and interlobular veins, and is usually so intense in these parts that in stained preparations the infiltrated patches are easily discernible under a low power of the microscope. The cellular aggregations are most numerous in the outer zone of the cortex and in the boundary zone between the cortex and medulla, the middle part of the cortex being seldom much affected." He says nothing of the character or origin of the cells, and thinks the condition may run a subacute course, gradually passing into the parenchymatous type.

The best description of the gross and microscopic condition in such kidneys is given by Orth (34). He says:

" It is rare that œdema is the most essential inflammatory change in the interstitial tissue. I have often seen kidneys in which the tubules and glomeruli were normal and in which the only change consisted in a

small-celled infiltration of the interstitial tissue. Such cases have been described as acute interstitial nephritis, as productive nephritis, as granulating nephritis, and as lymphomatous nephritis. These kidneys are more or less enlarged and softer; the surface is mottled, of a grayish-red or grayish-white color, the markings cannot be distinguished. Such kidneys can be distinguished from those of acute parenchymatous nephritis by the absence of the markings and the cloudiness of the cortex. Microscopically there is an irregular distribution of cells between the urinary tubules. These cells have a round vesicular nucleus, they are not similar to emigrated leucocytes, and I regarded them as due to growth of the connective-tissue cells, although their frequent relation to the small veins would rather speak in favor of emigration."

I have previously (35) reported eight cases of this lesion in the kidney; three of these were from scarlet fever; two from diphtheria; one followed a criminal abortion, and two were of unknown origin. In all the cellular infiltration of the interstitial tissue was the most marked, and in some cases the only change. Since then I have had the opportunity of examining microscopically the kidneys from a great many cases of diphtheria, scarlet fever, and other acute infectious diseases, and in the routine microscopic examination have found cases which showed every degree of alteration and most of which would have been overlooked without microscopic examination. The result of the further study of this important lesion in the kidney has thrown some light on the subject, and certainly caused me materially to change my views as to the origin of the cells in the interstitial tissue. In my previous communication I regarded the interstitial cells as derived from proliferation of the fixed cells of the tissue, particularly from the endothelium of the blood-vessels.

MACROSCOPIC CHANGES.

In the most marked cases the kidneys are greatly enlarged; in one case of diphtheria and measles in a child aged two years the combined weight of the kidneys was 480 grammes. In another child aged eight years, with scarlet fever, the kidneys weighed 400 grammes; in two other cases of diphtheria, one in a child of five, the other in a child of two and a half years, the kidneys weighed 250 and 225

grammes. This extreme size, which may be more than three times the normal, as in the first case mentioned, is rare. In most cases the kidneys were but slightly if at all enlarged. The appearance varies. In the most marked cases the kidney presents an appearance which can be mistaken for nothing else unless it be the leukæmic kidney. The capsule is distended, thin and easily removed, often separating spontaneously on section of the kidney. The fœtal markings are less distinct and often obliterated. The surface is pale, of a peculiar grayish-opaque color, somewhat resembling the amyloid kidney, mottled, with irregular, more hyperæmic areas; the stellate veins of the surface are injected, often showing small punctate ecchymoses around them. In some cases the surface is irregular, due to the projection of small irregular nodules which are more opaque than the surrounding tissue.

On section of such kidneys the normal markings of the cortex are obliterated, and the contrast between pyramids and cortex is less distinct. The great increase in size is principally in the cortex, which may be three or more times thicker than normal. The glomeruli are not injected, and cannot be distinguished. The general color of the cut surface is grayish and opaque, with scattered areas of injection, and a few small scattered ecchymoses. Corresponding to the elevated areas on the surface, there are often areas more opaque than the general cut surface, which extend in lines from the pyramids through the cortex. At the bases of the pyramids the same opacity of the tissue is seen. The tissue of the kidney is soft, lax, and easily broken. It is very moist, and an opaque milky fluid may be pressed out, and often flows from the cut surface. On scraping the tissue with a knife a milky fluid with small granular masses may be removed. In the less marked cases there is usually some degree of mottling, the cut surface is moist, and there are fine opaque lines or points. In many cases the changes are most evident at the bases of the pyramids and marked by a swelling and greater opacity of the tissue here. A very marked degree of change, as shown microscopically, may be present without producing macroscopic differences in the appearance of the kidney.

MICROSCOPIC CHANGES.

Sections of the fresh kidneys, to determine the presence of fatty degeneration, showed this change to be generally present, though in slight degree. Fat was found in the epithelium of the tubules, and principally in the smaller collecting tubules. In a few cases foci of more intense fatty degeneration were found in the convoluted tubules. Occasionally a slight amount of fat was found in the interstitial tissue, but not in the cells infiltrating this.

For microscopic examination thin sections of the tissue were hardened in Zenker's fluid, in corrosive sublimate, in alcohol, and in Flemming's solution. In general the best results are obtained after hardening in Zenker's fluid, and this was used in all of the routine examinations. The other solutions were only used in special cases and where the lesions were evident on macroscopic examination. Various stains were used, the most satisfactory results being obtained by staining deeply with eosin, followed by Unna's alkaline methylene-blue solution.

