# SUBACUTE GLOMERULONEPHRITIS *

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Subacute glomerulonephritis is the transitional phase between the acute and the chronic stages. As such, it provides an opportunity to examine the development of pathologic alterations which lead to eventual glomerular obsolescence and chronic renal failure. Clinically, subacute glomerulonephritis encompasses the period 2 to 12 months after the onset of illness, and is characterized by albuminuria, edema, hypertension, and uremia. The typical anatomic feature is a large, smooth, pale kidney, which, on microscopic examination, shows cellular proliferation and fibrosis in the glomerular tufts, epithelial crescents, and alteration of the capillary walls.

With recent advances in microscopic technique, it has become possible to study glomerular lesions in greater detail by means of thin (0.5 $\mu$) sections stained by newer procedures or examined under the phase microscope. In a previous communication this technique was applied to the kidney in acute glomerulonephritis.[1] The present paper deals with observations in the various forms of subacute glomerulonephritis.

## MATERIAL AND METHODS

The tissues were taken from the files of the Department of Pathology of the Mt. Sinai Hospital and the Barnert Memorial Hospital. Case 23 was obtained from the Newark Beth Israel Hospital through the courtesy of Dr. M. Kannerstein, and case 24 from the Knickerbocker Hospital, New York City, through the courtesy of Dr. W. Finkelstein.

Twenty-eight cases were examined. Most of these fulfilled both the clinical and the pathologic criteria outlined above. However, for the sake of completeness, one case with prominent epithelial crescents was also included. The patient had a very short history of only two weeks. At the other extreme, there were a number of patients (8) with manifestations of renal disorder of 14 months' to 3 years' duration but who presented the anatomic and histologic features of the subacute stage.

The methods employed have been described previously.[1] Kidney tissues from paraffin blocks were re-embedded in celloidin-paraffin

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and cut serially at a thickness of 0.5 $\mu$. Sections were stained with hematoxylin and eosin, the periodic acid-Schiff reagent (PAS),[2] a modified Mallory chromotrope-aniline blue stain (CAB),[3] and the periodic acid-silver methenamine method (PA-SM).[4] Some sections were also stained with PAS-colloidal iron by the method of Ritter and Oleson,[5] and some were examined by phase microscopy.[6]

## Observations

### *Glomeruli*

The two classical histologic characterizations of the lesion in subacute glomerulonephritis are designated as the extracapillary and intracapillary, or better, intercapillary, types. In recent years "membranous glomerulonephritis" has been added as a separate form. In our experiments the division into these 3 types is somewhat artificial, because many patients show various combinations of changes, including proliferation of epithelial cells with crescent formation, proliferation of intercapillary cells and fiber production, and alteration of the capillary walls. However, for the sake of clarity, these changes will be discussed separately.

*Intercapillary Space.* The intercapillary alterations in subacute glomerulonephritis are the direct continuation of those seen in the acute phase. The onset of the subacute stage is signaled by the deposition of fibers among the proliferated mononuclear cells in the intercapillary space (Fig. 1). At the beginning of this stage, mononuclear cells still predominate in this region; a small number of polymorphonuclear leukocytes may be evident, and there is a variable degree of edema (Fig. 3). The fibers are generally slender and tortuous, and stain red with the PAS and blue with the CAB stains. The entire intercapillary space is enlarged. The capillaries are shifted to the periphery of the lobule and are partly compressed (Fig. 1). They may contain a few red cells but are often empty. With progression of the disease, edema and leukocytes disappear completely, the mononuclear cells are fewer, and fibers increase in number and thickness. In many cases, hyaline material appears in the intercapillary space (Fig. 2). This substance stains red with PAS and pink to red with CAB. It appears to lie between the fibers, though often it fuses with them. Occasionally one gains the impression that the fibers themselves undergo hyaline transformation. Toward the end of the subacute stage, the intercapillary space becomes converted into a fibrous or fibro-hyaline mass containing but few cells. The size of the scar varies from case to case and from lobule to lobule. Some of the capillaries remain patent while others are completely collapsed.

