KIDNEY LESIONS IN STILLBORN AND NEWBORN INFANTS*

"CONGENITAL GLOMERULOSCLEROSIS"

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Pathological changes in the kidneys of fetuses and newborn infants have not been the subject of morphological investigation to any great degree in the past. Textbooks and reference works in pathology make little or no mention of such lesions, and the literature contains surprisingly few contributions in this field. Congenital anomalies, uric-acid infarcts, bile-pigment infarcts and tumors of the kidneys are briefly described and dismissed with a few sentences or paragraphs. However, pediatrists and urologists have studied clinically diseases of the kidneys in infants and young children to a greater extent.

In 1908, Karsner [1] described a case of congenital acute nephritis in an infant who died less than 1 hour after birth, and collected three additional cases from the literature. Three cases of neonatal nephritis were described by Conrad,[2] in 1938. Fishberg [3] mentioned having studied pathologically the kidneys of an infant, 4½ months old, who died from subacute glomerulonephritis. Lesions of pyelonephritis have also been described in the newborn by Craig,[4] Helmholz,[5] Hunt [6] and others.

The lesion which constitutes the subject matter of this communication was first described in 1909 by Herxheimer [7] (cited by Gruber [8]). According to him, destroyed, hyalinized glomeruli are found not infrequently in the kidneys of newborns, nurslings and also of older children as the result of developmental defects. His description can hardly be improved upon today. A free translation is as follows:

Hyalinized glomeruli are found in all layers of the cortex but most often near the surface. Sometimes they are grouped about the divisions of an interlobular artery. He found them thirty-eight times in 43 children and felt that further study might also have revealed their presence in the 5 negative cases. The incidence of the lesion did not parallel the severity of the pathological alterations. The earliest change noted by him was thickening of the parietal layer of Bowman's capsule, the result of deposition of fibrous connective tissue lamellae. Hyaline change may not be present at first. When it appears it can be seen, by means of the van Gieson stain, as a red ring of tissue about the membrana propria of Bowman's capsule. Frequently, however, the hyaline material is present only in the form of solitary foci in the

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periphery of the tuft. In these instances, he felt that serial sections might have revealed a continuity between the capsule and the tuft. In mild cases, a cleft can be seen between the glomerulus and the hyalinized capsule, the capsular epithelium having been destroyed. Further solution of the affected portion of the glomerulus may take place with gradual hyaline change; or only a sharply circumscribed area of the tuft may be affected, in which case the capsular epithelium may appear distinctly hyperplastic. Adhesions between the capsule and glomerulus are frequently noted. In some glomeruli the hyalinization appears in a more or less ball or pear-shaped form. Completely hyalinized glomeruli are also seen, spindle-shaped cells indicating the capsular boundaries. Should the hyalinization be incomplete, the unaffected portions of the glomeruli may be normal or compressed. Since the capsular portions of the tufts are often lined by rather tall epithelial cells with unusually deeply-staining nuclei, Herxheimer [7] concluded that the loops were retarded in development. Evidence of inflammatory disease was not found in the vicinity of the lesions.

Herxheimer [7] explained the basis of the eventual hyaline formation in the glomerulus by a disturbance in the synchronous development of the epithelial and mesenchymal portions of the malpighian corpuscle. The primary steps are obscure, as it is not known whether the disturbance in the stromal portion antecedes or follows the epithelial irregularity. The former was considered more likely. He saw these structures as "Hamartien" * in the sense of Albrecht, which disintegrate in the subsequent development of the kidney and then disappear.

In 1928, Schwarz [9] studied the kidneys of 80 newborn infants. There was a widespread pneumonic process in 22 infants and in 19 of these, inflammatory and infiltrative changes in the kidneys, in the form of an interstitial nephritis, were found. Lesions of the glomeruli, similar to those described by Herxheimer,[7] were found in 45 of 80 cases, an incidence of 56 per cent. However, in the cases in which inflammatory and infiltrative changes in the kidneys were present, the aforementioned glomerular changes were invariably demonstrable. Before the age of 3 weeks, however, he found the glomerular lesions in barely 30 per cent of his cases. He concluded that the changes were due to the excretion of toxic substances by the kidneys rather than to congenital anomalies, as suggested by Herxheimer.

