STUDY XIX.*

GLOMERULAR LESIONS IN ACUTE EXPERIMENTAL (URANIUM) NEPHRITIS IN THE RABBIT.†

HENRY A. CHRISTIAN, M.D., AND JAMES P. O'HARE, M.D., BOSTON.

(*From the Laboratory of the Department of the Theory and Practice of Physic, Harvard University.*)

In a previous paper one of us[1] described a lesion in the glomeruli of the rabbit's kidney following injections of uranium nitrate. This lesion consisted in the appearance of hyaline droplets in the walls of the capillaries of the glomerular tuft and appeared in kidneys which showed degenerative lesions in the epithelium of the tubules. In a second paper[2] another type of glomerular lesion was described in the kidney of a rabbit (Rabbit 106) that had received four subcutaneous injections of five milligrams of uranium nitrate at twenty-four-hour intervals, and was found dead twenty-four hours after the last injection. This lesion consisted in the formation of fibrin thrombi in the capillaries of many glomeruli.

In connection with studies on the effects of diuretics in acute experimental nephritis and from animals dying early in an attempt to produce chronic lesions by means of a chemical and bacteria, many kidneys showing the lesions of acute nephritis of the uranium nitrate type have become available for the study of the glomerular lesions in the rabbit.

The glomerular lesion consisting of the appearance of hyaline droplets in the capillary wall has been found with great frequency, but it is not necessary to describe it in this paper, as its relative frequency of occurrence in the rabbit and its relation to dosage of uranium nitrate is quite well shown in Table A in Study IV. (loc. cit.).

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*There have been published previously a series of studies on experimental cardio-renal disease by Drs. H. A. Christian, R. M. Smith, and I. C. Walker: Studies I. and II., Boston Med. and Surg. Jour., 1908, clviii, 696, and 1908, clix, 8; Study III., Jour. A.M.A., 1909, liii, 1792; and Studies IV., V., VI., VII., VIII., IX., X., XI., XII., XIII., XIV., and XV., Archives of Int. Med., 1911, viii, 468–551 and by Dr. H. A. Christian and James P. O'Hare: Studies XVI., XVII., and XVIII., in press.

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The glomerular lesion consisting of fibrin thrombi (Fig. I., Rabbit 396) in the capillaries is not very frequently encountered. It was found in only one (Rabbit 106) of thirty-eight rabbits in Table A (loc. cit.), while the hyaline droplet lesion was encountered in eighteen. In a very considerable number of rabbit kidneys examined since then this thrombotic lesion has been seen in six additional animals. Sometimes almost every glomerulus contains fibrin thrombi, sometimes only an occasional one. In some glomeruli practically every capillary loop shows thrombi, in others only an occasional loop.

Rabbit 377. — Weight, 2,580 grams. January 29 and 30, 3⅛ milligrams of uranium nitrate subcutaneously per kilo of body weight; January 31, February 1, 2, 3, and 4, 5 milligrams of caffein by stomach tube per kilo of body weight. Found dead February 5. Microscopic: a few glomeruli show fibrin thrombi and others show hyaline droplets.

Rabbit 380. — Weight, 1,960 grams. December 30 and 31, 3⅛ milligrams of uranium nitrate subcutaneously per kilo of body weight. Found dead January 6. Microscopic: numerous glomeruli show a few fibrin thrombi, and many show hyalin droplets.

Rabbit 387. — Weight, 2,590 grams. January 29 and 30, 3⅛ milligrams of uranium nitrate subcutaneously per kilo of body weight. January 31, February 1, 2, 3, 4, and 5, 5 milligrams of caffein by stomach tube per kilo of body weight. Found dead February 6. Microscopic: slightly more glomeruli than in Rabbit 377 show fibrin thrombi, but no hyaline droplets are seen.

Rabbit 389. — Weight, 2,200 grams. January 13 and 14, 3⅛ milligrams of uranium nitrate subcutaneously per kilo of body weight. January 15, 16, 17, and 18, 28.6 milligrams of diuretin by stomach tube per kilo of body weight. Found dead January 19. Microscopic: almost every glomerulus shows thrombotic lesion, but no hyaline droplets are seen.

Rabbit 396. — Weight, 1,770 grams. January 13 and 14, 3⅛ milligrams of uranium nitrate subcutaneously per kilo of body weight. January 15, 16, and 17, 28.6 milligrams of diuretin by stomach tube per kilo of body weight. Found dead January 18. Microscopic: almost every glomerulus shows thrombotic lesion and there are numerous hyaline droplets.

Rabbit 504. — December 11, 12, and 13, 3⅛ milligrams uranium nitrate intravenously per kilo of body weight. December 15 found dead. Microscopic: a very few glomeruli show fibrin thrombi. Hyaline droplets are found in some of the glomeruli.