In the most marked cases examination with low power shows the tubules to be widely separated and an intense cellular infiltration of the interstitial tissue. This is marked in all parts, but is more intense in certain areas. These are most often situated beneath the capsule (Plate XXXVII, Fig. 1) and at the bases of the pyramids, and from these places the infiltration sometimes extends downward or upward. In the middle of the cortex there are also smaller areas of intense infiltration which seem not to be connected either with the areas beneath the capsule or with those at the base of the pyramids. In these areas the interstitial cells are closely packed together, with no intervals between them. Where the infiltration is less intense, the cells lie singly in the tissue. Around all the glomeruli, but outside of the capsules, there seems to be more marked infiltration than elsewhere, save in the areas mentioned. In the pyramids the infiltration is often as intense as in the cortex, extending down to the pelvis.

With high power (Plate XXXVII, Fig. 2) the cells in the interstitial tissue present a striking appearance. Most, and in some cases all of them, are of the same character. They vary somewhat in size

and in shape. They are generally much larger than the polymorphonuclear leucocytes, and may be from two to four times the diameter of a red blood-corpuscle. Their shape varies; the single cells not in contact with one another may be round; but where they are packed together the shape is influenced by the mutual pressure. The nuclei present some variation in size, they are never vesicular, the periphery stains deeply, and there are intensely stained points of variable size in the interior. The stained periphery often projects at certain points into the interior of the nucleus, and in most of the nuclei an intranuclear network connecting the brightly stained points within the nucleus and the points on the nuclear rim can be made out. The general body of the nucleus stains deeply. In most cases there is but a single nucleus in a cell. In others two or even three may be present. The nucleus occupies a very characteristic position. It is eccentric, and when the cells are elongated it lies usually at one of the ends. This eccentric position of the nucleus is sometimes so marked that it apparently projects from the protoplasm.

The amount of protoplasm around the nucleus varies. Most of the cells have a large amount, while in others the nuclei are found with but little surrounding them. The protoplasm is dense and often finely granular. In some of the cells the granulation is much more evident than in others. Even in the cells lying singly in the tissues the contour is not always sharp and round. In many cases both the cells here and in the masses have an irregular outline due to the protrusion of elongated and often knob-like masses of protoplasm. These present every resemblance in shape to leucocytes fixed while in emigration, and there is little doubt that these irregularities of form are due to amœboid movements. There is no appearance of a membrane around any of these cells. Their most characteristic feature is the staining of the protoplasm. With most of the nuclear stains used singly the protoplasm stains faintly, but more intensely than that of the epithelial cells. With strongly alkaline methylene-blue the protoplasm stains deeply, and the blue color is preserved after counter-staining with eosin. A faint bluish tint, giving with the eosin a lilac tint, is often seen in the protoplasm of the epithelial cells, but in the inter-

stitial cells the color is a deep blue. The cells can be instantly distinguished in a section even with a low power by their characteristic color. Nuclear figures are very numerous. As many as three or four are often seen in the field of an oil immersion. The cells in which the nuclear figures are found are large and have an abundant and distinctly granular protoplasm, the granules staining a deep blue.

These cells are found in the interstitial tissue. In all of the sections examined I have never found one of them within a tubule. In the interstitial tissue they lie loosely in the spaces of the tissue, and a few are constantly found in the blood-vessels. They are not phagocytic; neither leucocytes, red blood-corpuscles, nor detritus of other cells are found inclosed in them.

In the very marked cases, in which the kidneys are soft and enlarged, other cells are constantly found in varying numbers in the interstitial tissues. The most numerous are cells corresponding to the lymphoid cells (Plate XXXVII, Fig. 2); the nuclei of these stain very much as do the nuclei of the large cells, and every gradation can be seen between the naked nuclei of the lymphoid cells and the large cells. Polynuclear leucocytes are usually present in varying numbers, depending on the degree of degeneration in the epithelium. In a few cases, especially where the lesions are very marked and the tissue is disintegrated, I have also found cells of the epithelioid type in the interstitial tissue. These cells are, as a rule, larger, the protoplasm is finely granular, staining with eosin, the nucleus is less intensely stained than are the nuclei of the interstitial cells, and clearly vesicular. They can be easily distinguished from the blue-staining cells and there is no transition between them. These epithelioid cells, which are probably derived from proliferation of the tissue cells, are eminently phagocytic. I have found red blood-corpuscles, leucocytes, and in some cases the blue-stained cells inclosed within them. Nuclear figures are occasionally seen in the epithelioid cells, but never to the extent observed in the blue cells.

The epithelium shows various degrees of degeneration, and in places the tubules seemed to be actually destroyed.

The tubules are separated by wide areas of interstitial cellular infil-

tration, and often no tubules can be found in comparatively large areas. The slightest change found in the epithelium is a marked degree of cloudy swelling. In places the cells contain globular masses of hyaline, and the lumen of the tubule may be filled with the same material. In other cases the cells are swollen, vacuolated, and the greater part of the protoplasm may be lost, leaving only a small granular mass about the pale and rather shrunken nucleus. In places the tubules may contain desquamated epithelium or granular masses derived from it. The number of leucocytes present seems to depend upon the degree of destruction of the epithelium; they may be seen in the interstitial tissue, in the epithelial cells, and in the lumina of the tubules. The glomeruli usually show no changes, although cases of typical glomerulo-nephritis may be met with in which acute interstitial nephritis is present as a complication. Granular coagulated material may be present in the capsular space, but even this is often absent.