Materials and Methods

We first noted the lesion as an incidental finding in the course of routine microscopical examinations of the kidneys of 13 stillborn and newborn infants. Some of these lesions had been previously considered

* Hamartien: defects in tissue combination during development (authors' note).

possible manifestations of a subacute glomerulonephritis. Recently the kidneys from 100 consecutive stillborn, newborn and other infants under 14 months of age were carefully examined for these lesions and 17 more examples were found. Blocks of tissue were fixed in a 4 per cent solution of formaldehyde. Hematoxylin and eosin, Mallory, McGregor and Weigert preparations were made.

Histology of the Glomerulus in the Neonatal Period

Before proceeding with a description of the lesions, review of the histogenesis of the glomerulus in early postnatal life is essential. Gruenwald and Popper [10] recently investigated this subject. The description appended below is taken from their paper:

The glomerulus before birth consists of "an undivided globule covered by a uniform layer of high columnar epithelium which does not extend between the loops. The lumen of the glomerular loops is partly visible and contains a few erythrocytes. . . . The loops are in close contact with each other and no free spaces are left between them. At the vascular pole of the corpuscle the reflection of the visceral to the parietal layer is clearly visible.

"After birth the glomerular loops expand and contain more red cells indicating an increased blood flow. Between the individual loops, clefts are visible which proceed toward the vascular pole, separating 3 to 8 lobules from each other. Parallel to this process changes in the epithelial covering take place. The originally continuous layer of high columnar epithelium is broken up by the clefts. Within the clefts the surface of the glomerular loops is partly covered by epithelium; in other parts no distinct epithelial covering can be seen. The further development leads to a stage in which the almost completely expanded loops show small islands of epithelium on most of their surface. Only on the peak is a continuous layer of high epithelium visible as a remnant of the original visceral layer. Many histological pictures suggest that a part of this high epithelium is cast off during this period, gradually losing its connection with the glomerular loops. This may account for the albuminuria during the first days of postnatal life which is indicated by clotted material in Bowman's space and the tubular lumen. . . . All these changes start in embryonic life in a greater or smaller number of glomeruli. After birth the number of maturing glomeruli increases considerably and the expansion of the capillary loops proceeds rapidly. . . .

"This development is completed within the second year. . . .

"The reabsorptive parts, as Henle's loops and the medullary reabsorptive capillary tufts, are fully developed at the time of birth."

The Lesion

The lesion is found indiscriminately in both kidneys. Grossly the kidneys show no abnormalities and are of average size, shape and weight. Microscopically, the lesion is distributed focally in the cortex of the kidney and is seen most often in the juxta-medullary zone.

In the 13 cases which constituted the original study, the lesion was sufficiently widespread to warrant a tentative diagnosis of "subacute glomerulonephritis" although it was recognized that the process was not a diffuse one. In the control series of 100 consecutive kidneys, 17 showed similar lesions, although not to the same extent. This might

be explained by the fact that an insufficient number of blocks were taken from these kidneys.

The lesion involves essentially the arterioles and the appertaining glomeruli. In the earliest stages there is a proliferation of the endothelium of the arterioles and of the smooth muscle cells of the media (Fig. 1). Concurrently there is an increase in the number of endothelial cells in the tuft (Fig. 2). Their nuclei are large, round or oval, and vesicular; a few are deeply stained. The epithelial cells apparently do not partake in the process at this time and their number remains unchanged. As a result of endothelial proliferation, the lumina of the capillary loops become markedly narrowed or even obliterated. The entire glomerulus becomes ischemic and only occasionally are red blood cells seen within the tufts. At the same time or shortly thereafter, but in some instances preceding the aforementioned alterations, there appears a proliferation of the parietal layer of Bowman's capsule (Figs. 3, 4 and 5). Concentric laminae of spindle-shaped cells with delicate, branching, pink-staining cytoplasm and narrow, elongated and vesicular nuclei appear. These layers, as a rule, are two to five cells in thickness and are rather loosely arranged. It is to be noted that sometimes only the tuft may partake in the process, the parietal layer of Bowman's capsule undergoing no changes. In some instances, the reverse appears to be the case. Not infrequently there is fusion of the tuft with the proliferated capsule, resulting in the formation of "crescents" (Figs. 2 and 3). During this process the walls of the vasa afferentia and arterioles have become progressively thickened and their lumina have become narrowed and even obliterated. Ischemia of the glomerulus is the natural result of such a process. Following this, homogeneous pink-staining material, staining deep blue with the Mallory and McGregor stains, appears within the tuft, or capsule, or both (Figs. 4 to 8). It is apparently deposited between the capillary loops. The deposition of this material may begin peripherally and proceed centrally or vice versa. Only a sector of the glomerulus may be involved and the remainder show no alterations. Concomitantly the number of nuclei of endothelial cells within the corpuscle diminishes until only a few remain. Within the capsule the same process takes place. Ultimately the tuft and capsule may fuse with the formation of a hyaline sphere (Fig. 8). Such occurrences are infrequent, although it is not unusual to see the glomerular tuft represented by a hyaline globule upon which is mounted a single layer of low cuboidal epithelium, separated by a broad or narrow space from Bowman's capsule. The lesion was most frequently seen in the stages of partial hyalinization of the tuft and capsule. Rarely, a few round cells and plasma cells are seen in the interstitial tissue adjoining the affected glomeruli. In