*Epithelial Cells and Bowman's Space.* Proliferation of epithelial cells may occur early in the disease. Some of the patients dying within 2 to 4 weeks after the onset of acute glomerulonephritis reveal luxuriant epithelial crescents. Whether crescents appear early or late, their structure is the same. The proliferating cells are, as is well known, those of the parietal layer of Bowman's capsule. Thin fibers lying between the cells contribute toward formation of so-called pseudo-tubules. The fibers often appear to originate from the inner layer of Bowman's capsule and to branch among the epithelial cells (Fig. 14). This suggests that they are products of the basement membrane of Bowman's capsule rather than newly formed fibers. The membranes or fibers are at first thin and delicate, staining red with PAS and blue with CAB stains. However, they undergo rapid transformation, becoming thicker and less intensely eosinophilic, and losing their affinity for PAS. As the fibers increase in thickness, the epithelial cells decrease in number and eventually disappear, giving rise to so-called "fibrous crescents."

Not all fibrous crescents arise from the epithelial crescents. It is our impression that some of them are the result of repeated splitting, fibrosis, and hyalinization of Bowman's capsule. Alterations of this nature can be observed even in the acute stages of glomerulonephritis, and they are common in the subacute stage.

The visceral glomerular epithelium is often prominent in glomerulonephritis. Whether this is the result of actual multiplication or merely of swelling is difficult to state. These cells frequently contain hyaline droplets analogous to droplets observed in the epithelium of the tubules, or in the parietal epithelium of Bowman's capsule (Fig. 13). The hyaline droplets are usually accompanied by the appearance of hyalin in the intercapillary spaces.

*Capillary Wall.* Changes in the capillary wall may proceed in two directions. Attenuation of the basement membrane and even complete local disappearance sometimes accompany deposits of hyaline material in the capillary lumen. The hyaline appears to spill through a break in the wall into Bowman's space.

Much more frequently encountered is thickening of the capillary wall. This may be due to splitting or reduplication of the wall, so that internal to the basement membrane and separated by a space of varying width (pericapillary space) there is another membrane which varies in thickness and is sometimes discontinuous (Fig. 8). This second ("endothelial") membrane probably represents the innermost layer of the original basement membrane split off by extension of exudate from the intercapillary space, as observed in acute glomerulonephritis.[1] Connection between the intercapillary space and the peri-

capillary space can often be demonstrated (Fig. 10). The pericapillary space may contain a few cells but otherwise appears empty in sections (Fig. 8); in life it is probably filled with fluid or other substance that is easily washed out in processing tissue.

Splitting or reduplication of the wall is usually focal and variable. It rarely affects the whole glomerulus and rarely affects the majority of the glomeruli. If hyaline deposits are found in the intercapillary space, they may also be present in the pericapillary space. The hyalin is strongly eosinophilic, staining red with PAS and CAB. The affected capillary bears a considerable resemblance to the "wire loop" of lupus erythematosus (Fig. 10). Splitting of the capillary wall may also occur as a result of deposits of hyalin, causing separation of the endothelium (*membrana attenuata*)[7] from the basement membrane. This type of "wire-loop" thickening appears homogeneous with hematoxylin and eosin and PAS stains (Fig. 11), but the deposits can be clearly distinguished from the basement membrane by the PA-SM stain (Fig. 12).*

Another type of thickening of the capillary wall frequently associated with the nephrotic syndrome is the "membranous glomerulonephritis" described by Bell[8] (Figs. 3 to 6). The endothelium and basement membrane here appear little altered. However, between the basement membrane and the epithelial cells, there is a layer which can be quite wide (1 to 2 $\mu$ or more). This layer consists of two elements: hair-like or spike-like projections perpendicular to the basement membrane and spaced about 0.5 to 1.0 $\mu$ apart; and hyaline material deposited between these spikes. The spikes rest with their narrow points upon the basement membrane and widen toward the periphery. They sometimes appear to merge at their bases, creating a scalloped edge covering the hyaline deposit. The edge and the spikes stain red with PAS and blue with CAB. They are also strongly black with the PA-SM stain[4] and are blue when stained by the Ritter-Oleson procedure. The hyalin stains pale pink with PAS, red with CAB, and does not stain with PA-SM stains. Preliminary studies with electron microscopy suggest that the hyalin accumulates between the basement membrane and epithelial cells (podocytes) and that the spikes are in some way related to the epithelial trabeculae and foot processes. Within the cytoplasm and parallel to the basement membrane, one can frequently see a row of fine dots which stain red with the CAB stain. The significance of these dots is not clear at the present time.