In the less marked cases (Plate XXXVII, Fig. 1) the general diffuse interstitial infiltration is absent. A few scattered blue-staining cells may be found, but the lesions are eminently focal. In some cases the foci are so numerous that on holding a section to the light they appear as scattered blue specks or lines (Plate XXXVIII, Fig. 3). Most of these areas, when observed with the naked eye or a very low power, have their longitudinal axes in the direction of that of the pyramids. In these foci the cells in the interstitial tissue are in great numbers, but not so numerous as in the foci in the most marked cases. These foci are principally found in three places in the tissue. As a rule, they are most numerous and largest at the bases of the pyramids, and from this point they may extend upward in the pyramidal extensions. Occasionally they are in large masses around the interlobular vessels. Next in frequency the foci are found beneath the capsule around the large branches of the stellate veins, which are often greatly dilated. Smaller foci may be found at various places throughout the cortex, but in the cortex they are most frequent around the glomeruli. The number of foci around the glomeruli varies greatly in different cases. In some there are cell masses around practically every glomerulus, in

others only scattered glomeruli are affected. I have never found a case in which the interstitial areas were confined to the tissue around the glomeruli, but there were numerous cases in which the infiltration was confined to the bases of the pyramids or to the subcapsular cortex.

These focal areas seem to stand in no relation to focal degeneration of the epithelium. In all cases degeneration of the epithelium is present. Where the infiltration is most intense there is apt to be extensive degeneration and even necrosis of the epithelium of the tubules, but this is probably secondary, and due to compression of the tubules and vessels. In these larger areas there are usually numbers of pus cells which may be found within the tubules (Plate XXXVII, Fig. 2). In the smaller areas no evidence of greater degeneration of the epithelium can be found than elsewhere in the kidney, and a high degree of degeneration may be found without any interstitial changes.

These changes in the interstitial tissue are always accompanied by changes in the vessels (Plate XXXVIII, Figs. 4, 5, 6, 7). The interstitial cells are found in the vessels as well as in the tissue, and they may be so crowded in these and in the surrounding tissue that it is difficult to distinguish the vessels. Most of the cells in the vessels have the same character and the same peculiarity of staining as the cells outside. Nuclear figures (Plate XXXVIII, Figs. 5 and 7) are found in these cells, but not in such numbers as in the cells in the interstitial tissue. There are few polynuclear leucocytes among them. The numbers of cells in the vessels are not always proportionate to the numbers in the interstitial tissue. Vessels blocked with cells may show but slight interstitial change, and occasionally interstitial foci are found where but few cells can be made out in the vessels.

In making a systematic study of the kidneys in a large number of cases of acute nephritis special attention was given to the presence of these cells in the vessels. The vessels in which the greatest number were found are always the branches of small veins in the upper part of the pyramid. In a large number of cases such cell accumulations were found in the vessels without any change in the interstitial tissue and without any more than the ordinary degeneration of the epithelium. In some cases all of the veins in this part of

the kidney were so blocked up with cells that on holding a stained specimen to the light there was a decided blue color of the upper part of the pyramid. Such cell collections were occasionally seen in the stellate veins of the cortex and elsewhere, but in many cases they were confined to the veins of the pyramids. Most of these cells in the veins were of the same character as those in the interstitial tissue. The main difference between the cells in the vessels and those in the tissue was that the vessel cells were round and regular in shape. These cell accumulations in the vessels without interstitial lesions were found in 16 out of 103 cases of pure diphtheria; in 1 case out of 19 in pure scarlet fever; in 3 out of 23 in diphtheria and scarlet fever; in 2 cases of diphtheria and measles; in 1 case of pyelo-nephritis, and in 1 case of acute endocarditis; in 24 cases in all.

There can be but one source for the cells in the interstitial tissue; they must come from the blood-vessels. In the first place, there are no cells in the tissue outside of the blood-vessels which could give origin to them. Practically the only cells which we have in the interstitial tissue of the kidney outside of the small collections of lymphoid cells, sometimes seen around the larger veins, are the cells of the blood and lymphatic vessels. It is probable that there are cells belonging to the connective tissue, but it is difficult to demonstrate their presence. These cells in the most advanced cases, in which there is actual destruction of the tissue, do proliferate and mingle with the other cells in the interstitial tissue. The resulting cells are the epithelioid cells, and can be distinguished by the nucleus, the staining of the protoplasm and their marked phagocytic properties, from the interstitial cells. Cells similar to the interstitial cells are found in the blood-vessels in the interstitial cases and in cases in which there are no interstitial lesions. It is impossible to see the irregular shapes and protrusions of the protoplasm of many of the cells in the interstitial tissue without being convinced of their amœboid properties. In a few cases similar changes of form were seen in the cells within the vessels, and in several instances such cells were found in the act of emigration, part of the cell being within and part without the vessel (Plate XXXVIII, Fig. 10). The cells are principally confined

to the vessels in the places I have mentioned. A few may be found in the larger veins, and they are occasionally seen in the vessels of the glomerulus.