some arterioles no changes were demonstrable, while the glomeruli were the site of the alterations described; especially when the number of lesions was extremely scant and only a few were discovered in a whole section. This may be due to the fact that the vasa afferentia supplying the involved glomerulus did not appear in the section. It is also possible that these arterioles had recovered completely.

These lesions were rarely found in infants above 18 months of age. The altered glomeruli were probably completely hyalinized, leaving a delicate scar which eventually cannot be recognized.

Clinical Features

Age. The average age of the infants whose kidneys were studied was 2.7 months; 78 were less than 3 weeks of age and 22 were more. There were 4 stillborn infants. The oldest child was 14 months of age. The lesion was observed in premature infants as well as in those born at term and in first-born as well as subsequent offspring.

Sex. Among the 30 infants showing the lesion there were 22 males and 8 females, a preponderance of the former in a ratio of 2.7 to 1.

Race. Both white and colored children were affected. The greater number of white babies (24 of 30) is proportionate to the greater number of admissions of white patients.

Symptoms and Signs. There were no characteristic symptoms or signs, nor could any definite clinical syndrome be established. One patient showed anasarca, hydrothorax and ascites, which could be ascribed to renal damage; another showed only edema of the extremities. One infant died in uremia. Other symptoms and signs were referable to accompanying illnesses.

Urinalysis. In ten cases urinalysis was not performed. In the others the results of urinalysis were essentially negative, except for two cases in which occasional red blood cells were noted in the urinary sediment. Five infants showed mild albuminuria, attributable to other causes, such as fever.

Etiology and Associated Pathological Findings

The factors which theoretically may contribute to production of the lesion may be maternal or fetal, or a combination of these.

Concerning maternal factors, nothing definite could be established. There was no evidence or record of renal disease, or toxemia of pregnancy in any of the mothers. There was no high incidence of maternal infections. It is true that some of the mothers had colds during pregnancy, but whether this plays any significant rôle could not be ascertained. Five of the mothers had syphilis; active, latent, or cured. In only two instances did the children born of these mothers show positive serological tests and in only one of these were evidences of congenital

syphilis found at necropsy. The other child died from hemorrhagic encephalitis following therapy with arsenical derivatives. It is theoretically possible that some maternal factors—toxic, infectious, or hormonal—acting singly or together on the fetus *in utero*, may be responsible for the lesion described. That some of these lesions develop *in utero* cannot be questioned inasmuch as they were observed in stillborn infants. It is possible that some of the lesions of older children may have developed after birth.

As to the child itself, the lesions may be developmental, inflammatory, degenerative or vascular in origin. According to Herxheimer,[7] the frequency of the condition, its occurrence in newborn infants and the absence of evidence of any inflammatory reaction indicated to him that it was probably non-inflammatory in origin. He attributed the condition to retarded development of the kidney. Although Herxheimer made no mention of vascular changes, they were conclusively demonstrated in almost all sections studied by us. Our impression is that alterations in the blood vessels are the significant etiological factors in this condition. What causes these vascular changes is still a problem.

The associated pathological findings may be classified as follows (there is some overlapping, more than one condition having been disclosed at necropsy in many of the infants):

I. Infectious diseases
  - Meningitis, 3
  - Abscesses of skin, 2
  - Sepsis, 2
  - Peritonitis, 1
  - Otitis media, 3
  - Pneumonia, 8
  - Empyema, 1
  - Acute bacterial endocarditis, 1

II. Anomalies of the heart and great vessels, 5

III. Cerebral lesions
  - Porencephaly, 1
  - Anencephaly, 1
  - Hydrocephalus, 1
  - Hemorrhagic encephalitis, 1
  - Laceration of tentorium cerebelli with hemorrhage, 1

IV. Blood dyscrasias
  - Thrombocytopenia, 1
  - Leukemic myelosis, 1
  - Unexplained widespread hemorrhage, 1
  - Erythroblastosis, 1

V. Anomaly of kidney, 1

VI. Metabolic disorders
  - Rickets, 2

VII. Obstetrical abnormalities
  - Prematurity, 2
  - Breech presentation, 1
  - Difficult labor, 1
  - Premature separation of placenta, 1

From a consideration of these findings it is quite evident that nothing definite as to the etiology can be concluded. The lesions noted are commonly found as causes of death in infants and there is no preponderance of any single factor.