Another type of glomerular lesion, not previously described

by us, has been found in seventeen rabbits studied in connection with the experiments referred to earlier in this paper. This lesion, when well marked, consists of the appearance in the glomerulus of a rounded mass in size varying from one-eighth to three-fourths the diameter of the glomerular tuft and composed in large part of fibrin which is usually rather coarse (Fig. II., Rabbit 626). In the fibrin are caught blood or polymorphonuclear leucocytes in varying amount. The remaining uninjured part of the glomerulus is often crowded aside and compressed by the fibrin mass. In kidneys showing this lesion extensively the hyaline droplet lesion of the glomeruli is usually well marked and there is considerable evidence of degeneration of the cells in the tuft (Fig. III., Rabbit 626, see glomerulus only partially in field). The tufts themselves are distinctly more cellular than normal and the capillaries less filled with blood than under normal conditions (Fig. IV., Rabbit 340). Examination of different stages of the lesion here described indicates that it is essentially a hemorrhage into the glomerular tuft. In some glomeruli a small pool of blood may be seen (Fig. V., Rabbit 336); the blood appears to be outside of the lumen of the capillary, but within that portion of the capsular epithelium reflected over the capillary tuft. At least in these early stages no blood appears in the space between the tuft and the capsule. This blood clots gradually (Fig. III.) and in clotting enmeshes in the fibrin varying numbers of red blood corpuscles and leucocytes. Sometimes a sort of hyaline transformation of red blood corpuscles and fibrin takes place in part of the clot (Fig. VI., Rabbit 561; Fig. VII., Rabbit 557; Fig. VIII., Rabbit 336). As the lesion progresses hemorrhage may occur into the capsular space (Fig. IX., Rabbit 367) and blood be found in the lumen of the tubules. This is particularly apt to occur when the process is severe and develops rapidly. It would seem that the degenerative lesions described above (hyaline droplets, etc.) result in a weakening of the capillary wall of the tuft. Endothelial proliferation may cause impeded circulation. Under these conditions any factors increasing the circulation through the

glomerulus would be likely to result in rupture of the capillary and hemorrhage. In some glomeruli a slightly different development of the lesion may have taken place. Areas were seen suggesting that first a considerable cell proliferation took place, then degeneration with disintegration of the central portion, finally red blood cells found their way into the central degenerated part and clotting took place (Fig. X., Rabbit 336). With either mechanism the developed lesion would present the same appearance. These lesions may be termed hemorrhagic in distinction from the thrombotic glomerular lesions described in the first part of this paper.

The hemorrhagic lesions were seen in the following rabbits; in some they were very numerous, in others very infrequent:

Rabbit 310. — Three and one-third milligrams of uranium nitrate subcutaneously per kilo of body weight on three successive days, followed by .1 gram caffein subcutaneously per kilo of body weight on two successive days. Killed 24 hours after last dose. Microscopic: numerous glomeruli show hemorrhagic lesion.

Rabbit 312 — Weight, 1,140 grams. Treatment same as 310, except one more dose of caffein given. Killed 24 hours after last dose. Microscopic: very many glomeruli show hemorrhagic lesion.

Rabbit 324. — Weight, 1,400 grams. Three and one-third milligrams uranium nitrate subcutaneously per kilo of body weight on three successive days. On day following last dose was given .1 gram caffein intravenously, and 24 hours later was killed. Microscopic: glomerular lesion as in Rabbit 310.

Rabbit 329. — Weight, 1,320 grams. November 1, 2, and 3, 3⅓ milligrams uranium nitrate subcutaneously per kilo of body weight. November 4 and 5, caffein .1 gram per kilo of body weight by stomach tube. November 6, found dead. Microscopic: glomerular lesion as in Rabbit 310.

Rabbit 330. — Weight, 1,160 grams. November 1, 2, and 3, 3⅓ milligrams uranium nitrate subcutaneously per kilo of body weight. November 4, 5, and 6, .1 gram caffein per kilo of body weight by stomach tube. Animal died immediately after last dose, probably from asphyxia. Microscopic: glomeruli rarely show hemorrhagic lesion.

Rabbit 336. — Weight, 1,260 grams. November 7, 8, and 9, 3⅓ milligrams uranium nitrate subcutaneously per kilo of body weight. November 10, .1 gram caffein per kilo of body weight by stomach tube. November 11, killed. Microscopic: very many glomeruli show hemorrhagic lesion.

Rabbit 349. — Weight, 1,780 grams. November 22, 23, and 24, 5

milligrams uranium nitrate subcutaneously. November 23, 24, and 25, .4 gram diuretin by stomach tube. November 26, killed. Microscopic: few glomeruli show hemorrhagic lesion.

