HISTOLOGICAL CHANGES IN THE ISCHEMIC KIDNEY *

WITH SPECIAL REFERENCE TO THE JUXTAGLOMERULAR APPARATUS

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Since the discovery by Goldblatt [1] that persistent elevation of blood pressure may be induced by renal ischemia, there has been extensive investigation of the mechanism responsible for the hypertension, as well as a search for some humoral pressor factor or substance. The site of origin of this substance is unknown, although some investigators [2-5] have suggested that it may be a product of the ischemic kidney or formed in the blood flowing through the ischemic kidney, or, if formed elsewhere, retained by the kidney under the conditions of ischemia experimentally produced. Because there may be no demonstrable interference with the excretory functions of the ischemic kidney, it is unlikely that the vasopressor effect is due to a defect of glomerular filtration.

It has been demonstrated that at the vascular pole of the renal glomerulus, in the angle between the afferent and efferent arterioles, there exists a group ("Polkissen") of cells of special structure forming part of a juxtaglomerular apparatus.† These cells, which have been discussed by Ruyter,[6] Oberling,[7] Goormaghtigh,[8] and Spanner,[9] resemble those of smooth muscle, except for their lack of myofibrils. Cells of similar appearance are seen in the cutaneous myoarterial glomus (Spanner,[9] Masson,[10] Schumacher,[11] Clara,[12, 13] and Popoff [14]), in the glomic structures of the carotid body and the cardioaortic zone (Goormaghtigh and Pannier [15]), and in arteries and arterioles elsewhere (Goormaghtigh [16] and Spanner [9]). Characteristic pathological changes occur in these cells of animals with experimental hypervitaminosis D_2 (Goormaghtigh and Handovsky [17]), and in human beings with scarlet fever (Goormaghtigh [8]).

This report presents a description of the changes seen in these cells in dogs and rabbits in which persistent hypertension had been

* Received for publication January 15, 1940.

† The juxtaglomerular apparatus is in fact composed of two distinct cell groups, one of which is not mentioned in this paper.

induced by renal ischemia. A more detailed report on the cytology of these cells in the kidney of the rabbit has been published.[18]

Methods and Materials

The kidneys of 12 dogs in which experimental hypertension had existed for periods ranging from 24 hours to 17 months were removed, and portions of the organs were fixed in Bouin-Hollande's fluid or in Zenker-formalin. Serial paraffin sections stained by the trichrome method of Masson were made in numbers sufficient to reconstruct the course of an interlobular artery with its terminal arterioles and glomeruli (Fig. 1).

Moderate constriction of the left renal artery (method of Drury [4]) was effected in 3 young rabbits weighing 500 gm. After 3 weeks their kidneys were removed, fixed, sectioned and stained in the same manner as those of the hypertensive dogs. Control observations were made on similarly treated tissue from the kidneys of normal dogs and rabbits.

I am grateful to my colleagues of the J. F. Heymans Institute (C. Heymans, J. Bouckaert, K. Grimson and A. Samaan), and to my former associate, L. Elaut, for ischemic kidneys of dogs. The kidneys made ischemic with externally adjustable clamps (Grimson [19]) were especially valuable. A tabulation of this material is shown in Table I.

Observations

Dogs: After 24 hours of renal ischemia the cells of the juxtaglomerular apparatus are always enlarged and increased in number, and bulge into the glomerulus. After 8 to 17 months of renal ischemia the intraglomerular protrusion is less prominent, but granules have appeared in the afibrillar cells and there is intercellular lipoid infiltration, fibrosis and hyalinization.

The changes in the juxtaglomerular apparatus are accompanied by others in the glomerulus, in the afferent arteriole, in the interlobular arteriole and in the cells of the intercalated segment,* which is anatomically in contact with the juxtaglomerular apparatus.[20, 21, 22] In the afferent arteriole the afibrillar cells may become large and reduce the lumen of the vessel.

* By intercalated segment is meant the distal part of the tubule contortus II (*cf.* G. C. Huber, in Special Cytology, Cowdry, E. V., 1928, 1, 686, lines 28, 29, 30).