Comment

The significance of the pathological changes in the arterioles and glomeruli described above remains to be determined. They appear to be of no moment where only scattered glomeruli and arterioles are involved. Certainly their presence in 17 of 100 consecutive cases places them almost within the realm of the normal. However, when sufficiently widespread, renal functional damage may occur with the appearance of anasarca or uremia. Whether these lesions play any rôle in predisposing or leading to renal lesions in later life, such as glomerulonephritis or arterial and arteriolar sclerosis, is, of course, only conjectural.

We hesitate to apply any name to the pathological picture described. Until the etiology is ascertained, such a step would be premature. Since the lesions are both proliferative and degenerative in nature, it might be worth while, *pro tempore,* to apply the descriptive term of "congenital glomerulosclerosis" to these lesions. Their focal character possibly may be explained by irregularities in the distribution of functioning glomeruli. This is based upon the belief of some authorities that certain groups of glomeruli or even portions of a single glomerulus function at given periods of time.

These lesions were found by Herxheimer [7] in 88 per cent of the kidneys studied and by Schwarz [9] in 56 per cent. We found them in 30 of 113 cases. This low figure can be ascribed to the small number of sections studied from each case; in some only single sections of each kidney were studied.

Schwarz's [9] observation that the condition is more frequent above the age of 3 weeks has been confirmed. The incidence in infants below this age was 12.8 per cent and above this age, 31.8 per cent. We have been unable to explain this difference in incidence.

In studies upon the renal circulations, Huber,[11] Lee-Brown,[12] Loomis [13] and MacCallum [14] have described atrophic, pathologically altered glomeruli in otherwise normal kidneys (the number increasing with age) and in association with non-glomerulus-bearing blood vessels. It is believed that these vascular and glomerular changes represent involution of renal elements associated with the aging process. These lesions, we conclude, bear no relation to the condition described in this paper.

Summary

1. Certain glomerular and vascular changes in the kidneys of stillborn and newborn infants are discussed.

2. The lesions involve the arterioles and their appertaining glomeruli and are associated with hyaline changes in the tufts and capsules. They are bilateral and focal in distribution and are recognizable only by microscopical examination.

3. They are not associated with any clinical syndrome nor is their etiology or significance understood, although they are congenital and may be of vascular origin.

4. It is suggested that this lesion be termed congenital glomerulosclerosis.

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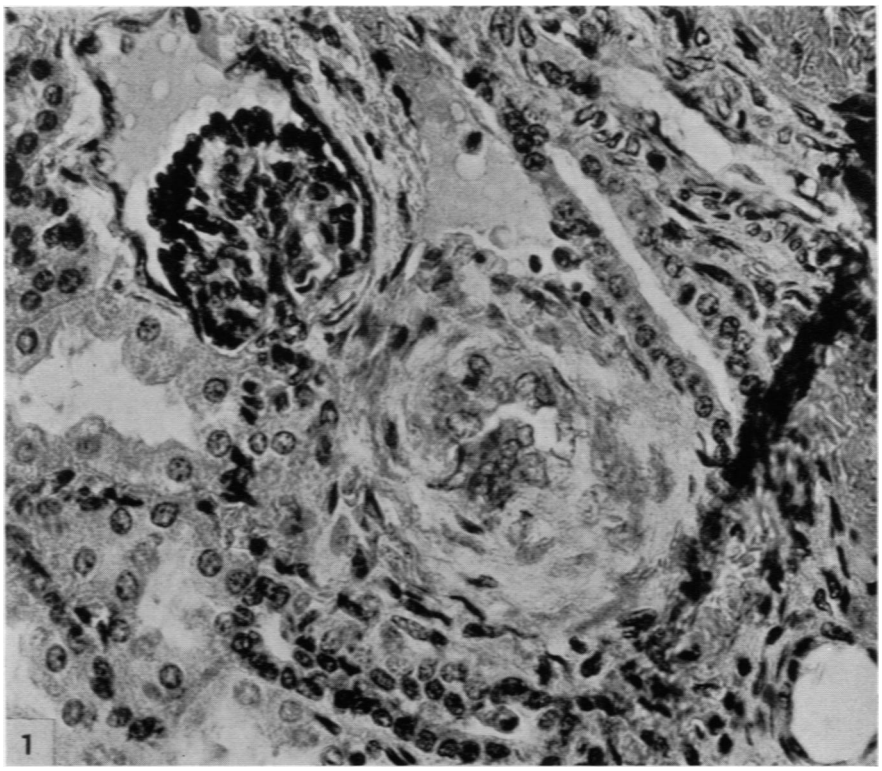
DESCRIPTION OF PLATES