* Though both the PAS and PA-SM stains are supposed to demonstrate the same chemical groupings, our experience has shown that there are consistent differences between the results obtained by the two methods which may serve differential staining purposes.

*Endothelial Cells and Capillary Lumen.* The endothelial cells often appear enlarged and have prominent nuclei. In some of the cases with manifestations of the nephrotic syndrome, the cytoplasm of the endothelium is markedly swollen and filled with fine vacuoles presumably because of lipid imbibition (case 25). The lumen of the partly collapsed capillaries is sometimes filled with homogeneous material which stains pale pink with eosin and PAS. Presumably this represents inspissated blood plasma.

In summary (Tables I and II), among the 28 examples examined, significant alterations (2+ or greater) in the various components of the glomerulus were distributed as follows: alteration of the intercapillary space, 19; crescent formation, 13; changes in the capillary wall, 17 (3 showed splitting; 7, splitting and hyaline deposit; and 7, membranous transformation). Vacuolization of endothelial cells was noted in one patient. These figures add to more than 28 because of frequent multiplicity of lesions. The actual distribution among the 28 cases was as follows: lesions predominantly intercapillary in location, 12 (8 with hyalinization and fibrosis; 4 with fibrosis alone); lesions predominantly extracapillary in location, 7; entirely or predominantly membranous, 5. Four cases were classified as mixed; cases 26 and 28 had combined extra- and intercapillary lesions of about equal intensity; case 26 also showed widespread splitting and deposit of hyalin in the capillary walls. Two other cases (25 and 27) exhibited mild membranous alterations and also epithelial crescent formation and intercapillary inflammation.

### *Renal Tubules and Stroma*

A brief mention should be made of the tubular alterations encountered. These were characterized by the appearance of hyaline droplets, vacuolization of epithelium, and varying, generally moderate, degrees of atrophy. In many instances there was slight and occasionally even marked thickening and reduplication of the tubule basement membranes (Fig. 15). In some, the interstitial tissue showed slight to moderate inflammation.

### *Blood Vessels*

As a rule, the arteries exhibited little abnormality. In a few instances, particularly in older patients, there was moderate to advanced arteriosclerosis. In specimens in which hyaline deposits appeared in glomeruli, arterioles were often affected by the same process (Fig. 16). In 3 patients there were thrombi in the renal veins; in one of these the thrombosis was bilateral. In two cases the thrombi were recent; in one the thrombus was old and recanalized. In all 3 cases

TABLE I

*Summary of Alterations in Patients with Subacute Glomerulonephritis, Intercapillary and Extracapillary Types*

