CHEMOPATHOLOGICAL STUDIES WITH COMPOUNDS OF ARSENIC.

II. Histological Changes in Arsenic Kidneys.

By LOUISE PEARCE, M.D., and WADE H. BROWN, M.D.

(From the Laboratories of The Rockefeller Institute for Medical Research.)

Plates 61 to 67.

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The idea that arsenicals as a class produce a vascular type of injury in the kidney has gained general acceptance, and workers in experimental nephritis have substantiated this idea for such compounds as have been employed to produce so called arsenical nephritis. However, as we have shown in the preceding paper,[1] all compounds of arsenic do not produce the same type of injury, and from the gross appearance of the kidneys of dogs poisoned with various well known arsenicals, we are able to recognize two widely separated types of kidney, the red and the pale, with many transitional varieties or subgroups, each being more or less characteristic for a given compound. In like manner, we have found that the histological changes in these given types are equally different and characteristic.

EXPERIMENTAL.

Tissues from the kidneys described and illustrated in the preceding paper[2] were fixed in Zenker's fluid, sectioned in paraffin, and stained with hematoxylin and eosin. The histological changes, therefore, may be related directly to the descriptions and illustrations in this paper.

Red Kidneys.

Arsenious Acid.—The most characteristic acute lesions produced by arsenious acid consist in a uniform dilatation and congestion of

[1] Pearce, L., and Brown, W. H., *Jour. Exper. Med.*, 1915, xxii, 517.

[2] Pearce and Brown, *loc. cit.*

the blood vessels of the kidney with an escape of blood into the interstitial tissues throughout the cortex and medulla (Fig. 1). The glomeruli are swollen, and the tuft completely fills the capsular space. Occasionally there is desquamation of swollen, disintegrating cells of the capsular epithelium and a slight albuminous precipitate in the capsular space. The tuft vessels are widely dilated and filled with blood; some contain hyaline plugs. The changes in the tubular epithelium are less marked, the cells are greatly swollen and vacuolated, often occluding the lumen of the tubule and are frequently stripped up from the basement membrane. Parenchymatous and fatty degeneration are marked, but necrosis of tubular epithelium is relatively slight. Some of the tubules contain an albuminous precipitate; others, especially in the boundary zone, contain blood.

Salvarsan.—While vascular injuries dominate the histological changes produced by poisoning with salvarsan, the lesions differ in essential respects from those produced by arsenious acid. Throughout the cortex and medulla the vessels are dilated and congested, but patches of hemorrhage are more numerous in the outer cortex and are especially prominent in the boundary zone. The glomeruli are all large, with the tuft practically filling the capsular space; the tuft capillaries are widely dilated and filled with blood; and there is a slight accumulation of polymorphonuclear leucocytes in the capillaries. The cells of the outer portion of many of the tufts are markedly swollen, granular, and pale-staining, and many of these swollen cells appear to be desquamating into the capsular space (Fig. 4). Hyaline thrombi are numerous (Fig. 3). Occasionally there is a slight amount of albuminous precipitate in the capsular space. The changes in the tubules are relatively more pronounced than with arsenious acid. The epithelium of the tubules shows an extreme degree of parenchymatous and fatty degeneration with definite necrosis. The cells are very granular and ragged with frayed edges, and many are actually disintegrating (Figs. 3 and 4). In many areas there is a protrusion of swollen tubular epithelium into the glomerular space. Practically all the tubules contain albuminous precipitate and some of the cortical and many of the medullary tubules contain blood (Fig. 3). Of especial interest is a fairly extensive and regular edema of the labyrinth, particularly of the

lower two-thirds of the cortex extending but little into the medulla (Fig. 4).

Neosalvarsan.—The histological changes produced in the kidney by neosalvarsan are still further removed from those produced by arsenious acid, both in type and degree, although they conform in general to the changes observed in other red kidneys. Here again vascular dilatation and congestion are present, and hemorrhage, as with salvarsan, is most marked in the outer cortex and boundary zone.

The glomeruli are large, but the tuft itself is small and compressed, occupying approximately only one-third to one-half of the capsular space. The remaining space is filled with an extensive albuminous precipitate (Fig. 5). The tuft vessels are irregular, many being enormously dilated and filled with blood and numerous hyaline plugs; in consequence, other vessels are completely collapsed. There is an increase in the number of polymorphonuclear leucocytes in the capillaries of the tuft. The injury to the tubular epithelium is distinctly more prominent than with either arsenious acid or salvarsan. The epithelium of the convoluted tubules, particularly of the outer half of the cortex, is almost completely necrotic, the epithelium of many of the tubules being converted into homogeneous, pink-staining masses (Fig. 5). There is less tubular necrosis in the inner cortex, but there is marked parenchymatous and fatty degeneration with an albuminous precipitate in the lumen of the tubules. A considerable number of the ascending limbs of the loops of Henle shows an extreme degree of degeneration occasionally going on to necrosis. Many of the tubules in the boundary zone and medulla contain blood. In the lower portion of the cortex and in the boundary zone there are a few irregular patches of interstitial edema.

Galyl.—In general, sections from kidneys after injection of galyl resemble those of salvarsan and neosalvarsan, but there are certain relative differences. The tuft capillaries are uniformly dilated and contain blood and irregularly distributed hyaline thrombi. There is a considerable amount of swollen cells desquamated from the capsule into the capsular space (Fig. 2). The epithelium of the convoluted tubules, especially in the outer half of the cortex, shows disintegration, desquamation, and necrosis, but there is very little necrosis *en masse*. The epithelium of the loops of Henle shows de-

generation, although comparatively little necrosis. The cortical tubules contain much albuminous precipitate, and the majority of the tubules of the medulla contain blood.