The part which these cells play in pathology has received but little attention. Similar collections are most frequently described as small-celled infiltration, and no attention has been directed to their character and source. Unna was the first one who separated out from the cell collections in the interstitial tissue certain cells marked by a peculiar stain of the protoplasm, to which he gave the name plasma cells. Since then they have received considerable attention from the dermatologists and but little from pathologists. I consider the cells I have described in the interstitial tissue identical with Unna's plasma cells. Unna (36) describes in lupus cells, whose protoplasm stained deeply with alkaline methylene-blue, and which do not decolorize as the other cells. He considers them identical with the cells described by Waldeyer as plasma cells, and gives them the same name. As these cells appear in the tissue the connective-tissue cells disappear, and he supposes that they are derived from the connective-tissue cells. In his first article on the subject Unna supposes that these cells were peculiar to the tuberculous process. He subsequently (37) describes the cells more fully, modifying his first description in several particulars. In this article he considers them as greatly hypertrophied connective-tissue cells. The blue staining is due to the presence of fine granules imbedded in the substance of the cell. He finds that they play an important part in the pathology of skin diseases, and that certain new formations in the skin, to which he gives the name plasmomata, may be composed of them. The tumor cells in the round-cell sarcoma are derived exclusively from these cells, and they form the chief part of the cellular infiltration around other tumors. They are exclusively a pathological product, and are never found in embryonic or in normal tissues.

Jadassohn (38), while confirming the presence in the tissues of the cells described by Unna, denies that they are to be differentiated from the other cells of the tissue solely by Unna's method of staining. He finds them in various inflammatory affections of the skin, and thinks

they may be present in any form of acute inflammation with the exception of the suppurative. While he is uncertain about their origin, he denies that they are related to the connective-tissue cells.

Waldeyer at first believed that the cells described by Unna were identical with his plasma cells, but he afterward (39), in an article on the cells of the connective tissue, declares that the latter belong to the group of Mast-cells, which are different from the cells described by Unna. He does not think the word plasma cell should be used to designate any of the connective-tissue cells.

Marschalkó (40) has written an important article bearing on the presence and origin of these cells. He finds them not only in various tumors and chronic inflammatory conditions, but also in acute inflammation produced by the injection of carbolic acid into the liver, and in acute suppurative inflammations produced in the subcutaneous connective tissue. They appear in the tissue within twenty-four hours, and are derived from the lymphoid cells of the blood. These accumulate in the vessels in the periphery of the inflamed area, pass through the walls, and change into plasma cells in the tissues. He lays more stress on the morphology of these cells, the character of the protoplasm and nucleus, and the constant eccentric position of the latter, than on any peculiarity of staining. He finds them in the vessels of the liver at a distance from the inflammatory focus and in the vessels of the spleen. He also finds them in small numbers in the spleen, lymph-glands, and bone-marrow. He makes the very important observation that after the injection of tuberculin their numbers in the vessels of the spleen are greatly increased.

Hodara (41), working under the direction of Darrier, took up again the question of the presence of plasma cells in the normal tissues. He does not find them in the bone-marrow, lymph-glands, or spleen, in the normal embryo, child, or adult. He thinks that Marschalkó confounds the plasma cells with certain large mononuclear leucocytes, for which he proposes the name polyeidocytes, the name having reference to the variability of form which characterizes these cells. In some instances these cells may so resemble the plasma cells in size, form, character, and staining of the nucleus and protoplasm, as to be

indistinguishable from them. In general the difference between the polyeidocyte and the plasma cell consists in the great irregularity of form of the polyeidocyte and the variability in form, size, and staining of its nucleus. The only other article of importance concerning the plasma cells is that of Justi (42), who takes up the part which they play in the formation of the granulation tissue. Justi has included among the plasma cells large cells in the granulation tissue containing several nuclei. These cells are characterized as much by the character of the nucleus and protoplasm as by their manner of staining. Justi places the plasma cells among the leucocytes, and thinks they are derived from the lymphocytes.

It is perfectly evident that the cells we have described in the interstitial tissue, and many of those in the cell accumulations in the blood-vessels of the kidney, are the plasma cells of Unna. As to their origin, I hold the same opinion as Marschalkó, and they are derived from the lymphocytes. In the kidney they enter into the interstitial tissue by emigration from the blood-vessels. They may emigrate from the vessels as plasma cells, or they may be formed from emigrated lymphoid cells. They have been seen in the act of emigration, and the shapes of many of the cells in the interstitial tissue can leave no doubt as to their amœboid character. A great part of those in the interstitial tissue come from proliferation. It is difficult to understand why previous observers of these cells should have been so uncertain as to their mitotic division, and should have found it necessary to resort to the very uncertain theory of multiplication by direct division of the nucleus. Nuclear figures are as numerous in the interstitial cells, and as definite considering their size, as will be found in a rapidly growing carcinoma. Certainly there is no difficulty in explaining the numbers of these cells met with in the kidney by emigration and proliferation. Nuclear figures are also found in the cells within the blood-vessels, but not to the same extent as in the interstitial tissue.

With few exceptions, we have examined in every case of diphtheria and scarlet fever sections hardened and stained in the same way not only from local lesions, but from the liver, spleen, lungs, lymph-

glands, and bone-marrow. A detailed account of these examinations will appear later. It will be sufficient to say here that in nearly every case of both diphtheria and scarlet fever, but particularly diphtheria, both those in which interstitial lesions in the kidney were marked and where they were absent, great numbers of plasma cells are found in the spleen and bone-marrow. They are also found in the lungs, liver, capillaries, and lymph-glands. The principal seat of their formation seems undoubtedly to be the spleen, where they are formed from the lymphoid cells. Sections of the spleen in some cases show nearly the whole of every Malpighian body converted into plasma cells. Groups of them were also found in the pulp of the spleen and in the vessels. In all these places there are numerous nuclear figures. It is not probable, as Unna assumes, that direct nuclear division ever takes place in these cells. In the bone-marrow, which is red in nearly every case, numerous groups of plasma cells are also found. In the lungs they are found in great numbers in the blood-vessels, but especially in the connective tissue of the lung around the bronchi and blood-vessels. In places they play an important part in the cellular exudation in the focal pneumonia, but are found principally in the vessels and interstitial tissue, rarely in the alveolar exudation. In the lymph-glands, save in those in the immediate vicinity of the throat lesions, they are much less numerous than in the spleen and bone-marrow. In the liver they are in the capillaries, and probably come there from the spleen. Sections from the larger blood-vessels containing blood, and of decolorized blood-clot from the heart, are not so satisfactory for examination as the tissues, but they are found here in small numbers.