| Case no. | Sex | Age (yrs.) | Period of illness (mos.) | Blood pressure | Edema | Urine: Specif. gravity | Urine: Albumin | Urine: Red blood cells | Blood urea nitrogen (mg.) | Cholesterol (mg.) | Albumin/globulin ratio | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 4 | 14 | 160/90 | 3+ | 1034 | 4+ | 1+ | 8–17 | 880 | 1.7/2.7 | Pneumococcus peritonitis; sepsis |
| 2 | M | 12 | 24 | 160/64 | 0 | 1012 | 1+ | 0 | N.D. | N.D. | N.D. | Pneumococcus sepsis |
| 3 | F | 14 | 30 | 160/90 | 0 | 1016 | 4+ | 1+ | 50–110 | 280 | N.D. | Meningococcus meningitis; uremia |
| 4 | F | 29 | 3 | 170/104 | 1+ | 1020 | 3+ | 1+ | 36–85 | 240 | 2.5/1.6 | Cardiac failure |
| 5 | F | 10 | 3 | 200/110 | 2+ | 1018 | 3+ | 3+ | 125 | 300 | 2.1/1.9 | Uremia |
| 6 | F | 11 | 10 | 170/130 | 3+ | 1010 | 3+ | 1+ | 16–30 | 1000 | 1.7/1.9 | Postop. heart failure |
| 7 | M | 15 | 5 | 100/60 | 1+ | 1006 | 3+ | ± | 238 | N.D. | N.D. | Uremia |
| 8 | F | 15 | 18 | 185/135 | 3+ | 1016 | 4+ | 1+ | 17–28 | 500 | 2.5/2.1 | Pneumonia |
| 9 | M | 21 | 12 | 176/116 | 1+ | 1012 | 3+ | 3+ | 98–180 | N.D. | 3.2/1.3 | Uremia |
| 10 | M | 21 | 2? | 220/140 | 1+ | 1011 | 3+ | 1+ | 98–228 | 290 | 4.1/2.1 | Uremia |
| 11 | M | 35 | 18 | 190/110 | 3+ | 1017 | 4+ | 1+ | 50–396 | 600 | 2.3/2.9 | Uremia; pneumonia |
| 12 | M | 38 | 18 | 135/110 | ± | 1020 | 2+ | 1+ | 12–70 | 225 | 3.5/1.9 | Cardiac failure; anemia |
| 13 | F | 8 | 3 | 170/110 | 2+ | 1020 | 4+ | 3+ | 156–234 | N.D. | 2.5/3.8 | Uremia |
| 14 | M | 10 | ½? | 150/90 | 4+ | 1020 | 4+ | 3+ | 240 | 190 | 3.1/2.2 | Uremia |
| 15 | M | 36 | 2½ | 120/70 | 0 | Low | 3+ | 3+ | 146 | N.D. | N.D. | Uremia |
| 16 | F | 38 | 2½ | 160/86 | 0 | 1021 | 1+ | 2+ | 136 | N.D. | N.D. | Uremia |
| 17 | M | 41 | 12 | 170/70 | 3+ | 1012 | 1+ | 2+ | 15–64 | 230 | 2.4/2.0 | Cerebral hemorrhage |
| 18 | F | 45 | 2½ | 175/90 | 2+ | 1012 | 3+ | 1+ | 70 | N.D. | N.D. | Cardiac failure |
| 19 | F | 49 | 9 | 110/80 | 3+ | 1020 | + | + | 56 | N.D. | N.D. | Pneumonia |

Numbers 1 to 4 (4 patients) represent intercapillary type without hyalinization. Numbers 5 to 12 (8 patients) represent intercapillary type with hyaline deposits. Numbers 13 to 19 (7 patients) represent extracapillary type.

the clinical course was marked by a nephrotic syndrome and there was membranous transformation of the glomerular capillary walls.

### *Clinico-pathologic Correlation*

The salient clinical data and the main pathologic features are listed in Tables I and II. A few points relating to clinico-pathologic correlation are worthy of notice. The average age at the time of death was lowest in those in whom the lesions were predominantly intercapillary

TABLE I (continued)