Some glomeruli become smaller and many probably disappear. Glomerular hyalinization is seen. In one instance, of the 35 glomeruli counted, 9 were atrophic (but not sclerotic). The others were moderately enlarged. Fibrous adhesions between the glomerular tuft and Bowman's capsule sometimes appear. The vascular pole of the glomerulus is always enlarged and contains more cells than normal, especially in the early stage of glomerular

TABLE I

Animal number	Weight	Duration of renal ischemia		Systolic blood pressure	
		Right kidney	Left kidney	Before renal ischemia	During renal ischemia
	kg.			*mm. Hg.*	*mm. Hg.*
26139	10	10 days	10 days	120	188 170
7239	6	8 days	8 days	144	216
17239	10	24 days	24 days	110	170
24239	12	24 hrs.	24 hrs.	...	...
27339	7	14 days	3 days	...	208 204
28339	9	24 days	7 days	146	238
30339	12	8 days	22 days	140	176
18439	10	21 days	25 days	120	190
10539	17	15 days	7 days	...	206
23539	8	8 days	15 days	...	200
101138	6	Nephrectomy	8 mos.	154	182 206 200
21635	8	Nephrectomy	17 mos.	135	200 204

atrophy; the increased cellularity is still observed 17 months after clamping the renal artery.

In the primary divisions of the renal artery and in the interlobar artery, some of the medial smooth muscle cells become atrophic; others lose their myofibrils and often show active nuclear mitosis. In brief experiments edema, fluid and lipoid material appear in the intercellular spaces. In long experiments collagen is deposited in the intima and superficial media. These changes lead to the formation of fibrotic plaques in positions where medial smooth muscle cells have lost their myofibrils.

In the interlobular prearterioles, especially at their bifurcations,

large, multinuclear afibrillar cells appear and replace almost all the medial smooth muscle cells (brief experiments).

Rabbits: Renal ischemia in the rabbit induces the appearance in every juxtaglomerular apparatus of many large afibrillar cells, and most of these cells acquire cytoplasmic granules which normally are found only in the superficial layer of the cortex. Although in the rabbit most of the changes are found in the juxtaglomerular apparatus, a few granulated cells of the same type appear in the interlobar and interlobular prearterioles and in the afferent arteriole to the glomerulus.

In the intercalated segment the epithelial cells show vacuolization, and lipoid material accumulates between cells. The intercalated segment disappears entirely if the corresponding glomerulus becomes atrophic, while the remaining portions of the tubular system may persist.

In kidneys from both dogs and rabbits the afibrillar cell appears to be a smooth muscle cell which has become transformed into a cell of another type, without myofibrils, and with granules in the cytoplasm. The cellular transformation can be followed through by the observation of graded change from spindle cells with sparse granules to large epithelioid cells with numerous acidophilic and basophilic granules. Often the cells show mitotic figures or are multinuclear.

Recapitulated, the following changes [20–25] occur: (1) enlargement and lipoid infiltration of the cells of the juxtaglomerular apparatus, together with intercellular fibrosis; (2) transformation of smooth muscle cells to cells devoid of myofibrils, but presenting polychromic granules, vacuoles and hypertrophic nuclei; (3) vacuolization and intercellular lipoid infiltration of the intercalated segment; (4) atrophy of some glomeruli, enlargement of others and a decrease in their total number; (5) medial atrophy in renal arteries and arterioles; and (6) fibrotic patches in the interlobar arteries.

As I have indicated elsewhere,[18] afibrillar cells which contain polychromic granules intermingled with minute vacuoles are found in the superficial juxtaglomerular apparatuses of normal rabbits. The variations of their cytological features suggest the existence of a glandular cycle. The small granules which stain only after Zenker-formalin fixation are mitochondria. The large granules

are preserved by any fixative and are not a sign of retrogressive change, but may possibly indicate a stage in the formation of a vasopressor substance, perhaps an internal secretion of the afibrillar smooth muscle cell.

Discussion

Harrison and coworkers,[26] and Pickering and Prinzmetal[27] have reported extraction of a vasopressor substance from, and we have demonstrated the presence of granulated afibrillar cells in, the renal cortex of normal rabbits. In the normal animal the function of these cells may be that of the maintenance of vascular tonus. Since under the conditions of experimental renal ischemia these cells become larger and more numerous, it may be that the coincident hypertension is caused by their elaboration of a vasopressor substance.

In a study of the normal human kidney Becher[28] described cells which lie close to the arteriolar wall and ascribed to them an endocrine function. The term "Goormaghtigh-Becher cells," which Clara[12,13] gave them, is inaccurate, as the cells which Becher observed are probably part of the intercalated segment, whereas our own observations have shown that the afibrillar granular cells occur only in the arteries and arterioles.