Rabbit 367. — Weight, 1,790 grams. December 4, 3 milligrams uranium nitrate subcutaneously; December 9, 5 milligrams uranium nitrate subcutaneously; December 11, 3 milligrams uranium nitrate subcutaneously; December 13, 5 milligrams uranium nitrate subcutaneously; December 15 and 18, .25 cubic centimeter of 24-hour bouillon culture B. coli communis intravenously. December 21, found dead. Microscopic: very few glomeruli show hemorrhagic lesions.

Rabbit 387. — See page 228 for statement about the rabbit. Microscopic: in addition to thrombotic lesion already referred to, a few glomeruli show hemorrhagic lesions.

Rabbit 554. — Weight, 1,200 grams. January 13 and 14, 3½ milligrams uranium nitrate intravenously per kilo of body weight. January 17, found dead. Microscopic: fairly numerous glomeruli show hemorrhagic lesions.

Rabbit 557. — Weight, 1,120 grams. January 13 and 14, 3½ milligrams uranium nitrate intravenously per kilo of body weight. January 15 and 16, morning and afternoon, 14 milligrams diuretin intravenously per kilo of body weight. January 16, afternoon, died. Microscopic: a few glomeruli show hemorrhagic lesions.

Rabbit 561. — Weight, 1,400 grams. January 13 and 14, 3½ milligrams uranium nitrate per kilo of body weight. January 15, 10 A.M., 14 milligrams diuretin intravenously per kilo of body weight; 6.45 P.M., same. January 16, 9.45 A.M., same. Died January 16, 10.45 A.M. Microscopic: a considerable number of glomeruli show hemorrhagic lesions.

Rabbit 611. — Weight, 1,350 grams. January 28 and 29, 3½ milligrams uranium nitrate intravenously per kilo of body weight. January 30, 11 A.M., .42 milligram spartein sulphate intravenously per kilo of body weight; 4.30 P.M., same. January 31, 8.30 A.M. and 5.30 P.M., same. February 1, 8 A.M. and 1 P.M., same. February 2, 11.15 A.M. and 6 P.M., same. February 3, found dead. Microscopic: very occasional glomerulus shows hemorrhagic lesion.

Rabbit 620. — Weight, 1,350 grams. January 28 and 29, 3½ milligrams uranium nitrate intravenously per kilo of body weight. January 30, 11.30 A.M., 5 milligrams theocin sodium acetate intravenously per kilo of body weight; 5 P.M., same. January 31, 9.30 A.M. and 5.30 P.M., same. January 31, died almost immediately after last injection. Microscopic: very occasional glomerulus shows hemorrhagic lesion.

Rabbit 625. — Weight, 1,370 grams. February 4 and 5, 3½ milligrams uranium nitrate intravenously per kilo of body weight. February 6, 10.30 A.M., 4 cubic centimeters sterile water intravenously per kilo of body weight; 5.30 P.M., same. February 7, 9.30 A.M., same. February 7, found dead at 4 P.M. Microscopic: in a considerable number of glomeruli hemorrhagic lesions are seen.

Rabbit 626. — Weight, 1,370 grams. Treatment same as Rabbit 625.

February 8, died at 10 A.M. Microscopic: many glomeruli show the hemorrhagic lesions.

Rabbit 642. — Weight, 2,260 grams. February 8 and 9, $3\frac{1}{2}$ milligrams uranium nitrate intravenously per kilo of body weight. February 9, 4 cubic centimeters sterile water intravenously per kilo of body weight. February 10, 11, 12, 13, same twice daily. February 14, found dead. Microscopic: in fairly many glomeruli hemorrhagic lesions are seen.

Another type of glomerular lesion met consists of a moderate dilatation of the capsular space with slight compression of the capillary tuft. In this space is a finely granular eosin staining material representing, most probably, coagulated albumen (Fig. XI., Rabbit 377). Whereas this granular material is very frequently present in small amount, it is not so very often that we find any considerable dilatation of the capsular space with the presence of this granular material. Examples of this lesion are shown by Rabbits 377, 579, 586, 587, 596, 612, 617, and 619. One of these rabbits received two subcutaneous doses of uranium nitrate ($3\frac{1}{3}$ milligrams per kilo of body weight) and five doses of five milligrams of caffein by stomach tube per kilo of body weight. All the other rabbits received intravenous doses of uranium nitrate three and one half milligrams per kilo of body weight. Two of the latter received diuretin intravenously fourteen milligrams per kilo of body weight twice daily for ten and eight doses respectively; two received caffein intravenously five milligrams per kilo of body weight twice daily for five and six doses respectively; two received potassium acetate intravenously fourteen milligrams per kilo of body weight twice daily for six and seven doses respectively, and one received theocin sodium acetate intravenously five milligrams per kilo of body weight twice daily for five doses. All animals died the day following the last dose.