Investigations are now in progress to determine the presence and numbers of these cells in the peripheral circulation in cases similar to those in which they are found in the tissues.

With regard to the presence of the plasma cells in normal tissues, it is remarkable that those investigators who have taken up this question should have left out of consideration the organ in which they are always present in enormous numbers. In the alimentary canal, from the stomach to the anus, all the cells of the tissue between the epithe-

lium and the muscularis mucosa are practically plasma cells. They are comparatively rare in the follicles in this region.

In the tissues examined for fatty degeneration, both in fresh sections and after Flemming, there is no fat found in the plasma cells. Evidence of cell necrosis, as shown by nuclear detritus, is not found in them. The only evidence of degeneration which may be present in the plasma cells, both in those in the interstitial tissue and in those in the blood-vessels (Plate XXXVIII, Fig. 8), consists in the presence of vacuoles in the cells, or hyaline droplets which occupy the same position as to the vacuoles, and which often stain homogeneously with methylene-blue.

We are led to the belief that the plasma cells have their origin in the lymphoid cells from the similarity of their nuclei to those of the lymphoid cells, and from the presence of transitional forms between the lymphoid and plasma cells, as shown by the gradual accumulation of protoplasm of the same character as that of the plasma cell around the nucleus. This does not take place evenly around the nucleus, but always at one side. The constant eccentric position of the nucleus of the plasma cell is one of its marked characteristics.

In the examination of the kidneys of the autopsies in the last two and a half years I have found 42 cases of acute infectious diseases in which acute interstitial nephritis was present. The service in the hospital is an acute one, and there are comparatively few autopsies on chronic cases. All of the cases in which interstitial infiltration with plasma cells was found are included in the 42 cases; those in which only lymphoid cells were found around the large interlobular veins are not included. The majority of the interstitial cases come from the acute infectious diseases of children, which make up a large part of our autopsy material. In 103 cases of pure diphtheria a varying extent of interstitial change was found in 24. In 20 cases of pure scarlet fever interstitial lesions were found in 5. In 23 cases of mixed infection of diphtheria with scarlet fever, interstitial nephritis was found in 5, and in 2 out of 5 cases of diphtheria and measles. The other diseases in which the lesion was found were measles and whooping-cough, 1; empyæma, with subsequent diphtheria infection, 1;

lobar pneumonia and pericarditis, 1; epidemic cerebro-spinal meningitis, 1; lobar pneumonia, 1; acute glomerulo-nephritis, 1; acute endocarditis following abortion, 1.

Acute interstitial nephritis is far more common in the infectious diseases of children, and is occasionally seen in other acute infectious diseases. This fact and the focal character of the lesions suggest at once the agency of bacteria. The general diffuse degeneration of the epithelium which was so constantly found is evidently to be referred to the action of some soluble toxic substance. The results of the bacteriological investigation, both by microscopic examination of sections stained for bacteria and by cultures of the organs made at the autopsies, have not borne out the bacteriological theory. In all cases cultures were made at the autopsies from the primary lesions of the disease, whatever its character—from the blood, lungs, liver, kidneys, and spleen. The results of the cultures from the kidneys in the 42 cases of interstitial nephritis were as follows: In 24 cases of pure diphtheria the kidney was sterile in 6. In 11 the colon bacillus was found; in 1 case the staphylococcus aureus; in 5 cases the streptococcus pyogenes; in 8 the diphtheria bacillus, and in 1 the bacillus fœtidus. In the 5 cases of pure scarlet fever the colon bacillus was found in 2, the streptococcus in 3, and the staphylococcus in 1. In the 8 cases of mixed infection of diphtheria with scarlet fever or measles 2 were sterile; in 3 the streptococcus, and in 3 the colon bacillus was found. In the other 6 cases the colon bacillus was found in 3; the staphylococcus aureus in 2; the streptococcus pyogenes in 4; the pneumococcus in 1, and 1 case was sterile. I have included the colon bacillus in the result of the bacteriological examination, although I am not inclined to regard the presence of this as determined by cultures made at the autopsy as a matter of much etiological value. The result of the bacteriological examination of the kidneys in the same diseases, but in which interstitial lesions were not present in the kidneys, have shown the same results. The kidneys were sterile or the same organisms were present in about the same proportion. It is obvious from this that we cannot lay any weight on the presence of bacteria in the kidneys as a causative factor in the acute interstitial lesion.