Although afibrillar cells are present in the arterioles of other organs, it is only in the kidney that they acquire granules, which is of significance when considered with the fact that ischemia of organs other than the kidney does not produce hypertension.[1,29]

The proximity of the intercalated segment to the juxtaglomerular mass of afibrillar cells may imply some important functional relationship, and the observations described here demonstrate that pathological changes in one are always accompanied by changes in the other. That stimulation of the afibrillar cells is the exciting factor would seem probable from the following observations: Unilateral ureteral ligation in the rabbit does not lead to hypertension,[30] nor is there hyperplasia of the afibrillar cells in such animals. On the other hand, in scarlet fever, there is often hyperplasia and granulation of the afibrillar cells, and the transient hypertension may be followed by sustained elevation in blood pressure. Similarly, an adequate dosage of vitamin D_2 induces a marked hyperplasia of the afibrillar cells and these experimental

animals are hypertensive. Denervation of the carotid sinus and cardioaortic zones in dogs is followed by hypertension, and the kidneys exhibit hyperplasia of the juxtaglomerular apparatus, as Elaut has shown.[31, 32]

Summary

1. In dogs and rabbits renal ischemia is followed by hypertrophy and hyperplasia of afibrillar cells present chiefly in the walls of renal arteries and arterioles and in the juxtaglomerular apparatus. Accompanying this change there is atrophy of the ordinary smooth muscle cells of the arteriolar media and regression of some of the glomeruli.

2. In larger arteries afibrillar cells appear and lead to the subsequent formation of fibrotic patches in the arterial media and intima.

3. The close anatomical relationship which exists between the juxtaglomerular apparatus and the intercalated segment may indicate that cells of the segment in some manner influence the function of the afibrillar cells. Coincident pathological changes in the two structures are constantly seen.

4. Certain constantly observed anatomical features suggest that these specialized afibrillar cells secrete and liberate a pressor substance, and that in the hypertensive state this function is abnormally active.

Conclusions

On the basis of observations made by the author and others, it is suggested that a vasopressor substance may be formed in the afibrillar cells which exist in various portions of the renal vascular system, and that under certain conditions there may be liberation of an excessive amount of the pressor substance which leads to hypertension. The polychromic granules observed with appropriate fixation and staining may thus be actually incretory granules.

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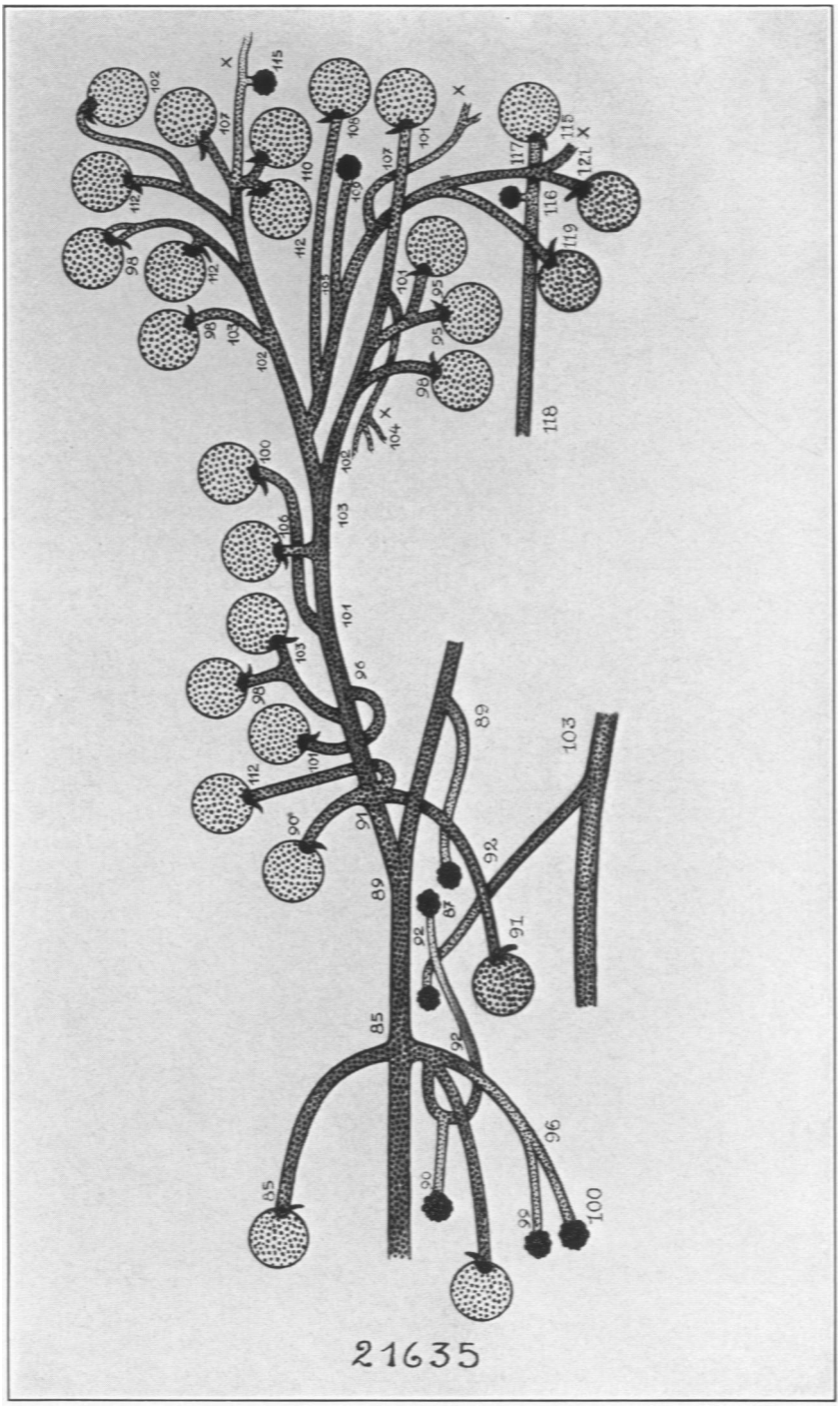
DESCRIPTION OF PLATES