Very many glomeruli in kidneys from rabbits that have received uranium nitrate show evidence of proliferation of the endothelial cells of the capillaries. The glomeruli are very cellular (Fig. IV.), and the capillary loops contain little blood. The intracapillary cells are larger than normal, the nuclei have a more distinct chromatic structure and stain a

rather richer blue in eosin and methylene blue preparations than is the case with the same cells in normal glomeruli. Mitotic figures, however, are very rarely seen. The cells lining the capsule of the glomerulus usually show little proliferation. Here and there they have increased in number and appear cuboidal with rather large nuclei rich in chromatin. Very occasionally glomerular tuft and capsular epithelium become more or less fused with considerable proliferation of the capsular epithelium as shown in Fig. XII., Rabbit 336, in which a mitotic figure is clearly in focus at the periphery of the glomerulus.

SUMMARY.

In acute nephritis produced in the rabbit with uranium nitrate several types of glomerular lesions occur. There is a type of degenerative lesion evidenced mainly by the appearance of hyaline droplets in the capillary walls. Another type of lesion consists in the formation of fibrin thrombi in the capillaries. A third type is hemorrhagic in nature and appears usually as a rounded mass of fibrin enmeshing blood corpuscles. A fourth type is a dilatation of the glomerular space with granular material. A fifth type is a proliferative lesion affecting chiefly the capillary endothelium, to a much less extent the capsular epithelium.

REFERENCES.

1. Christian. Study II., Boston Med. and Surg. Jour , 1908, clix, 8.
2. Christian. Study IV., Archives of Internal Medicine, 1911, viii, 469.

DESCRIPTION OF PLATES.

PLATE VI., FIG. 1. — Rabbit 396. x 535. Glomerulus showing fibrin thrombi in the capillaries.

FIG. 2. — Rabbit 626. x 535. Glomerulus showing large fibrin mass occupying more than half of the glomerulus.

PLATE VII., FIG. 3. — Rabbit 626. x 535. Glomerulus showing an extensive hemorrhage with fibrin at its periphery.

FIG. 4. — Rabbit 340. x 535. Glomeruli showing intracapillary proliferation.

PLATE VIII., FIG. 5. — Rabbit 336. x 535. Glomerulus showing small area of hemorrhage in the upper portion of the picture.

FIG. 6. — Rabbit 561. x 535. Glomerulus showing small area of fibrin at its periphery.

PLATE IX., FIG. 7. — Rabbit 557. x 535. Glomerulus showing fairly large area of fibrin at its periphery.

FIG. 8. — Rabbit 336. x 535. Glomerulus showing fibrin lesion occupying about two-thirds of the glomerulus.

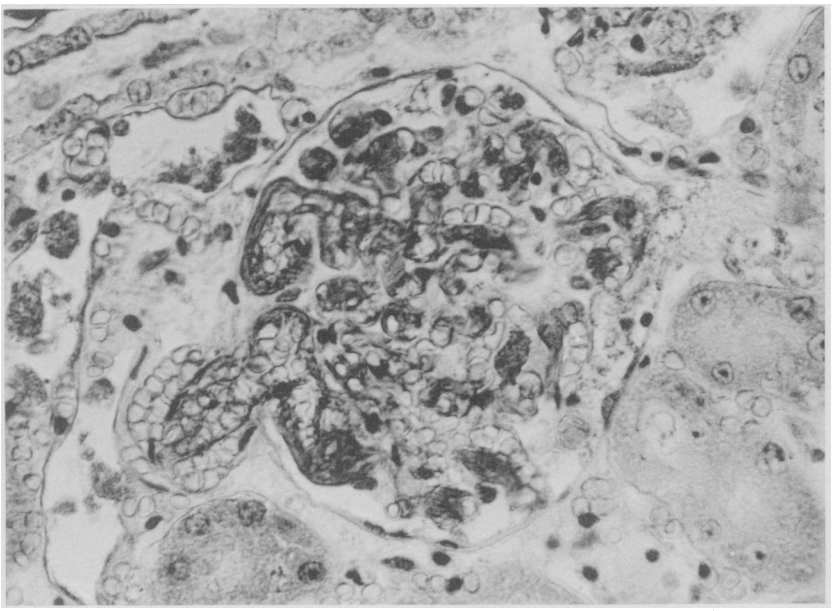
PLATE X., FIG. 9. — Rabbit 367. x 535. Glomerulus almost entirely disintegrated with hemorrhage into the capsular space and proliferation of the capsular epithelium.

FIG. 10. — Rabbit 336. x 535. Glomerulus showing fibrin and in addition degeneration of the glomerular cells.

PLATE XI., FIG. 11. — Rabbit 377. x 535. Glomerulus showing dilatation of the capsular space.

FIG. 12. — Rabbit 336. x 535. Glomerulus showing proliferation of the capsular epithelium with a mitotic figure in focus at the left border of the glomerulus.

(The photographs were taken by Mr. L. S. Brown of the Massachusetts General Hospital, for whose careful work we express our thanks.)