| Kidney | Obs. glom. (%) | Intercapillary space: Inflammation | Intercapillary space: Fibrosis | Intercapillary space: Hyalin | Capillary wall: Split | Capillary wall: Hyaline deposit | Capillary wall: Memb. trans. | Capillary wall: Epith. cresc. | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| Very large, 275 gm. both; pale, smooth, yellow | 10 | 2+ | 2+ | 0 | 0 | 0 | 0 | 1+ | Nephrotic syndrome |
| Large, 310 gm. both; smooth | 0 | 2+ | 3+ | 0 | 1+ | 0 | 0 | 0 | Acute and chronic rheumatic heart disease |
| Very large with yellow flecks | 10 | 4+ | 4+ | 0 | 1+ | 0 | 0 | 0 | |
| 300 gm. both; smooth, pale; many hemorrhages | 0 | 2+ | 1+ | 0 | 4+ | 0 | 0 | 0 | |
| Large, smooth | 5 | 2+ | 2+ | 2+ | 2+ | 1+ | 0 | 2+ | Nephrotic syndrome |
| Large, 280 gm. both; fine, yellow, granular | 0 | 3+ | 4+ | 2+ | 2+ | 0 | 0 | 1+ | Nephrotic syndrome; decapsulation |
| Large, smooth | 50 | 2+ | 3+ | 3+ | 1+ | 1+ | 0 | 0 | "Familial" type; few "wire loops" |
| Very large, 575 gm. both; smooth, yellow | <2 | 3+ | 2+ | 2+ | 1+ to 4+ | 0 to 4+ | 0 | 1+ | Nephrotic syndrome; "wire loops" |
| 330 gm. both; smooth | 50 | 2+ | 3+ | 3+ | 2+ | 1+ | 0 | 1+ | |
| Reduced in size; coarsely granular | 25 | 2+ | 3+ | 2+ | 2+ | 2+ | 0 | 2+ | Osteomyelitis; amyloid in liver |
| 320 gm. both; smooth, pale, yellow | 5 | 0 to 2+ | 0 to 2+ | 1+ | 2+ | 1+ | 0 | 0 | Nephrotic syndrome |
| Large, 450 gm. both; slightly granular | <2 | 2+ | 2+ | 2+ | 0 to 4+ | 0 to 4+ | 0 | 1+ | "Wire loops" |
| Large, 340 gm. both; pale; hemorrhages | 0 | 2+ | 2+ | 0 | 1+ | 0 | 0 | 4+ | |
| Very large, 360 gm. both; yellowish, slightly granular | 0 | 3+ | 1+ | 0 | 0 | 0 | 0 | 4+ | |
| Large, 430 gm. both; smooth | 0 | 2+ | 1+ | 0 | 0 | 0 | 0 | 4+ | |
| Large, edematous | 0 | 1+ | 1+ | 0 | 1+ | 0 | 0 | 3+ | |
| Large, 575 gm. both; smooth, pale; hemorrhages | 0 | 1+ | 1+ | 0 | 2+ | 0 | 0 | 4+ | |
| 290 gm. both; smooth | 5 | 1+ | 1+ | 0 | 1+ | 0 | 0 | 4+ | |
| Large, 480 gm. both; finely granular | 2 | 2+ | 2+ | 0 | 0 | 0 | 0 | 3+ | |

Key to abbreviations: Obs. glom. = Obsolete glomeruli. Memb. trans. = Membranous transformation. Epith. cresc. = Epithelial crescents. N.D. = No data. ± to 4+ = Degree of change: ±, minimum; 4+, maximum.

in location (20 years); those with extracapillary lesions were next, with an average of 32 years; and those with membranous alterations were older still (48 years). The average duration of the disease was shortest in the patients with extracapillary lesions (5 months) and longest in those with the membranous type of process (18 months). Those with the intercapillary type fell between with an average duration of 13 months (11 months for those with hyaline deposits and 18 months for those without such deposits). These points are generally in

TABLE II

*Summary of Alterations in Patients with Subacute Glomerulonephritis, Membranous and Mixed Types*