In seeking an explanation of the focal character of these lesions their situation must be taken into account. They are most marked: First, in the boundary zone of the pyramids; secondly, beneath the capsule; and thirdly, around the glomeruli. There can be but two explanations for the presence of these foci. Cells are brought to the foci by the vessels, they emigrate from the vessels into the interstitial tissue, but probably the greater part of those in the interstitial tissue come from proliferation. Either there must be some physical condition in the circulation which may account for their accumulation in the vessels, or there must be some substance in the tissues which exerts a positive chemotaxis for just these cells, and which causes both their accumulation in the vessels and their emigration into the tissues. There is much which seems on purely physical grounds to favor the accumulation of cells in the long veins of the pyramids. These veins are long, they are numerous, and the circulation in them is slow. It is possible that the large cells in the circulating blood might be mechanically retained in these vessels. Weight is given to such a supposition by the fact that even small substances in the circulating blood may be mechanically retained here.

The hæmatogenous abscesses of the kidney, both those produced experimentally and those seen in man, are more apt to be formed in the upper part of the pyramid than elsewhere in the kidney. The organisms for the most part pass through the capillaries of the cortex; they become attached to the walls of the veins, and increase there, finally occluding the vessel and producing necrosis in the surrounding tissue. The presence of large numbers of these cells without any emigration speaks in favor of such a mechanical theory. The same would hold true, though to a less extent, in regard to the cell accumulations in the stellate veins. Occasionally the cells are seen here without interstitial lesions, but to nothing like the same extent as in the pyramidal vessels. Nuclear figures are found in the cells within the veins. The cells can pass through the vessels into the interstitial tissue, and the same conditions which led to their production and proliferation in the first place could cause them to proliferate in the interstitial tissue. Tumor cells can act in this way, and there is cer-

tainly some temptation to regard the interstitial foci very much in the same light as tumor metastases.

Such a mechanical theory fails to explain the interstitial foci around the glomeruli. Occasionally a few cells may be found in the vessels of the glomeruli (Plate XXXVIII, Fig. 9) without any interstitial lesions. Not only do periglomerular foci speak against the mechanical theory, but these cells are not found to the same extent in the vessels elsewhere, even in organs where the conditions of the circulation would seem to favor their presence. A few are almost constantly found in the capillaries of the liver, but their production in the spleen would explain this. They are found in the vessels of the spleen and bone-marrow, and in both of these places they are evidently produced. On the other hand, assuming that their presence in the kidney is due to some substance which exerts a positive chemotaxis for them, there are equal difficulties in an explanation. They are not attracted by simple degeneration and necrosis of tissue, as are the polynuclear leucocytes, and are not simply secondary to epithelial degeneration. Dr. Morse in a study of cantharadin poisoning (not yet published) has shown most extensive degenerative lesions, and even necrosis, without any change in the interstitial tissue and without leucocytes.

Ribbert (43) has recently published an interesting article in which he endeavors to explain the focal accumulation of cells in the kidney. In this article he calls attention to the locality of the foci of cellular infiltration and atrophy. He finds in chronic nephritis the lesions in the same situations which I find in the acute interstitial process. Ribbert explains this localization by the degeneration produced in the irregular tubules (Schaltstücke) by the concentrated toxic urine, and by the toxic urine passing directly through the thin capsules of the glomeruli. The pyramidal lesions are due in part to the toxic action of the urine in the collecting tubules, and in part to toxic substances which have passed into the tissue, passing along the lymph spaces to the large lymphatics in the boundary zone. It is possible that the general degeneration of the epithelium which we find in these cases may be due either to the toxic qualities of the urine or of the blood. The interstitial lesion may be due to some substance excreted by the

kidney, the foci being determined either by the action of this material where it becomes more concentrated, or where it escapes into the tissue, or the paths which it takes in the tissue. It is possible that the physical conditions of the circulation in the kidney may play a part, and possibly an important part, in determining the foci.

But little is gained from the clinical study of these cases. There was albumin in the urine, as there is in all cases of diphtheria. In none of the cases was there marked diminution in the amount of urine, and in none was there œdema. There was apparently nothing in the clinical history of the cases which called especial attention to the condition of the kidneys. In the literature of the disease there are some cases in which the clinical history is given. In Biermer's case, the disease being scarlet fever, the renal symptoms began two weeks before death, with marked diminution in the amount of urine, and dropsy followed by uræmia. In 3 cases of acute lymphomatous interstitial kidney in scarlet fever which Wagner reports, 1 died on the tenth and 2 on the seventeenth day of the disease. All 3 of the cases had pharyngeal diphtheria. Klein found the condition most frequently in those patients with scarlet fever who died after the ninth day of the disease. Friedländer found the lesions, which he describes as interstitial septic nephritis, in those cases of scarlet fever which are accompanied by severe diphtheritic septic processes.

The disease has a rapid course, and normal urine may be seen even twenty-four hours before death. Usually there is no œdema. It is probable that the 12 cases which Friedländer described, and which were from 229 autopsies on scarlet fever, represented marked types of the disease in which the lesions were evident macroscopically. Had he made systematic microscopic examinations he must have found minor degrees of similar lesions much more frequently. Sörensen gives the clinical histories of 3 cases. He also says the interstitial form is most common in cases of severe diphtheritic septic scarlet fever, and appears early in the disease. In one of his cases there was slight œdema and ascites.

In addition to these 42 cases, in which the interstitial lesions of the kidney were due to a general disease, 3 were found in which the interstitial process was due to the local action of bacteria.