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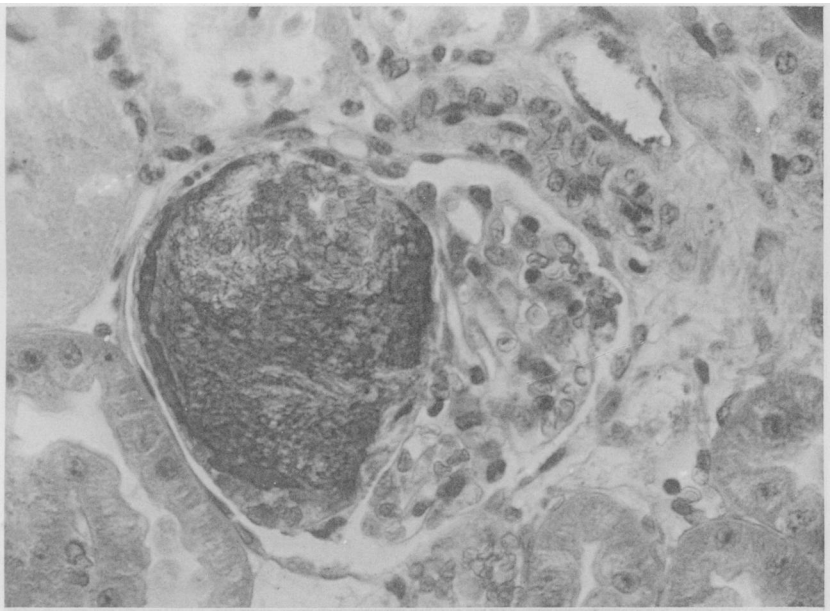

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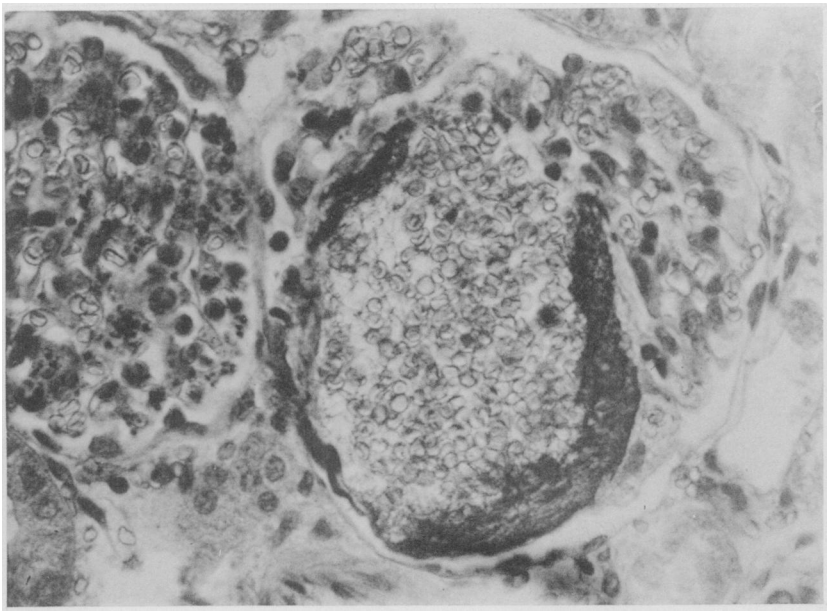

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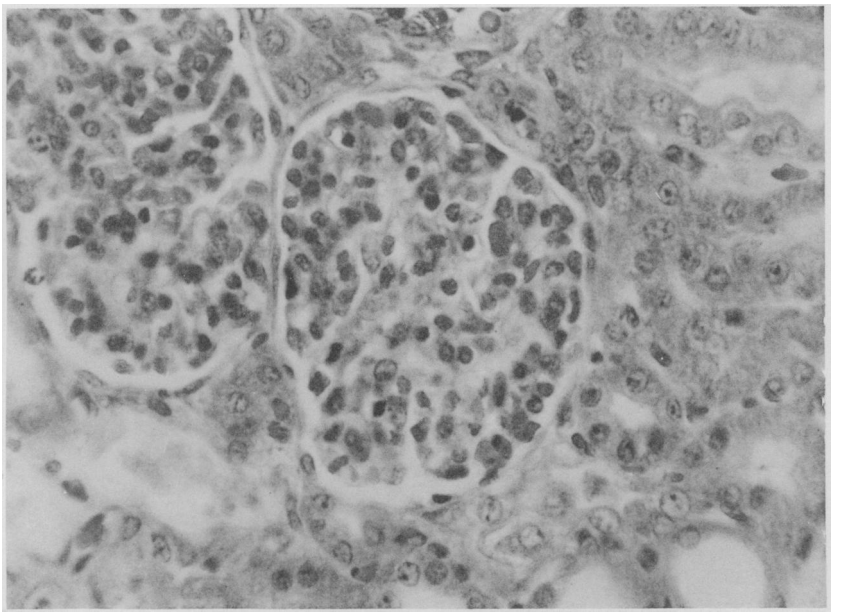