| Case no. | Sex | Age (yrs.) | Period of illness (mos.) | Blood pressure | Edema | Urine | | | Blood urea nitrogen (mg.) | Cholesterol (mg.) | Albumin/globulin ratio | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Specif. gravity | Albumin | Red blood cells | | | | |
| 20 | M | 23 | 36+ | 190/100 | 3+ | N.D. | 3+ | 1+ | 110–134 | N.D. | 3.9/2.1 | Paratyphoid fever |
| 21 | F | 48 | 9 | 155/100 | 4+ | 1028 | 4+ | 0 | 22 | 500 | 2.2/2.0 | Pulmonary embolism; nephrosis |
| 22 | M | 50 | 12 | 200/110 | 3+ | 1025 | 4+ | 0 | 16 | 530 | 2.3/1.8 | Convulsions; cerebral edema (?) |
| 23 | M | 53 | 18 | 210/110 | 1+ | 1014 | 4+ | + | 20–42 | 280 | 1.4/3.3 | Uremia |
| 24 | F | 68 | ? | 160/110 | 3+ | 1021 | 3+ | 1+ | 131 | N.D. | 2.4/2.4 | Uremia |
| 25 | F | 2 | 5 | 150/120 | 4+ | 1030 | 3+ | 1+ | 10–15 | 1280 | 1.0/2.7 | Generalized edema |
| 26 | F | 22 | 3 | 134/80 | 3+ | 1012 | 3+ | 3+ | 23–60 | 170 | 2.2/2.5 | Sepsis; staphylococcus |
| 27 | M | 58 | 3? | 154/90 | 0 | 1014 | 3+ | 3+ | 110–160 | N.D. | N.D. | Uremia; pneumonia |
| 28 | F | 67 | 3? | 150/90 | 1+ | 1010 | 1+ | 2+ | 51–110 | N.D. | N.D. | Uremia |

Numbers 20 to 24 (5 patients) represent membranous type. Numbers 25 to 28 (4 patients) represent mixed type.

agreement with the observations of Bell.[8] As expected in the subacute stage of glomerulonephritis, most patients had marked albuminuria and edema. Three plus or more albuminuria was found in 23 patients, and 3+ edema in 13 patients. The fully developed nephrotic syndrome was present in 10. In 5 patients intercapillary lesions with fiber splitting and "wire-loop" hyaline deposits in the capillary walls underlay the syndrome (ages 4, 10, 11, 15 and 35 years). In the other 5 patients (ages 2, 23, 48, 50 and 68 years) membranous lesions prevailed. Thus, among the 7 patients with membranous lesions, the nephrotic syndrome was manifest in 5, confirming the association noted by Bell. Membranous lesions were most pronounced in patients with the nephrotic syndrome of long standing. This was even more strikingly the case in patients who had had the nephrotic syndrome in the past but no longer exhibited the characteristic symptoms.

## COMMENT

The structure of the intercapillary space of the glomerulus and the nature of its cells and fibers in health and disease have been discussed elsewhere.[1,9] The cells are believed by various authors to be either of

TABLE II (continued)

| Kidney | Intercapillary space: Obs. glom. (%) | Intercapillary space: Inflammation | Intercapillary space: Fibrosis | Intercapillary space: Hyalin | Capillary wall: Split | Capillary wall: Hyaline deposit | Capillary wall: Memb. trans. | Capillary wall: Epith. cresc. | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 340 gm. both; pale, yellowish, slightly granular | 30 | o | o | o | o | o | 4+ | o | Nephrotic syndrome; renal vein thrombosis, recanalized |
| Large, 440 gm. both; smooth | o | o | o | o | o | o | 3+ | o | Nephrotic syndrome; bilateral renal vein thrombosis |
| Large, 320 gm. both | 2 | 1+ | 1+ | o | 1+ | o | 3+ | 1+ | Nephrotic syndrome; thrombosis in small renal veins |
| Large, pale, yellowish | 5 | 1+ | 1+ | 1+ | 1+ | o | 3+ | o | Operative specimen; patient died 6 mos. later |
| 335 gm. both; yellowish, slightly granular | 10 | o | 1+ | o | o | o | 3+ | o | Nephrotic syndrome |
| Very large, smooth, pale, yellowish | o | 2+ | o | o | o | o | 1+ | 2+ | Nephrotic syndrome |
| Large, smooth | <2 | 2+ | 2+ | 2+ | 3+ | 3+ | o | 2+ | "Wire loops" |
| 300 gm. both; smooth, pale; hemorrhages | 20 | 1+ | 1+ | 1+ | o | o | 2+ | 2+ | |
| 270 gm. both; slightly granular | 50 | 2+ | 2+ | 1+ | o | o | o | 3+ | |