PLATE 108

FIG. 1. Infant, aged 2 months. Arteriole with thickened wall, hyperplasia of endothelium and narrowing of lumen. Hematoxylin and eosin stain. × 600.

FIG. 2. Infant, aged 4 months. Endothelial and epithelial proliferation with "crescent" formation. Hematoxylin and eosin stain. × 350.



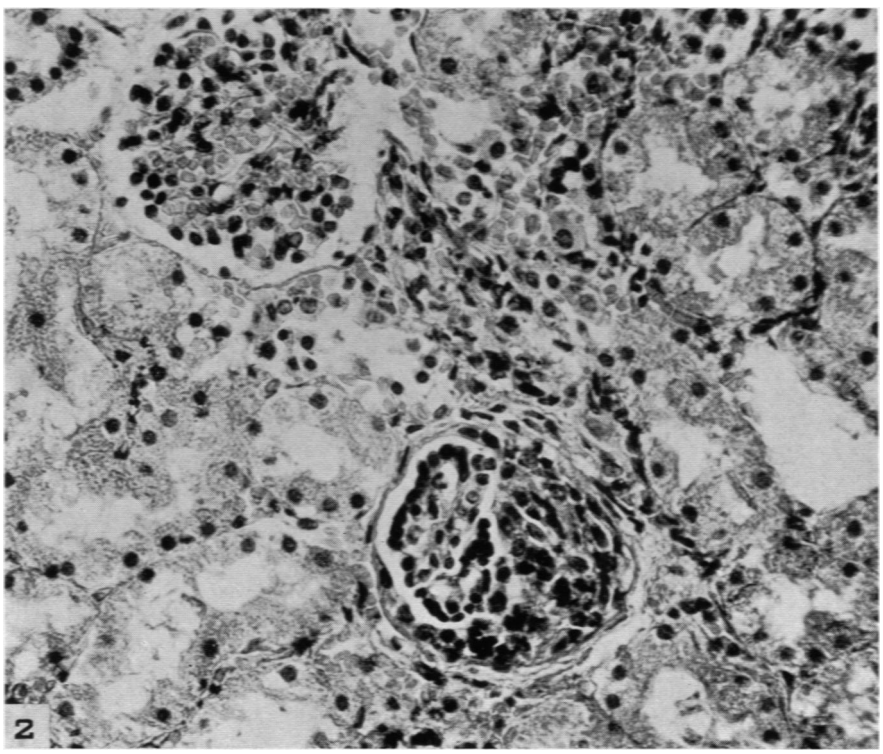


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PLATE 109

FIG. 3. Infant, aged 2½ months. Later stage than that of Figure 2 with marked proliferative changes, fusion of tuft and capsule with almost complete obliteration of subcapsular space. Hematoxylin and eosin stain. × 900.

FIG. 4. Stillborn infant. Beginning hyaline formation with slight capsular proliferation. Hematoxylin and eosin stain. × 525.