Pale Kidneys.

Arsacetin.—In the group of pale kidneys, of which the arsacetin kidney is taken as the type, the relative degree of vascular and tubular injury is the reverse of that observed in the red kidney. Following the injection of arsacetin, the vessels and capillaries of the kidney are not usually dilated or congested except to a slight degree in the boundary zone, and there is no hemorrhage. The glomeruli are practically normal in appearance; the tuft fills most of the capsular space but is not swollen; the capillaries of the tuft are moderately dilated and contain some blood. There is only a slight amount of albuminous exudate. On the other hand, practically all the epithelium of the convoluted tubules is necrotic, the tubules appearing as large, swollen, granular, pink-staining masses (Fig. 6). The cells which are not actually necrotic are extremely degenerated with pyknotic and fragmenting nuclei. The tubules are choked with masses of disintegrating cells or contain an albuminous precipitate. The epithelium of the loops of Henle is markedly degenerated, the cells are swollen, ragged, and vacuolated. In some instances, when a very large dose of arsacetin is given (Dog I),[3] the wide-spread necrosis of tubular epithelium includes that of the ascending limb of the loop of Henle. The collecting tubules show a moderate amount of parenchymatous and fatty degeneration.

Arsenophenylglycine.—The injury produced in the kidney by arsenophenylglycine combines both vascular and tubular changes. The vessels and capillaries throughout the kidney are moderately dilated and congested. There is slight escape of blood, if any, from the vessels in the cortex, but in the boundary zone there is a considerable amount of hemorrhage which extends in streaks into the medulla. The glomeruli are uniformly large, the tuft filling approximately one-third to one-half the capsular space. The capillaries of the tuft are irregular in appearance; some are moderately

[3] The designations of the dogs correspond to those given in the preceding paper (Pearce and Brown, *loc. cit.*).

dilated and filled with blood, but many are completely collapsed. The epithelium of the capsule and of the adjoining portion of the connecting tubule is enormously swollen, homogeneous, and pale pink. Many cells of the capsule and connecting tubule have desquamated into the capsular space (Fig. 7), and in certain instances the mass of degenerated and disintegrating cells in the space apparently comes almost entirely from the tubule. Practically all the convoluted tubules are necrotic and appear as solid, homogeneous, pink-staining cylinders, or the tubule is filled with disintegrating hydropic cells. The epithelium of the loops of Henle in the outer cortex is similarly necrotic but in the inner portion there is less actual necrosis. Here the cells are markedly swollen and granular with many large vacuoles and pyknotic nuclei. The tubules contain an albuminous precipitate. The epithelium of the collecting tubules is also degenerated. The lumen of almost all the tubules is completely occluded by necrotic cell masses or by enormously swollen, degenerated, and desquamated cells. In the medulla hyaline casts are quite abundant and many tubules contain blood. There are a few irregular patches of interstitial edema in the inner cortex.

Atoxyl.—Following a small dose of atoxyl (Dog F), the only distinctive pathological changes consist in parenchymatous and fatty degeneration of tubular epithelium and slight congestion and hemorrhage in the boundary zone. The epithelium of the convoluted tubules stains palely, the cells are ragged and granular with irregular vacuolization, as shown in Fig. 8. There is some fragmentation of nuclei and many tubules contain albuminous precipitate. With a larger dose of atoxyl, however, (Dog E) a greater variety of changes is encountered. The vessels throughout are dilated and congested and there is some escape of blood into the interstitial tissue and tubules of the cortex. There is an extensive hemorrhage into the medulla, obscuring much of its structure. The glomeruli are swollen, but the glomerular tufts are irregular in size, some filling the capsular space while others occupy only a portion of it. Most of the tuft capillaries are dilated and filled with blood, and there is an albuminous precipitate in the capsular spaces. The tubular epithelium shows a peculiar series of changes. In general, it stains poorly; the cells of the convoluted tubules are swollen, granular,

ragged, and very hydropic; many have desquamated, choking the lumen of the tubule (Fig. 9). There is great irregularity in the preservation of the nuclei; many are fragmented or pyknotic, others are entirely gone. An occasional mitotic figure is seen. Practically all the tubules contain albuminous precipitate and there are a few hyaline casts. In the inner portion of the cortex there is an extreme degree of irregularity in the tubules, so that it is difficult to identify with certainty the various types. In this region the loops of Henle show a striking change; they are markedly enlarged, the cells are widely separated from one another, and are swollen and hyaline with pyknotic nuclei as shown in Fig. 9. Some of these cells are necrotic and desquamated. Another prominent feature of the atoxyl kidney is a profuse exudation of polymorphonuclear leucocytes which is most marked in the inner half of the cortex and the boundary zone.

An increase in the length of survival of the animal (Dogs C and D) gives an opportunity for the development of still further pathological changes in the kidney. In such cases, the hemorrhage invades the inner cortex as well as the medulla (Fig. 11). The tubular epithelium shows more marked disintegration of cells, many of which are hyaline while others are hydropic and swollen. There is an increase in the exudate in the tubules which consists of albuminous precipitate, colloid droplets, red blood cells, leucocytes, and casts, causing, in many instances, a marked compression of the tubular epithelium (Fig. 10). The number of casts is distinctly greater in these dogs of longer survival. In the medulla the tubular epithelium is almost completely desquamated, and the cells are intensely hyaline with pyknotic nuclei. There is a marked exudate between the tubules consisting of serum, fibrin, red blood cells, and a few leucocytes; no interstitial structures can be distinguished. Numerous mitotic figures are present in the epithelium of both cortex and medulla. Moreover, there is a very marked increase in the interstitial leucocytic exudate in these dogs of longer survival (Fig. 11).