The first case was one of ascending ureteritis and pyelonephritis. The kidneys were enlarged, weighing 390 grammes (small, slender woman), injected, somewhat œdematous, and on section whitish-yellow streaks in the cortex extended from the bases of the pyramids toward the capsule. The tissues in these areas of infiltration were not softened. Cultures from these areas gave colon bacilli and a few colonies of streptococci. On microscopic examination of sections in some of the larger areas there was a mass composed of necrotic tissue and filled with nuclear detritus. There were small areas where the necrotic tissue seemed to have been composed of pus cells, but for the most part the remains of the cells and nuclei seemed to have come from large cells. In the periphery of the larger foci, and in the whole extent of the smaller, there was intense infiltration of the tissue with plasma cells. Sections from the ureter and pelvis of the kidney showed slight superficial necrosis, comparatively few pus cells, and great numbers of plasma cells. Plasma cells were found in the vessels in the neighborhood of the foci.

The second case was one of hæmatogenous abscesses of the kidney following carbuncle of the neck and thrombosis of the lateral sinuses. The kidneys contained numbers of small abscesses, which were most numerous in the boundary zone of the pyramids. Cultures showed a general infection with staphylococcus aureus. Sections showed typical metastatic abscesses with masses of large micrococci in the centre, and around these a mass of pus cells with much nuclear detritus. In the tissue on the outside of the abscesses there were numbers of large epithelioid cells which often contain micrococci and other cells inclosed in them. Outside of these there was extensive infiltration, with plasma cells. Plasma cells were found in the vessels.

The third case showed both processes, a general interstitial nephritis and small abscesses with surrounding infiltration with plasma cells. This was from a case of scarlet fever complicated with extensive abscess-formation beneath the scalp. Cultures showed a general staphylococcus infection.

In all three cases the spleen was enlarged, and on section showed large numbers of plasma cells in the tissue.

SUMMARY

Acute interstitial nephritis is found in the infectious diseases of children, particularly in diphtheria and scarlet fever, but may be met with in other infectious diseases.

The disease is characterized by general and focal infiltration of the interstitial tissue of the kidney with cells which correspond to those which Unna has described under the name of plasma cells. The focal character of the infiltration is marked; even in the cases in which all parts of the kidney show some interstitial cellular infiltration the cells are most abundant in certain foci. These foci are found in three places: in the boundary zone of the pyramids, in the subcapsular region of the cortex, and around the glomeruli. A considerable number of cases is found in which the blood-vessels of the boundary zone of the pyramids contain numbers of lymphoid and plasma cells without any infiltration of the interstitial tissue. The new cells in the interstitial tissue are due to emigration from the blood-vessels and multiplication by mitotic division of the cells which have emigrated. The cells can emigrate as plasma cells or as lymphoid cells, and the latter may change into plasma cells in the tissues. In the normal individual, plasma cells may be formed in the mucous membrane of the intestine, where they practically form the entire tissue between the epithelium and the muscularis mucosa, and to a limited extent in the spleen. In diphtheria, in scarlet fever, and probably in a number of infectious diseases, plasma cells are formed in great numbers in the spleen and bone-marrow, and to some extent in the lymphatic glands. In the spleen they are formed from the cells of the Malpighian bodies, which are often principally composed of them, and to some extent from the cells in the pulp. They are formed from the lymphoid cells.

No adequate explanation is found for the focal character of the lesions in the kidneys. There is some ground for believing that the physical conditions of the circulation may have something to do with their accumulation in the vessels in certain places. It is also possible that in the interstitial foci there may be soluble substances which exert a positive chemotaxis for them. Such substances may be found

in the urine, which may exert its influence on the interstitial tissue in different places. The explanation of the foci cannot be found in primary focal degeneration of the epithelium. Epithelial degeneration in these cases is always present, but it is diffuse. In foci where it is more intense and due to the interstitial changes, polynuclear leucocytes are found in the tissue, in the degenerated epithelium and in the tubules. Polynuclear leucocytes and not plasma cells are attracted by degenerated tissue. The foci are not due in these cases to the local action of bacteria.

In a number of the cases in which interstitial nephritis was found the kidneys were shown to be sterile both by cultures and by microscopical examination. In cases where bacteria were present they were found only in small numbers in cultures and not on microscopical examination, and their connection with the foci could not be demonstrated.

In three cases plasma cells were found in the interstitial tissue in definite bacterial diseases of the kidney. In these cases they were not found in connection with the lesions produced directly by the bacteria, but in the periphery of the purulent foci.

DESCRIPTION OF PLATES XXXVII AND XXXVIII.

PLATE XXXVII.

Fig. 1. Circumscribed focus of interstitial nephritis just beneath cortex. The large vein to the right of the specimen is a branch of the stellate vein. Zeiss AA, No. 2 ocular. All the other figures, with the exception of Fig. 3, are drawn with 1/12 Zeiss, ocular 2. All are drawn by camera.

Fig. 2. Plasma cells in interstitial tissue between tubules; the epithelium of the middle tubule is degenerated, the tubule contains polymorphonuclear leucocytes.

PLATE XXXVIII.

Fig. 3. Section of kidney magnified five times to show the granular appearance of the section, due to interstitial foci.

Figs. 4, 5, 6, and 7. Vessels in boundary zone, containing plasma cells. In 5 and 7 nuclear figures are seen.

Fig. 8. Vessel in boundary zone, containing two degenerated plasma cells.

Fig. 9. Section of vessel of glomerulus, showing plasma cells in vessel.