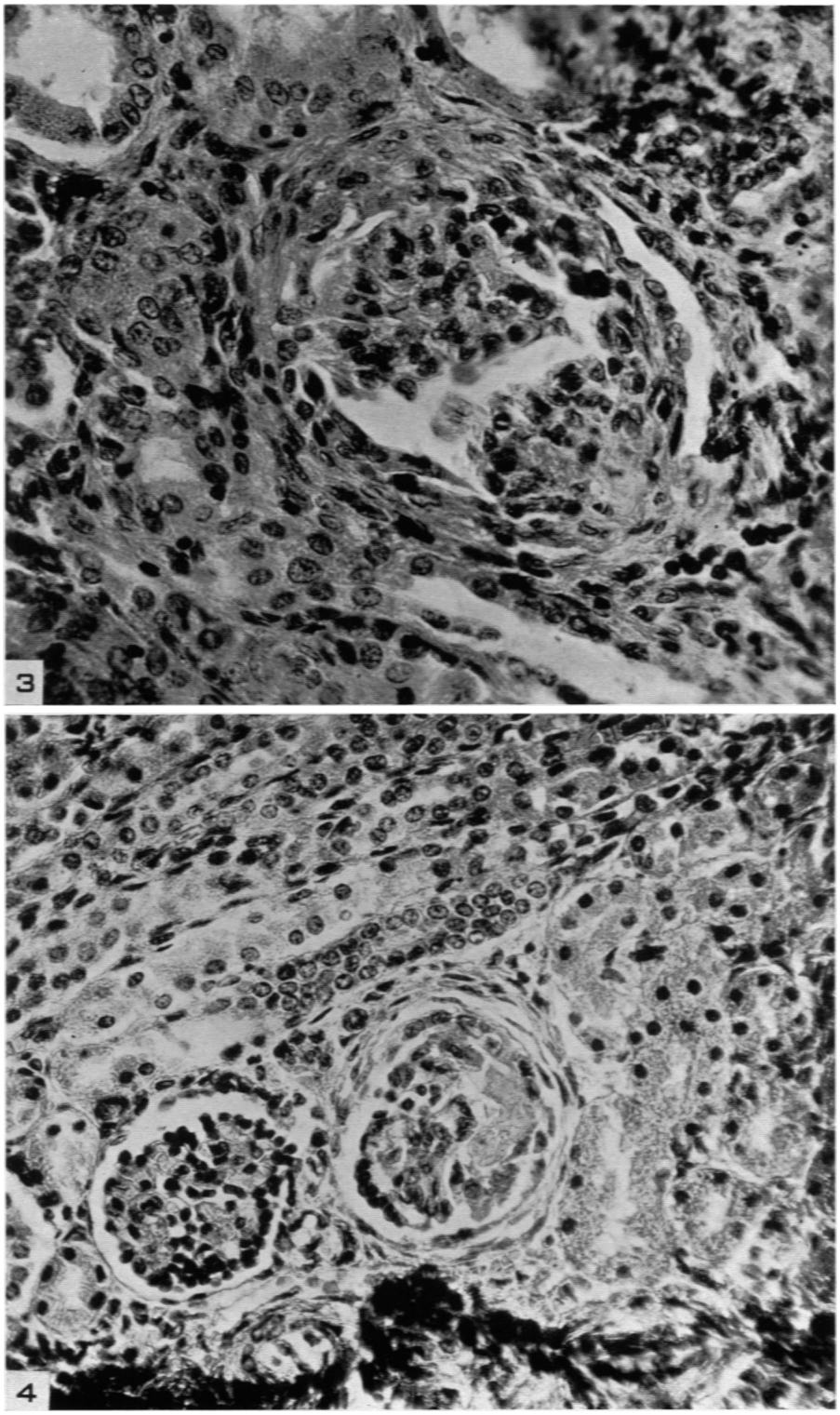

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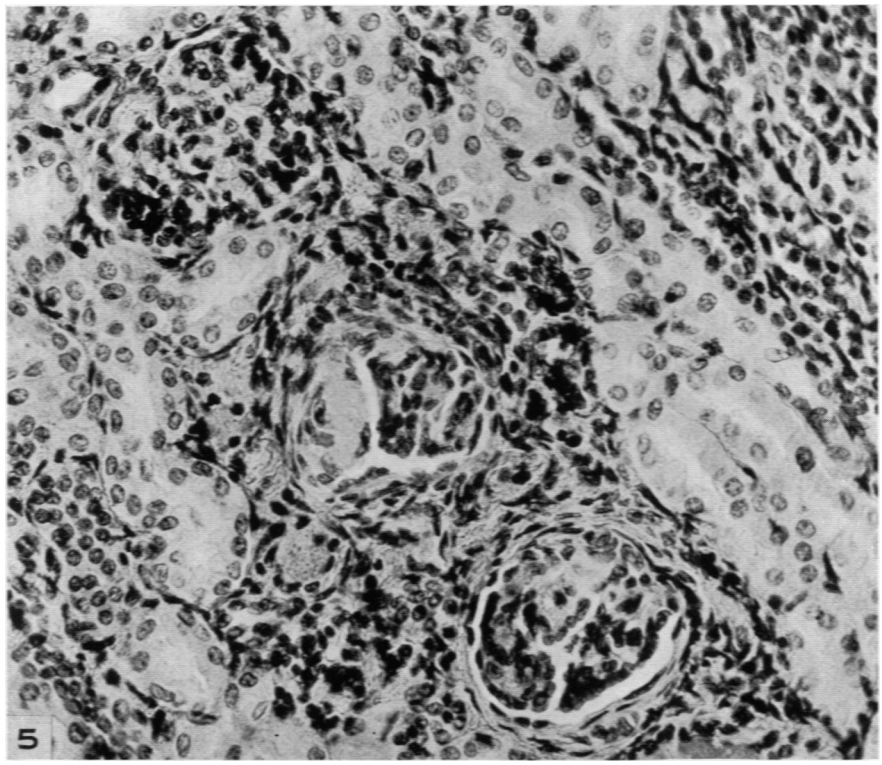
PLATE 110