DISCUSSION.

As far as we are able to determine from a pathological study of various arsenic kidneys, the idea that arsenical compounds as a class

produce vascular, in contradistinction to tubular, injury must be modified.

It is quite true that with a certain group of these compounds vascular lesions predominate, causing red kidneys, of which arsenious acid is the type. Even within this group of arsenicals, however, we are able to recognize certain differences in the character of the action of the different compounds. For instance, with salvarsan and neosalvarsan, hemorrhage tends to be restricted to the outer cortex or the boundary zone; the formation of hyaline thrombi in the glomerular capillaries is more pronounced; and there is a profuse albuminous exudate in the capsular space with desquamation of epithelial cells. Interstitial edema and degeneration and necrosis of the tubular epithelium are distinctly more pronounced than with arsenious acid.

As we study kidney lesions produced by other arsenicals, however, we find, as with arsacetin, that the predominating change is one of degeneration and necrosis of tubular epithelium. These pale kidneys offer a striking contrast to the red kidneys of vascular injury. Moreover, other pale kidneys, such as those produced by such substances as arsenophenylglycine and atoxyl, in which the tubular injury is the predominant feature, may show well marked vascular injury. In these cases, the hemorrhage may be zonal in character, involving much of the medulla or even the lower portion of the cortex. The tuft capillaries may be dilated and congested with more or less albuminous precipitate in the capsular space, and there may be an exudation of serum, fibrin, red blood cells, and leucocytes into the interstitial tissues.

The histological changes in the kidneys produced by a particular arsenical compound, while elastic, are quite characteristic of the action of the compound and accord with the gross appearance of the organ. Therefore, in surveying this series of arsenic kidneys from a microscopic as well as from a gross pathological point of view, we are able to differentiate two extreme types; *i. e.,* the red and the pale. The red kidney is essentially one of vascular injury, the pale kidney is predominantly one of tubular necrosis. In addition, various transitional or subgroups exist, in which the kidney, although belonging to the red type, shows relatively a great degree of

tubular injury and *vice versa.* In regard to the tubular necrosis in these kidneys, the prompt and active regeneration of the tubular epithelium following the injection of such compounds as arsacetin, arsenophenylglycine, and atoxyl, seems to preclude the possibility that the wide-spread tubular necrosis produced by these substances can be regarded as a purely anemic phenomenon. Hence, we cannot ascribe to arsenical compounds, as a class, the property of producing a purely vascular nephritis; but we must recognize the fact that arsenical compounds produce characteristic renal lesions which may be either predominantly vascular or tubular in type and that the mode of action and the character of the lesions produced are bound up with the chemical constitution of the compound.

SUMMARY.

1. We have shown that the type of renal lesion produced by compounds of arsenic varies widely: while some arsenicals produce changes in which vascular injury predominates, others produce an equally dominant tubular injury.

2. In either of these groups the character and degree of the vascular or tubular injury produced by different compounds shows further variation, such that the lesions of different arsenicals of the same group are not identical. Each compound of arsenic that we have tested, therefore, produces a lesion-complex in the kidney that is relatively characteristic for that compound.

3. The mode and character of the action of arsenicals are dependent upon the chemical constitution of the compound.

EXPLANATION OF PLATES.

The illustrations are all from untouched photomicrographs. Magnification, × 208.

PLATE 61.

FIG. 1. Arsenious acid. Dog B. Section from the outer cortex. There is marked dilatation and congestion of vessels, including the glomerular capillaries, with hemorrhage into the interstitial tissues. The tubular epithelium is swollen and degenerated.

FIG. 2. Galyl. Dog S. Section from the outer cortex. The vessels are congested and there is a slight interstitial hemorrhage. The tuft capillaries are uni-

formly dilated and contain blood and there is a slight albuminous precipitate in the capsular space. Tubular degeneration and disintegration are marked.

PLATE 62.

FIG. 3. Salvarsan. Dog Q. Section from the outer cortex. Dilatation and congestion of vessels with slight hemorrhage. The glomeruli are swollen and the tuft capillaries contain blood and numerous hyaline thrombi. There is an albuminous precipitate in the capsular space. Tubular epithelium shows degeneration and slight necrosis.

FIG. 4. Salvarsan. Dog Q. Section from the inner cortex. Marked interstitial edema. Partial disintegration of glomerular tuft and accumulation of epithelial cells and cell detritus in the capsular space. Degeneration and necrosis of tubular epithelium.

PLATE 63.

FIG. 5. Neosalvarsan. Dog R. Section from the outer cortex. The glomeruli are swollen; the tuft is compressed; the glomerular capillaries are congested and contain numerous hyaline thrombi. There is an abundant albuminous precipitate in the capsular space. Many tubules show a massive necrosis, others show degeneration and disintegration of epithelial cells with pyknotic nuclei.

PLATE 64.

FIG. 6. Arsacetin. Dog I. Section from the midcortex. Extensive necrosis *en masse* of the epithelium of the convoluted tubules with marked degeneration and slight necrosis of the loops of Henle. Vessels and glomeruli normal.