Fig. 10. Emigration of plasma cell from small vein in boundary line.

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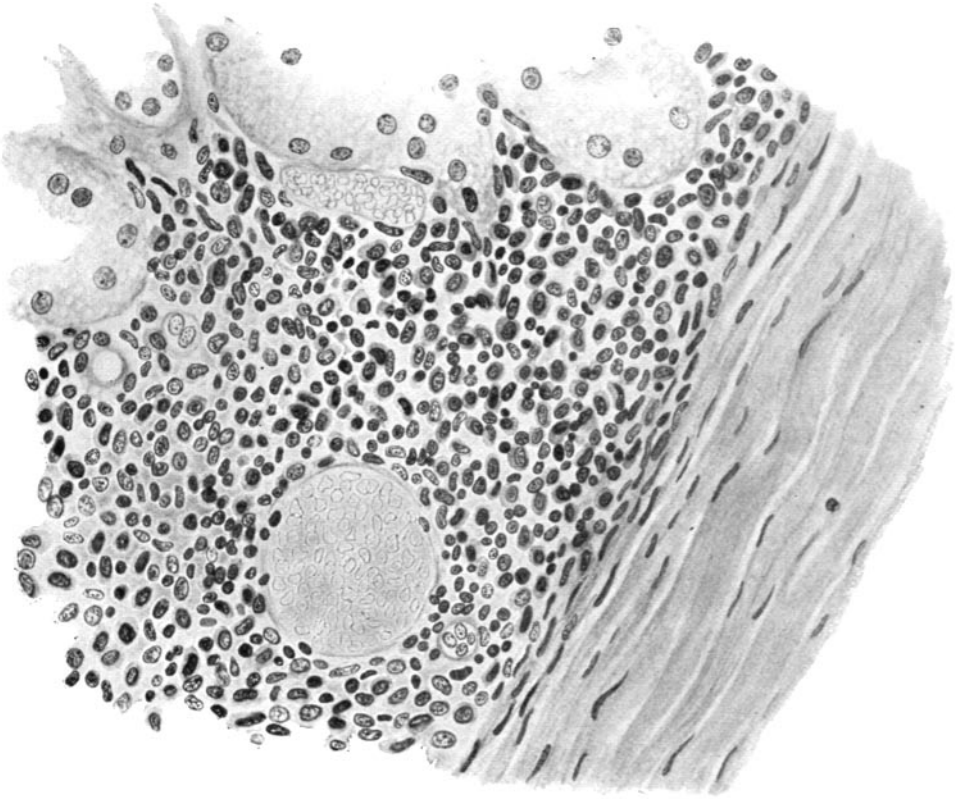

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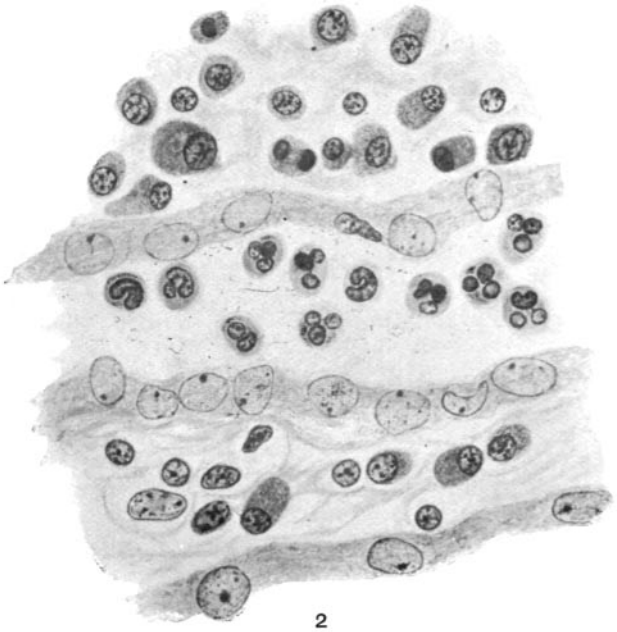

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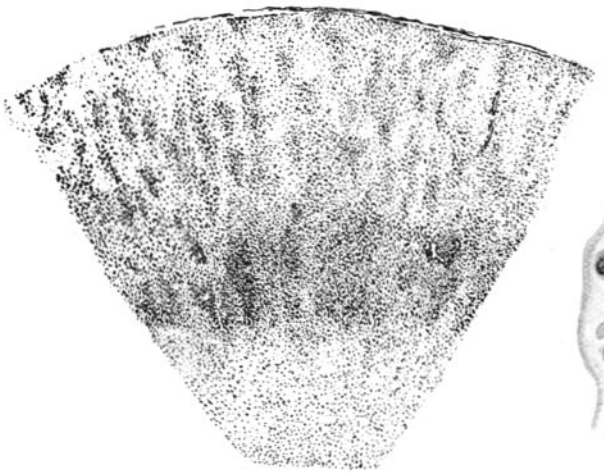

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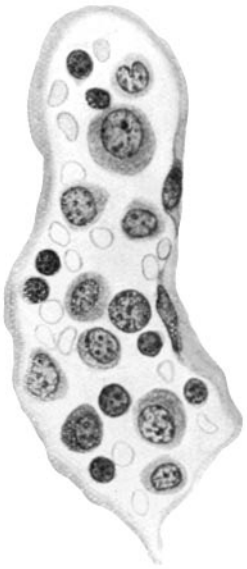

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