FIG. 5. Infant, aged 3 weeks. Fusion of tuft and capsule, early hyaline changes and intraglomerular clefts. Hematoxylin and eosin stain. × 525.

FIG. 6. Infant, aged 12 months. Fusion of tuft and capsule, early hyaline changes and intraglomerular clefts. Hematoxylin and eosin stain. × 525.



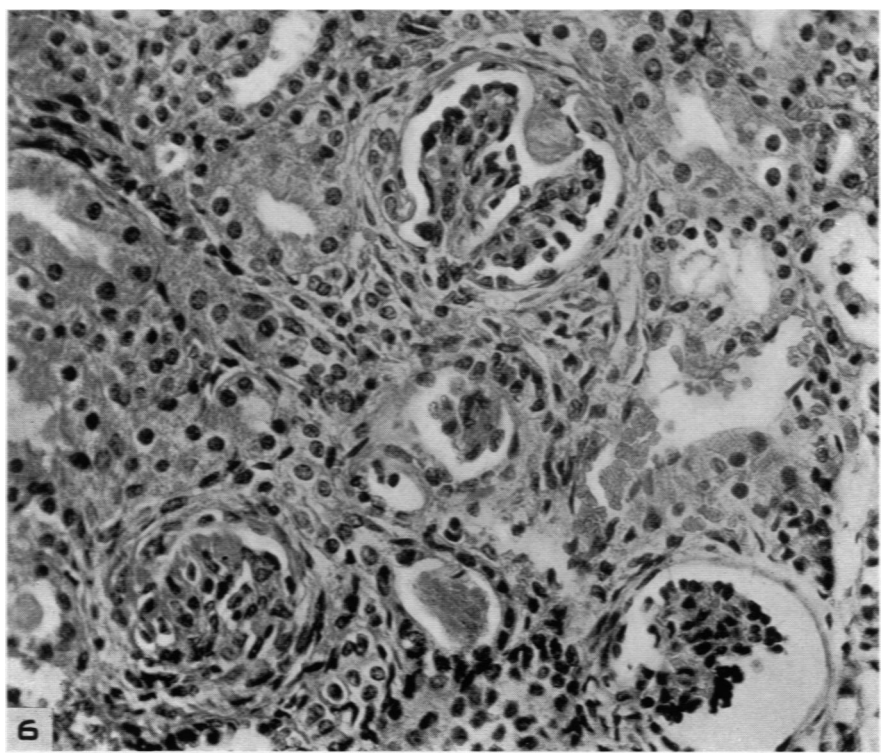


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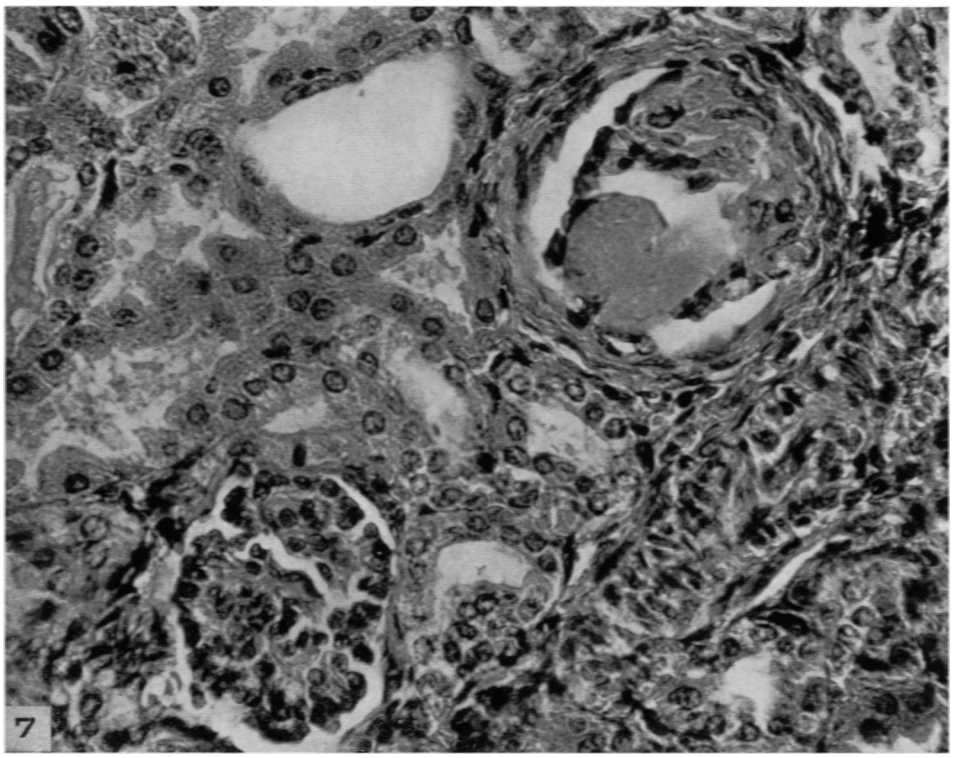