PLATE 65.

FIG. 7. Arsenophenylglycine. Dog L. Section from the outer cortex. The glomeruli are large, the tufts are compressed, and the glomerular vessels are partially collapsed. The capsular epithelium is swollen and desquamated and the capsular space is filled with necrotic cellular debris. Degeneration and necrosis of tubular epithelium are marked.

PLATE 66.

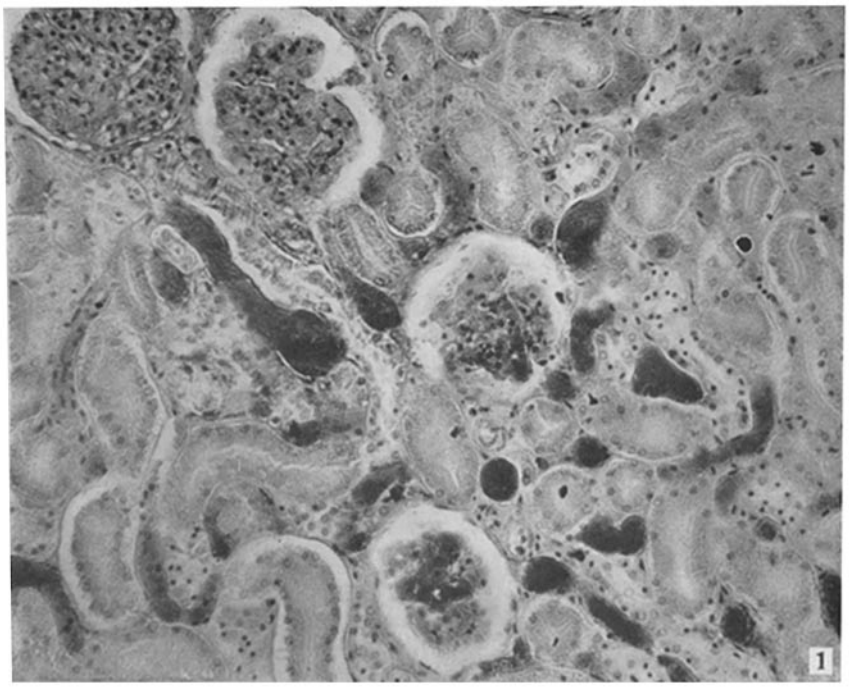
FIG. 8. Atoxyl. Dog F. Section from the outer cortex. The vessels and glomeruli are normal, except for a slight albuminous precipitate in the capsular space. The epithelium of the convoluted tubules is extremely ragged and degenerated with slight necrosis.

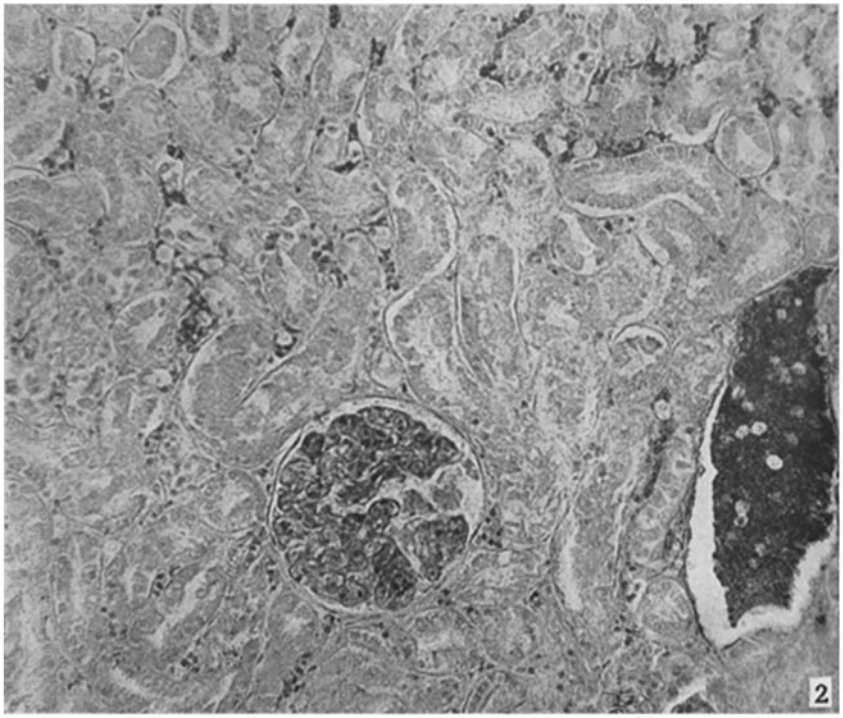
FIG. 9. Atoxyl. Dog E. Section from the midcortex. The glomeruli are slightly enlarged, the capillaries of the tuft are slightly congested, and the capsular space contains an albuminous precipitate. The epithelium of the convoluted tubules is swollen, granular, and hydropic, and in places shows necrosis. The loops of Henle are markedly dilated; the cells are hyaline with pyknotic nuclei and are widely separated from one another. Many cells are desquamated. There is a diffuse hemorrhage and polymorphonuclear exudate into the interstitial tissues and occasionally into the tubules.

PLATE 67.