PLATE 83

FIG. 1. Dog 21635. Renal ischemia 17 months. Diagram of a reconstructed interlobular prearteriole and its branches. The figures indicate the number of slides of a series (three sections on each slide). Enlarged glomeruli are stippled; atrophic glomeruli are solid black. At X are aglomerular Ludwig arterioles.



I

Goormaghtigh Histological Changes in the Ischemic Kidney

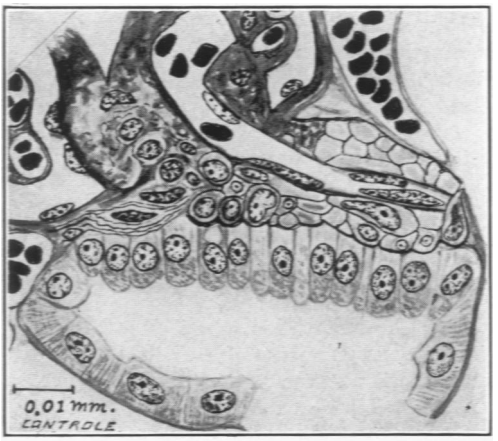
PLATE 84

FIG. 2. Normal dog. The vascular pole of a glomerulus. The afferent arteriole is cut in longitudinal section. The juxtaglomerular apparatus is composed mainly of afibrillar myoblasts with large nuclei. The columnar epithelial cells belonging to the adjacent intercalated segment are vacuolated at their bases. Zenker-formalin fixation. Masson's trichrome stain.

FIG. 3. Normal rabbit. The vascular pole of a glomerulus. The juxtaglomerular apparatus is composed of afibrillar myoblasts of varying size; some have clear cytoplasm, in others the cytoplasm is dark. In one large cell there are acidophilic granules. Bouin-Hollande's fixative. Masson's trichrome stain.

FIG. 4. Dog 24239. Renal ischemia 24 hours. The vascular pole of a glomerulus. The juxtaglomerular apparatus is enlarged and the afibrillar myoblasts are binuclear, vacuolated and swollen. There are vacuoles in the epithelium of the adjacent tubule. Bouin-Hollande's fixative. Masson's trichrome stain.

FIG. 5. Dog 24239. Renal ischemia 24 hours. An entire glomerulus. The juxtaglomerular apparatus is enlarged and afibrillar myoblasts bulge into the glomerular tuft. The vas efferens is seen in longitudinal section. There is vacuolization of the adjoining epithelium of the intercalated segment. Bouin-Hollande's fixative. Masson's trichrome stain.