Key to abbreviations: Obs. glom. = Obsolete glomeruli. Memb. trans. = Membranous transformation. Epith. cresc. = Epithelial crescents. N.D. = No data. ± to 4+ = Degree of change: ±, minimum; 4+, maximum.

connective tissue (histiocytic),[10,11] perithelial,[12] myoid,[13] or endothelial (endenchymal)[14,15] origin. The fibers are variously considered to be special connective tissue fibers (fibromucin),[16] "branches" of the basement membrane,[7] or "basement membrane like" material.[17]

Subacute glomerulonephritis of the intercapillary type is characterized by gradual replacement of the proliferated cells by fibers and the eventual formation of central lobular scars. Deposition of hyalin in the intercapillary space is a frequent but not invariable accompaniment of fibrosis. The hyalin is similar in its staining characteristics to that seen in arteriosclerosis. Presumably it is derived from the blood stream and deposited rather than formed locally, but at the present time nothing definite is known of its origin. The presence of hyalin is associated with a more rapid and more severe clinical course, the majority of the patients dying in uremia.

The fibers in the epithelial crescents differ from those in the intercapillary space. They arise from the basement membrane of Bowman's capsule, and their appearance in thin sections is consistent with the assumption that they arise as "branches" of the basement membrane.[9] At first they stain as do basement membranes, but later they acquire

the staining properties of collagen. It is not known whether they possess the characteristic electron microscopic periodicity of collagen.

Alteration of the capillary wall in glomerulonephritis received scant attention before Bell's observations in membranous glomerulonephritis.[8] We prefer the term "membranous transformation" because evidence of inflammation is often lacking. Bell described thickening of the capillary wall and indicated its frequent association with the nephrotic syndrome. The alteration has been shown by Jones[16] and by ourselves[9] to have a very characteristic structure. Jones suggested that the silver-positive bands or spikes were part of the basement membrane. It was our impression that they were related in some way to the trabeculae and foot processes of the epithelial cells. The hyaline material between the spikes stains differently from that found in the intercapillary space, in that it reacts weakly with the PAS stain.

Membranous transformation of the capillary wall occurs in subacute and chronic glomerulonephritis but is often unaccompanied by evidence of glomerular inflammation. Furthermore, it has been observed by us in association with other diseases such as lupus erythematosus and amyloidosis when these are accompanied by the nephrotic syndrome. Of special interest is the fact that the most severe forms of membranous transformation occur in patients who have had the nephrotic syndrome, but who no longer exhibit any of its clinical manifestations. These facts suggest that membranous transformation is neither a form of glomerulonephritis nor the cause of the nephrotic syndrome, but rather a result of the syndrome and the severe proteinuria which accompanies it. These changes may very well be caused by the trapping of protein between the basement membrane and the epithelial cells (podocytes), or in the outer layer of the basement membrane.

In none of our cases of membranous transformation was there much evidence of inflammation in the glomeruli, and in cases 20 and 21 such evidence was lacking completely. One may doubt, with good reason, the desirability of classifying these two instances as glomerulonephritis. It should be mentioned at this point that in selecting cases for this study we have omitted all examples of the nephrotic syndrome in which there were no obvious changes in the glomeruli as determined by light microscopy, or those which merely showed vacuolation of the glomerular endothelium. These cases will be reported in a later communication. On the other hand, inclusion of two examples of membranous transformation from other hospitals serves to exaggerate the frequency of this alteration in subacute glomerulonephritis.

Among our examples of membranous transformation there were 3

instances associated with renal vein thrombosis. It is well known that the latter may lead to the nephrotic syndrome[18] and possibly to membranous transformation. However, in none of our cases was there any evidence of venous thrombosis elsewhere in the body. In particular, there was no thrombosis of the inferior vena cava. The possibility must be considered that isolated thrombosis of renal veins is not always the cause of the nephrotic syndrome but rather may be its consequence.