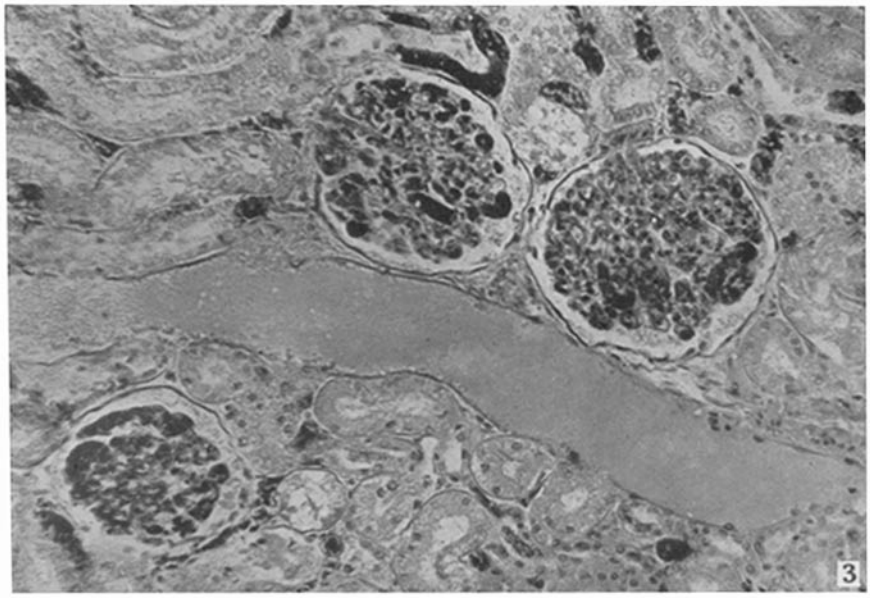
FIG. 10. Atoxyl. Dog D. Section from the outer cortex. The glomeruli are enlarged. The tuft is slightly compressed and the capsular space contains an abundant albuminous precipitate. The epithelium of the convoluted tubules is extremely ragged and hydropic and in some areas the cells are necrotic and desquamated. Other tubules are filled with a granular precipitate, hyaline droplets, and an occasional cast, and the epithelium of these tubules is compressed.

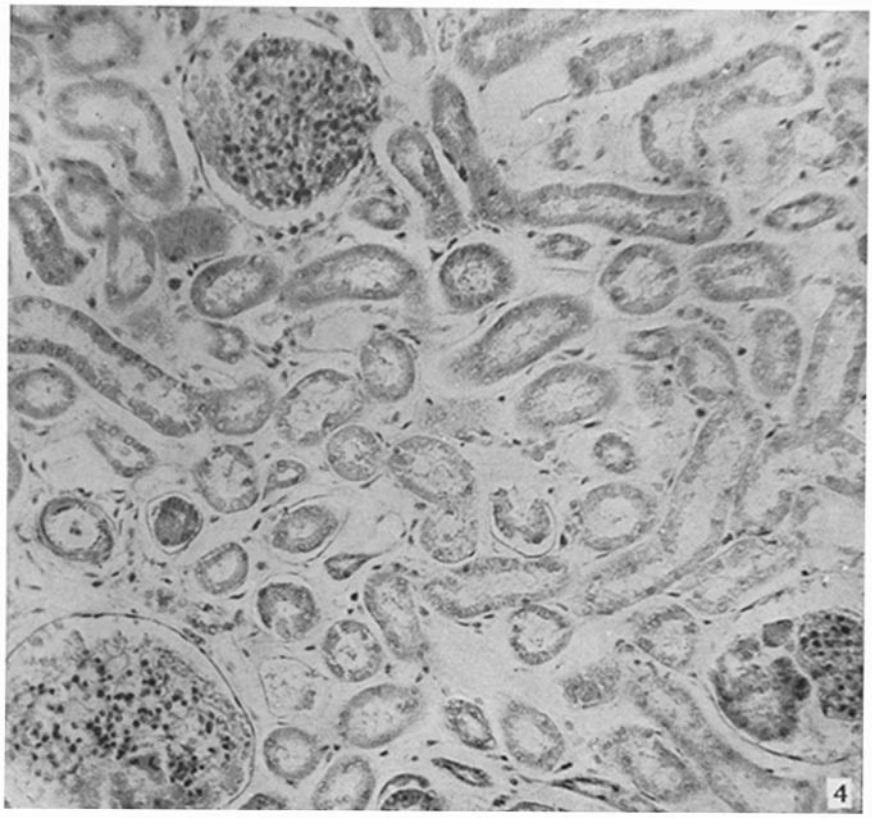
FIG. 11. Atoxyl. Dog D. Section from the inner cortex. The glomeruli are as in Fig. 10. The tubules throughout are necrotic, and filled with cellular detritus or granular casts. There is a marked interstitial hemorrhage with an exudate of polymorphonuclear leucocytes.





(Pearce and Brown: Changes in Arsenic Kidneys.)