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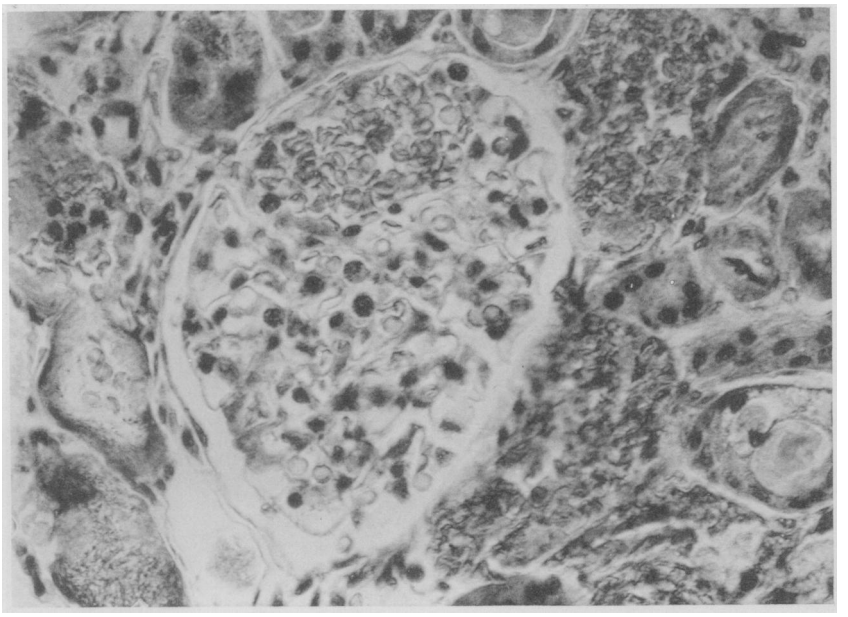

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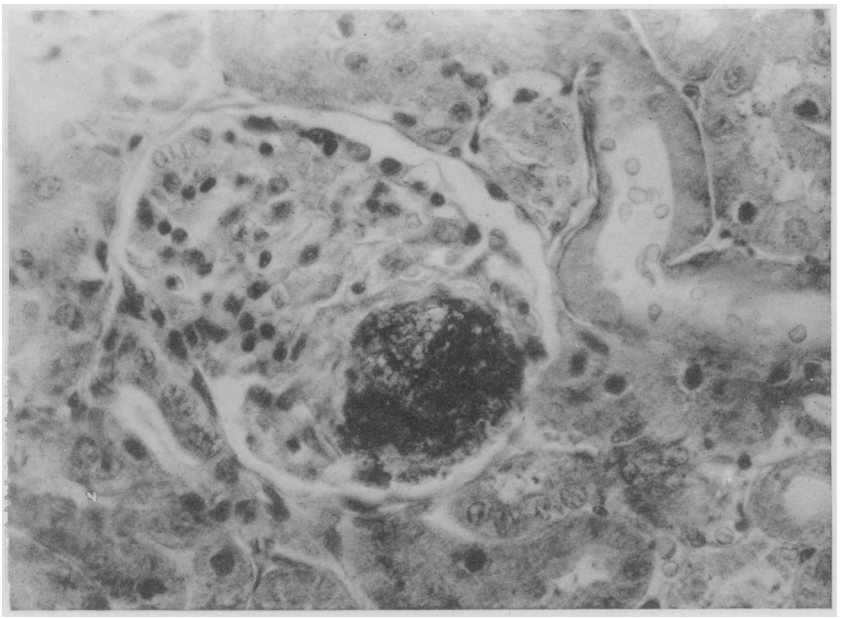

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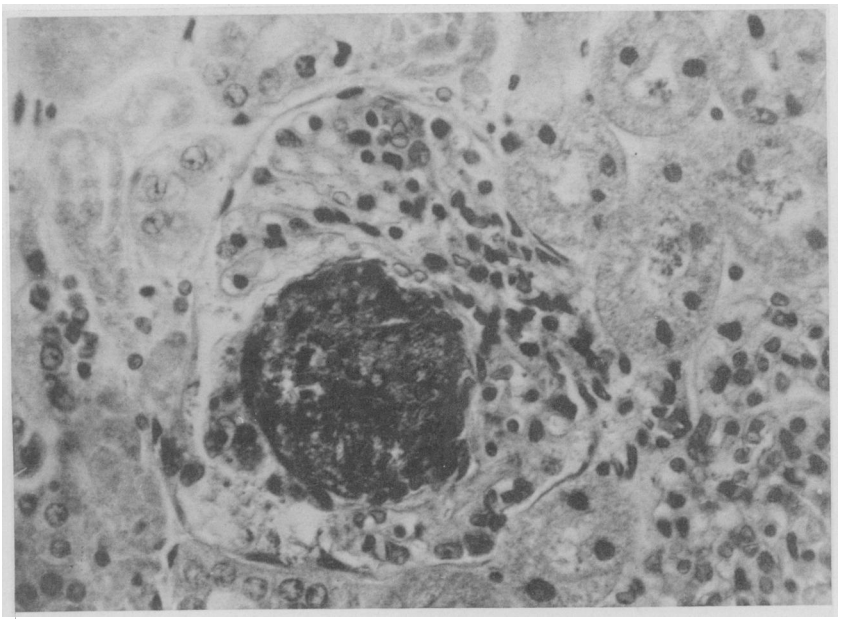