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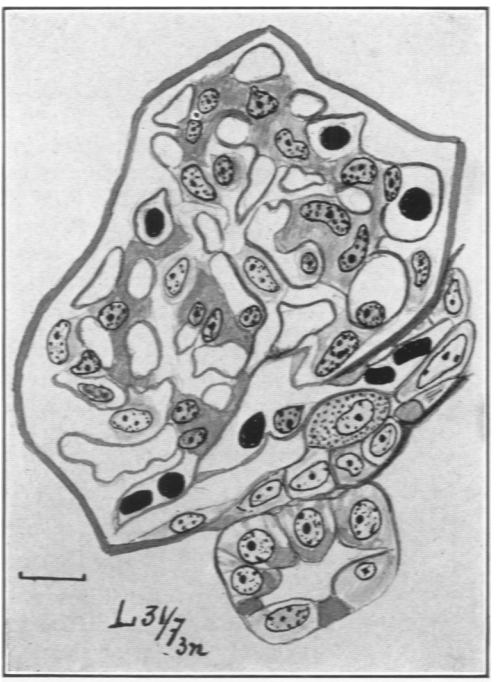

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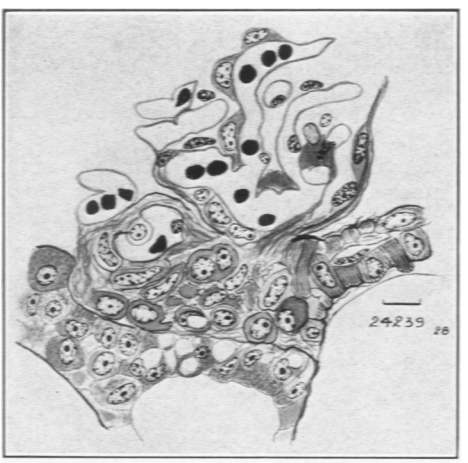

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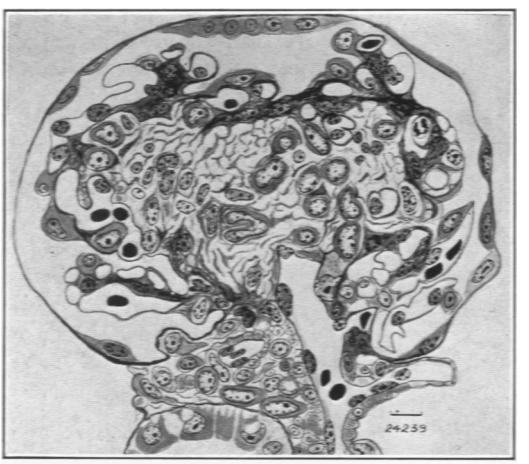

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Goormaghtigh

Histological Changes in the Ischemic Kidney

PLATE 85

FIG. 6. Dog 21635 (26). Renal ischemia 17 months. The vascular channels are engorged. The glomerulus and juxtaglomerular apparatus are enlarged, and in the latter there are lipoid infiltration and discrete sclerosis. There are vacuoles in the epithelial cells of the adjoining intercalated segment, but the cells are of different structure than those not in contact with the juxtaglomerular apparatus. Zenker-formalin fixation. Masson's trichrome stain.

FIG. 7. Dog 21635. Renal ischemia 17 months. The distal end of an afferent arteriole. An afibrillar cell with granules is in contact with the vacuolated epithelium of the intercalated segment. Fixation and stain as in Figure 6.

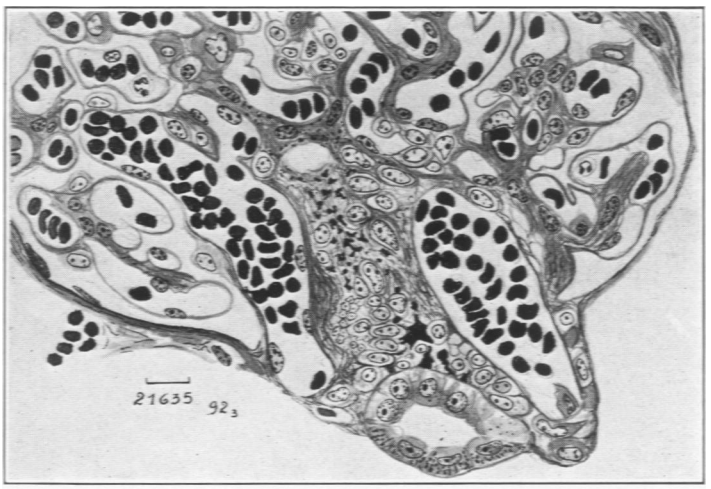
FIG. 8. Dog 30339. Renal ischemia 8 days. The bifurcation of an interlobular prearteriole. There are hypertrophy and hyperplasia of the afibrillar cells. Note the mitosis, the binuclear cell and the normal smooth muscle cells with distinct myofibrils. Bouin-Hollande's fixative. Masson's trichrome stain.