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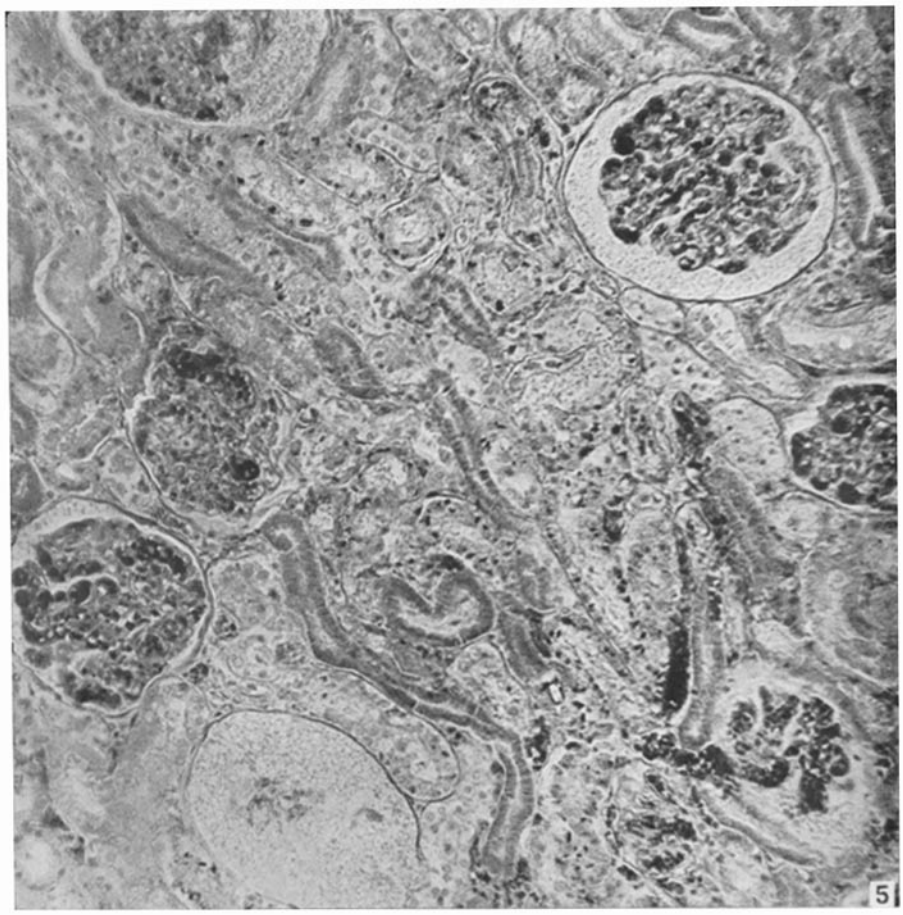

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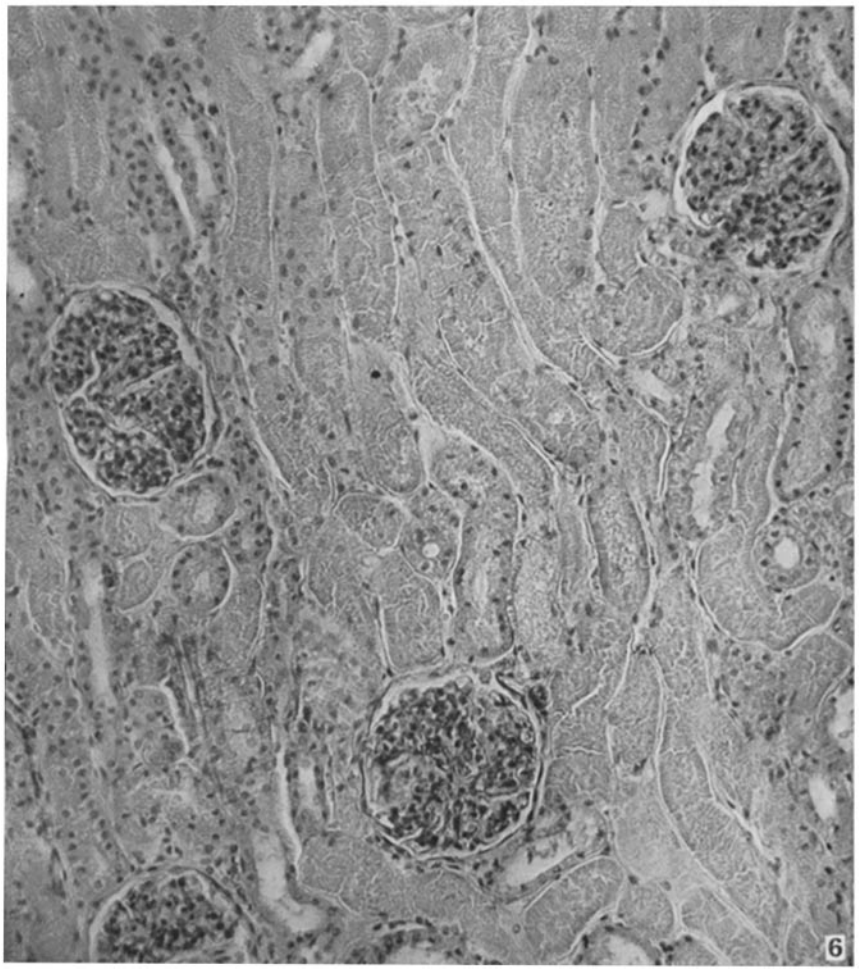