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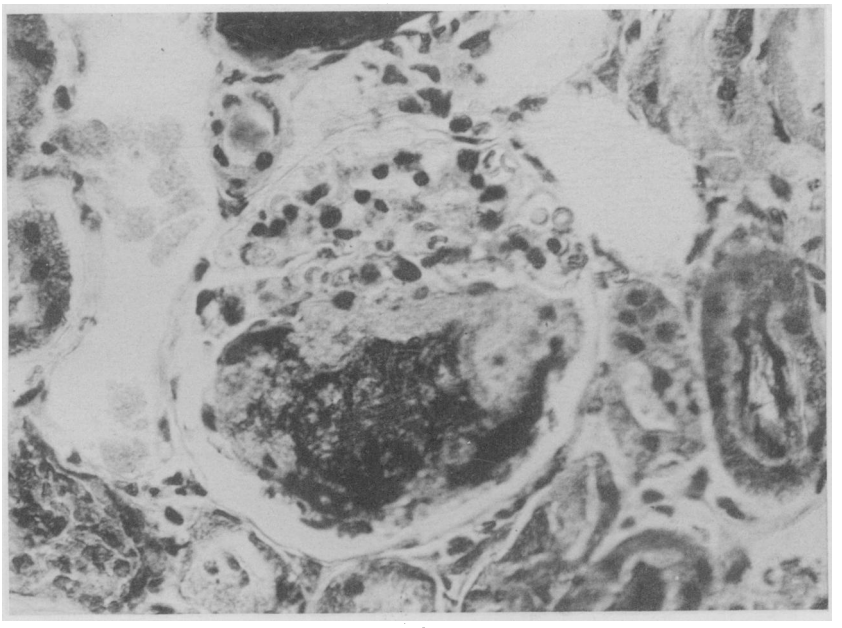

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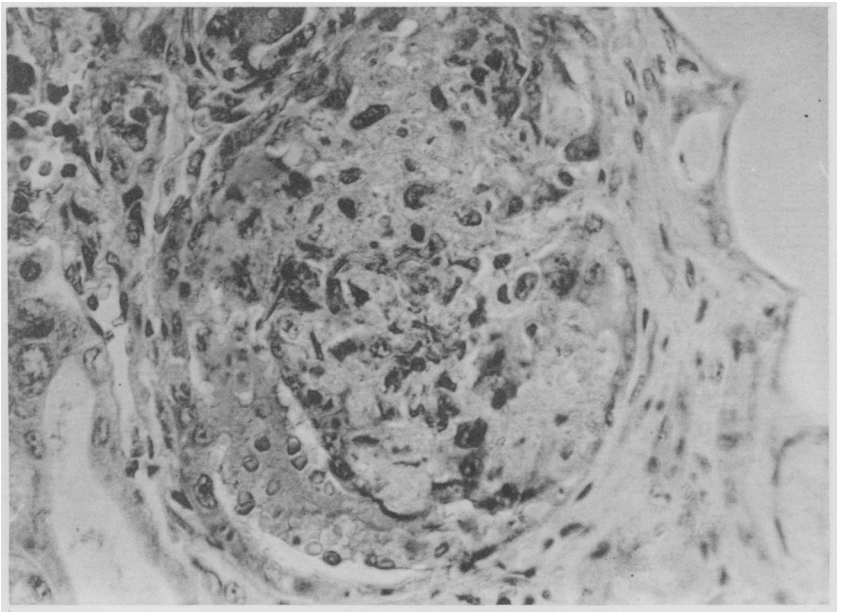

