THE RENAL LESION OF EXPERIMENTAL CANTHARIDIN POISONING.*

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PLATE 102.

The interest recently aroused in the study of experimental nephritis by physiological methods, and the tendency to classify the various forms of induced nephritis as either tubular or vascular, has resulted in a thorough investigation of the anatomical changes and physiological reactions in the experimental lesions. With almost unanimous consent the lesions caused by cantharidin and arsenic have been grouped as vascular nephritis, and those caused by potassium chromate, uranium nitrate, and corrosive sublimate as tubular nephritis. The distinction is based chiefly on the presence of striking histological changes in the latter group and their absence in the former, and also on the marked changes, in the first group, in the power of the vessels to respond to sensory stimuli, to adrenalin, and diuretics. Most investigators recognize, however, that while in a given nephritis either vascular or epithelial lesions predominate, the lesions are never exclusively vascular or tubular. The severe or long continued epithelial forms always give eventually the characteristics of the vascular form, and the vascular nephritis always shows some lesion of the epithelial cells of the tubules. This I have expressed elsewhere as follows: "By combining physiological and anatomical methods in the study of nephritis it is possible to distinguish types of nephritis in which either tubular or vascular changes predominate, and are essentially characteristic of the lesion produced, but it is not possible to say that a given poison produces

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exclusively tubular or exclusively vascular lesions." \(^1\) Still, at the time this statement was made I considered cantharidin to be essentially a vascular poison with little power of producing epithelial injury. This is the view also of others (Schlayer and Hedinger, Takayasu, and MacNider) who have attempted to differentiate vascular and epithelial forms of nephritis.

Doubtless all investigators in this field have seen the swollen granular and vacuolated tubular epithelium, with more or less solution or disintegration of the cells, but these lesions have been so slight in contrast with the extensive necrosis of chromate and uranium poisoning that they have been considered as relatively unimportant in view of the very definite vascular disturbance of cantharidin nephritis brought out by physiological methods of study.

A recent chance observation of the occurrence of abundant mitoses in the tubular epithelium in the stage of repair of cantharidin nephritis has, however, caused me to believe that the epithelial lesion is very important. I have therefore examined the material which has accumulated during several years' study of experimental nephritis and have also reviewed the literature of cantharidin nephritis.

It is of interest that Cornil and Brault, in 1884, described mitotic figures in the epithelium of the convoluted tubules in late poisoning (fourth day); but, with the exception of Lyon, in 1904, who also found them (after the fourth day), this has not been noted by later investigators. All investigators describe the presence of red blood cells, lymphocytes or polymorphonuclear leukocytes, or serum, or some combination of these in the capsular space and to some extent in the convoluted tubules (Cornil and Brault, and Eliaschoff). Browicz found a granular material without nuclei in the capsular space and lymphoid cell infiltration in the interstitial tissue. Aufrecht produced in the rabbit a chronic nephritis as the result of daily injections over a period of several weeks.

Degenerative changes in the epithelium of the convoluted tubules are described by all these investigators, and Welch, Lyon, and Opie regard the large pale cells seen in the capsular spaces as desquamated cells arising from the proximal convoluted tubule and not, as did Cornil and Brault and Eliaschoff, as swollen lymphoid cells.

It is in connection with this accumulation of desquamated tubular epithelium that the observation of numerous mitoses is of importance. The combination of desquamation and of repair, as shown by mitoses, indicates severe epithelial injury, and while the degree

\(^1\) Pearce, R. M., Hill, M. C., and Eisenbrey, A. B., loc. cit., p. 223.
of this injury cannot be determined by the study of the desquamated cells, which may pass out with the urine, it can be estimated by the study of the number of mitotic figures in the regenerating tubular epithelium. In a series of kidneys from ten animals (dogs and rabbits), I find four representing lesions later than the third day. Of these, three, one from the rabbit and two from dogs, show numerous mitotic figures in the tubular epithelium. The rabbit represents the third day and the two dogs the fifth day of cantharidin poisoning. The notes on one of these animals follow.

A dog weighing 7 kilos received daily 0.013 gm. of cantharidin in acetic ether, subcutaneously. The urine increased in amount on the second day and then decreased until the fifth day, with increase in specific gravity. Albumin was found in the urine daily. The sediment contained red blood corpuscles, epithelial cells, and hyaline and granular casts. On the fifth day physiological observations were made of the response of the kidney to various stimuli, and on introducing a bladder cannula anuria was found to be present.

Histological examination shows granular degeneration of the cells of the convoluted tubules and of the loops of Henle with free desquamated epithelial cells, more abundant in the loops of Henle than in the convoluted tubules. Such cells are for the most part large and swollen and very granular, with necrotic or pyknotic nuclei, and sometimes with hyaline droplets in the protoplasm. In both convoluted tubules and the loops of Henle mitotic figures are found, but only with difficulty in the latter; in the convoluted tubules they are very abundant. Two and three dividing cells in the cross section of a convoluted tubule are not uncommon and sometimes four or five may be seen (figure 1). The cells undergoing mitosis have a large amount of protoplasm which projects into the lumen and frequently when several such cells are close together the lumen appears to be blocked. No mitotic figures are seen in the collecting tubules. Frozen sections stained by Sudan III and hematoxylin show a moderate number of coarse fat globules in the loops of Henle, and here and there in the convoluted tubules foci of fine fat globules. Casts are only occasionally seen. The glomeruli are congested, but otherwise appear normal.

This extensive repair indicates that the preceding injury to the tubular epithelium must have been very severe, and that however
dominant the evidence of vascular injury may be, as shown by physiological methods, there is a concomitant epithelial destruction of unusual degree. The extent of this epithelial destruction was clearly indicated by Lyon, but his observations have been largely disregarded. He states: “In the rapid poisoning cases there is most diffuse necrosis of the secreting cells. The tubules are dilated, and there is entire disintegration of the inner portion of the cell, so that only the basal portion remains attached to the basement membrane. In this basal portion, which is granular and stains deeply, the nucleus is frequently retained.” The incomplete destruction of the cell, that is the persistence of the nucleus, would explain the rapid and profuse mitosis which I have described.

CONCLUSION.

Although the study of experimental nephritis by physiological methods shows that the most striking effect of cantharidin is injury of the blood vessels, the great abundance of mitotic figures in the tubular epithelium in the stage of repair points to an equally widespread and severe epithelial injury. Caution must therefore be observed in ascribing the physiological disturbances of kidney function caused by cantharidin as due exclusively to a vascular injury, and in regarding cantharidin nephritis as a pure type of vascular nephritis.

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EXPLANATION OF PLATE 702.

Fig. 1. The figure shows a convoluted tubule with five mitotic figures and a single mitotic cell of an adjacent tubule. The section is from the kidney of a dog that had received small amounts of cantharidin daily and was chloroformed on the fifth day. 1/12 oil immersion lens; No. 4 eye piece.
FIG. 1.

(Pearce: Renal Lesion of Experimental Cantharidin Poisoning.)