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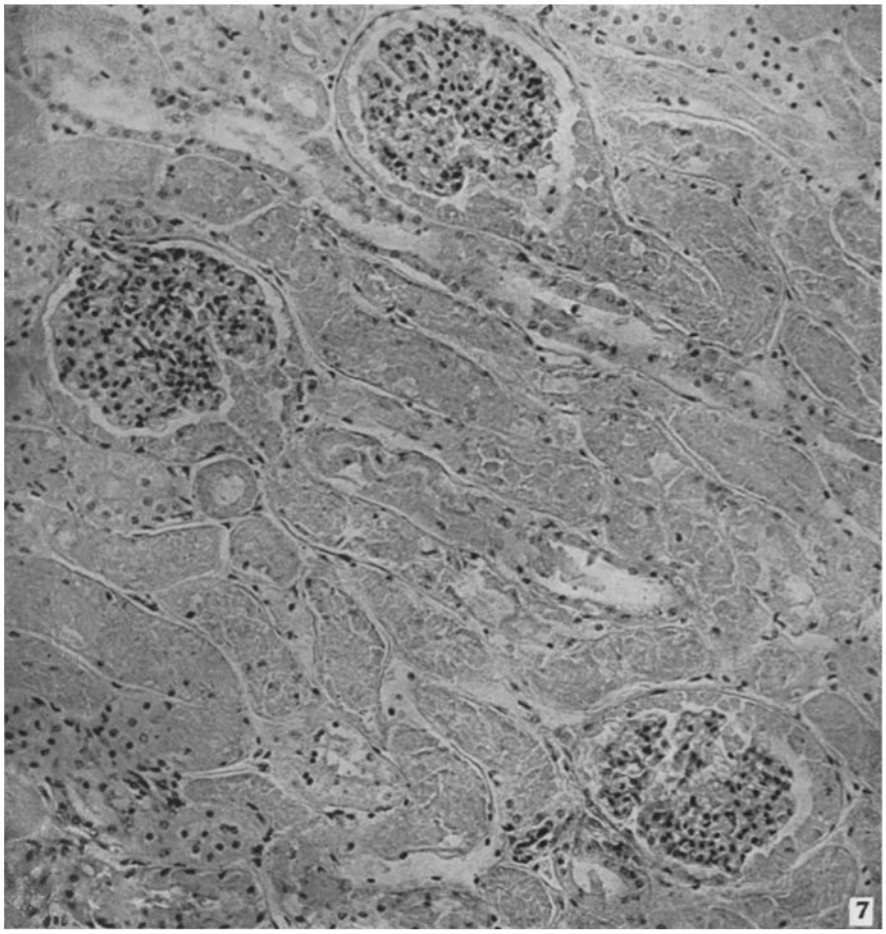

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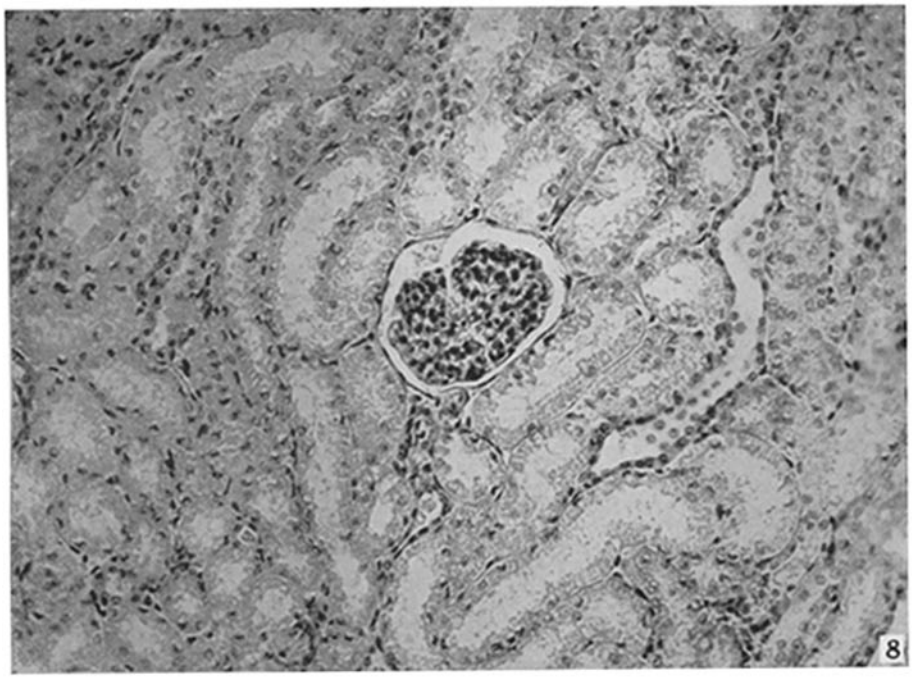