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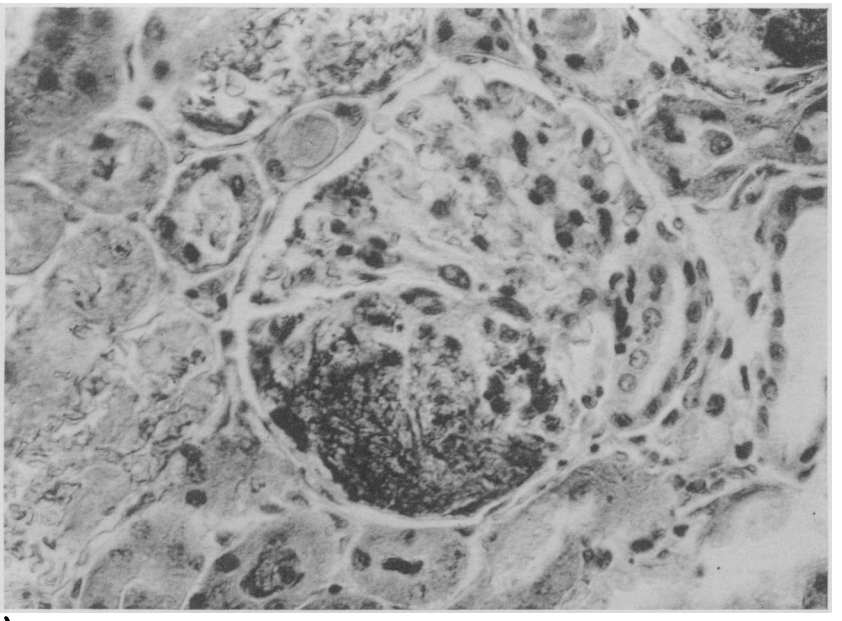

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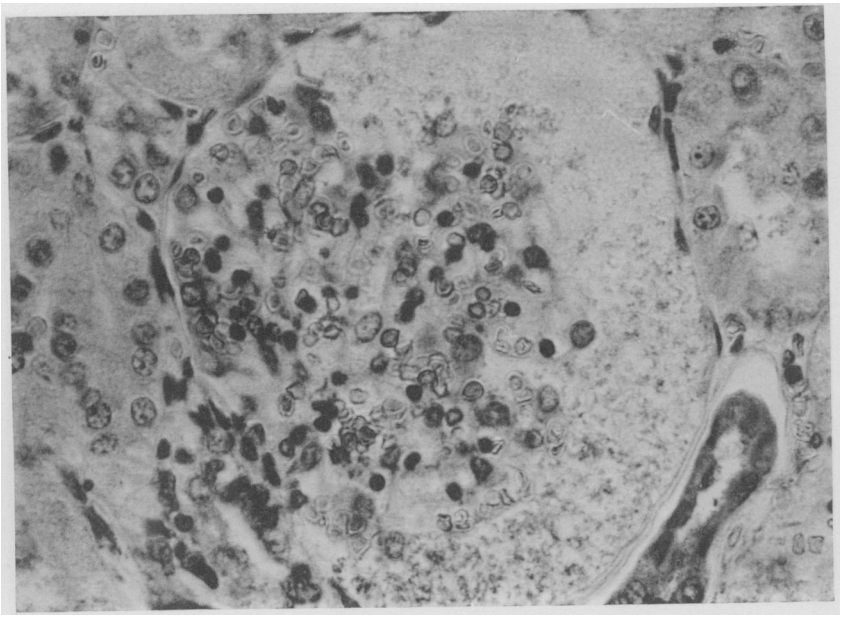

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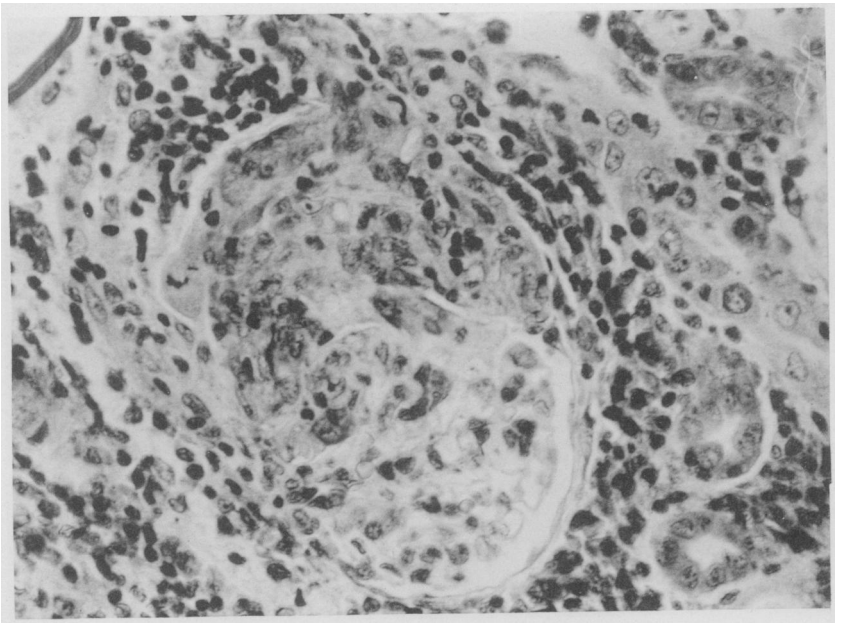

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