FIG. 9. Dog 21635. Renal ischemia 17 months. An interlobar artery. Notice the alteration in the medial smooth muscle cells and the thick intimal cushion of afibrillar myoblasts. Fixation and stain as in Figures 6 and 7.

FIG. 10. Dog 101138. Renal ischemia 8 months. A primary division of the renal artery. A multinuclear afibrillar myoblast lies in the midst of the atrophic medial smooth muscle cells. Bouin's fixative. Masson's trichrome stain.

FIG. 11. Dog 21635. Renal ischemia 17 months. The intercalated segment. A cell has become isolated from the segment which has undergone retrogressive changes. Zenker-formalin fixation. Masson's trichrome stain.

FIG. 12. Rabbit 31–96. Severe renal ischemia 3 weeks. A patent interlobular prearteriole. All of the smooth muscle cells have become afibrillar, and most of them contain polychromic granules. Notice that the nuclei are normal.



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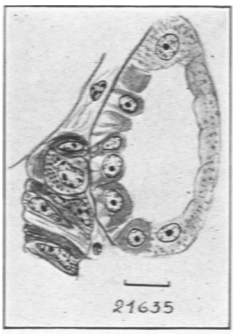

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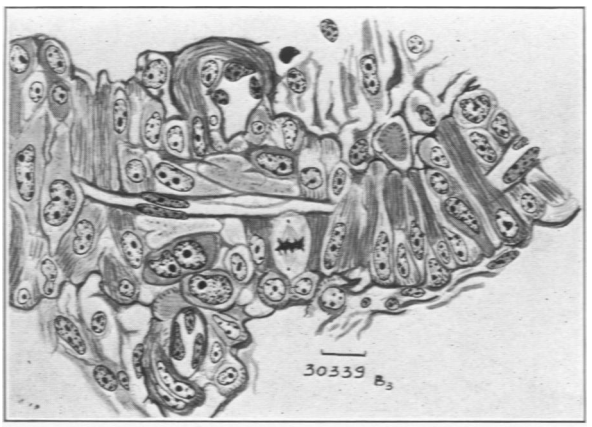

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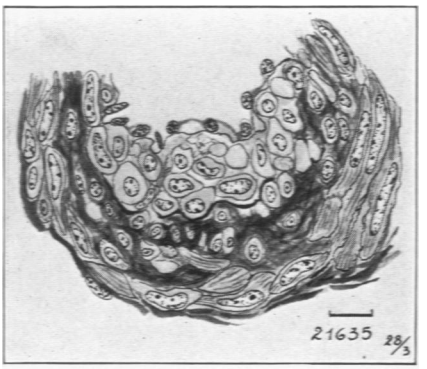

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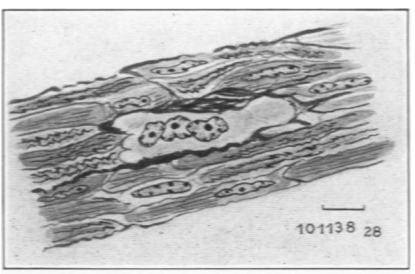

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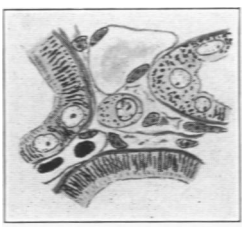

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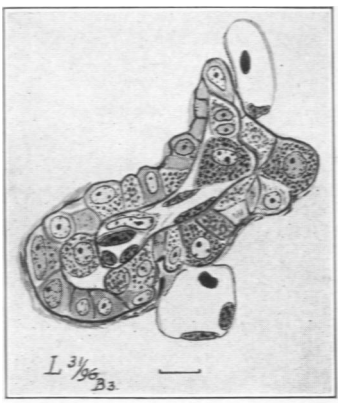

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