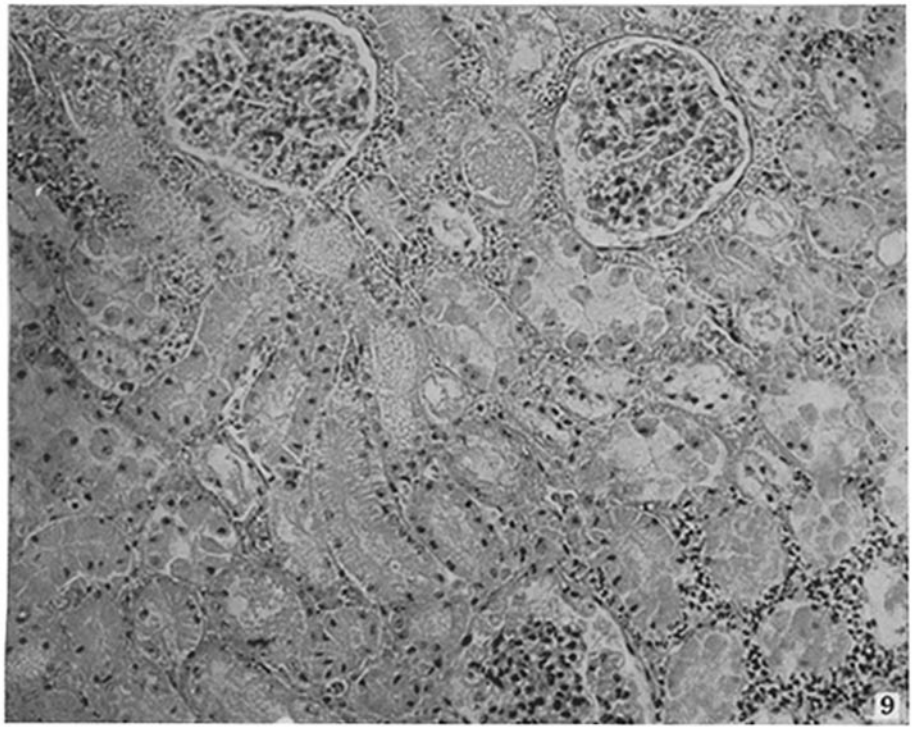

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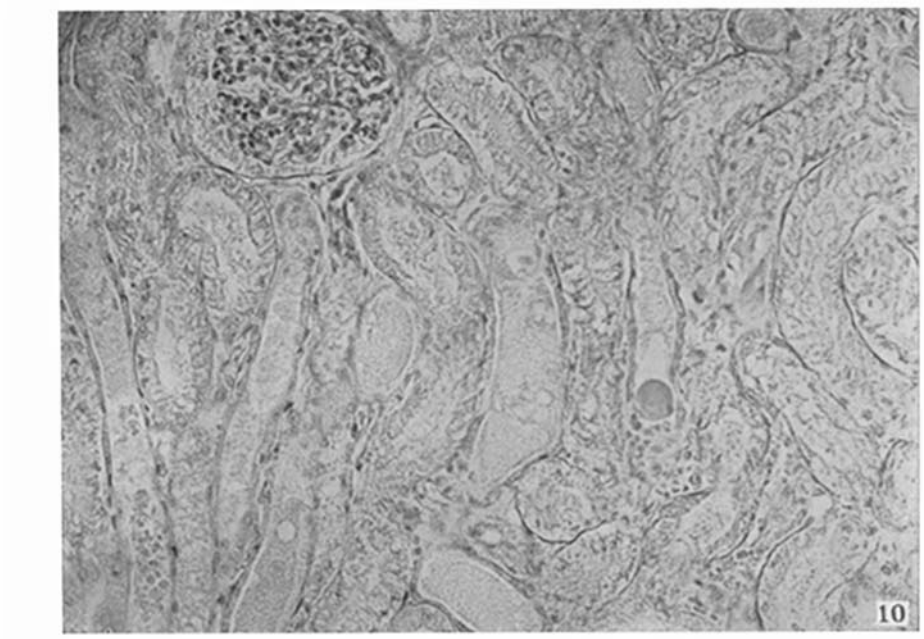

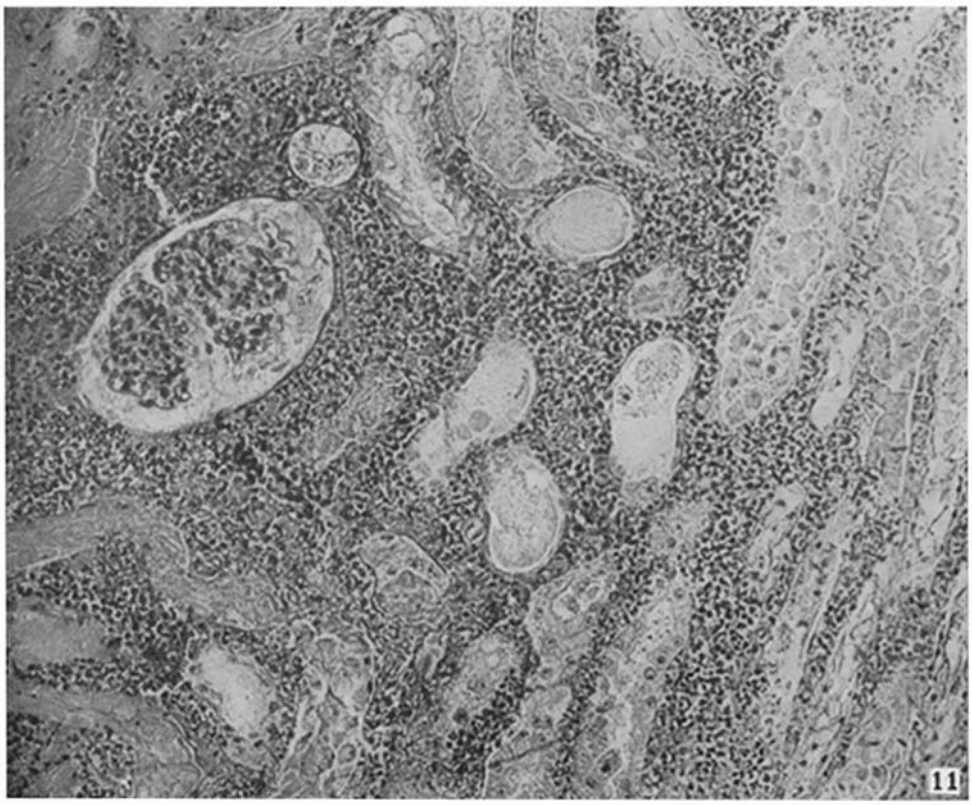

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