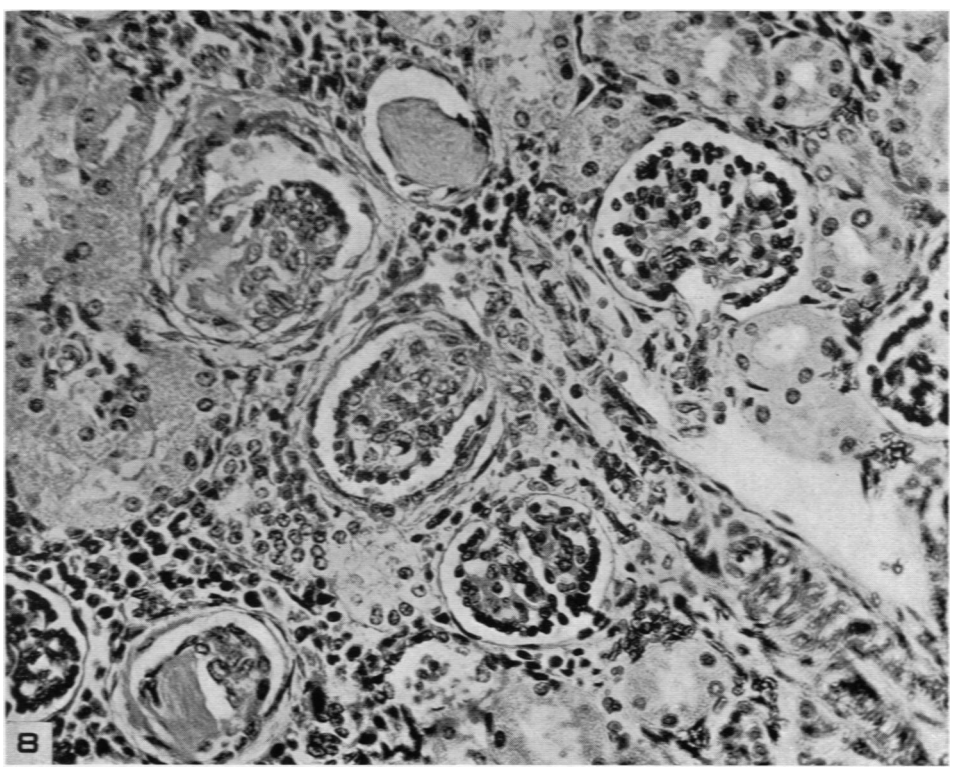
PLATE III

FIG. 7. Infant, aged 6 months. Advanced hyaline changes; thickening of parietal layer of Bowman's capsule. Hematoxylin and eosin stain. × 575.

FIG. 8. Infant, aged 10 days. Late lesion with partial to complete replacement of tuft by hyaline material. Hematoxylin and eosin stain. × 440.





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