Thickening of the capillary wall in subacute glomerulonephritis is most frequently the result of splitting of the wall into two layers. It is possible that such thickening may interfere with glomerular filtration. If hyalin accumulates between the split layers, the wall assumes the appearance of "wire loops." There has been some tendency in the literature to equate all thickening of the capillary wall with membranous transformation.[19] However, differences in the distribution and particularly in the structure of the various types of thickening militate against such generalization. We prefer to apply the term "membranous transformation" only to the lesion originally described by Bell, and to designate the other types of thickening as "splitting of the capillary wall" and "wire loop alteration" respectively.

The "wire loop" lesions of glomerulonephritis appear with less regularity and are less conspicuous than those in systemic lupus erythematosus and are also invariably associated with inflammation and hyaline deposits in the intercapillary space. It is our impression that the "wire loops" in lupus precede inflammation in the glomeruli or occur independently of it, while in glomerulonephritis they are secondary to the inflammation.

## Summary and Conclusions

Twenty-eight examples of subacute glomerulonephritis were studied by means of thin (0.5 $\mu$) sections.

The chief alterations observed in the glomeruli were: intercapillary inflammation and fibrosis, frequently accompanied by hyaline deposits; epithelial and fibrous crescents; thickening of the capillary wall caused either by splitting or reduplication, deposition of hyalin, or by "membranous transformation."

Each type of alteration is described and discussed in detail. Though most of the patients showed a predominance of one type of alteration, the great variety of possible combinations tended to impart an almost individual pattern to each case.

The nephrotic syndrome was present in 10 patients. In the younger age groups this was usually associated with intercapillary inflammation

and with splitting and hyaline deposits in the capillary wall. In the older age group it was more often accompanied by "membranous transformation" of the capillary wall.

"Membranous transformation" may be a feature in the lesion of subacute glomerulonephritis. It is suggested, however, that it is neither a part of the inflammatory process, nor the cause of the nephrotic syndrome, but rather a consequence of the latter.

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[ *Illustrations follow* ]

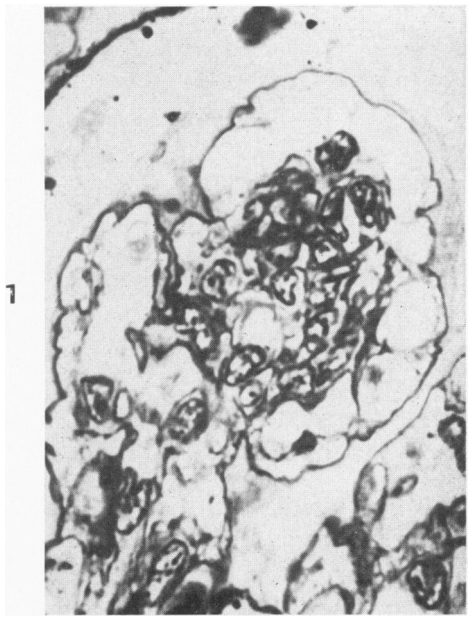
## LEGENDS FOR FIGURES

Standard sections were cut at 5 $\mu$, stained with hematoxylin and eosin, and photographed at a magnification × 600. Thin sections were cut at 0.5 $\mu$, stained with the periodic acid-Schiff reagent (PAS) or with periodic acid-silver methenamine (PA-SM) method, and photographed at magnification × 1,500.

FIG. 1. Case 8. Glomerular lobule, showing mononuclear cells and fibers in the intercapillary space. The capillary wall is thin and delicate, though some splitting is seen in the lower portion of the lobule. Thin section, PAS stain.

FIG. 2. Case 8. Lobule of another glomerulus, showing cells, fibers, and clumps of hyalin in the intercapillary space, and hyalin in the capillary walls. Thin section, PAS stain.

FIGS. 3 and 4. Case 25. Minimal thickening of the capillary walls is caused by early membranous transformation (arrows). Fig. 3. Standard section. Fig. 4. Thin section, PA-SM stain.



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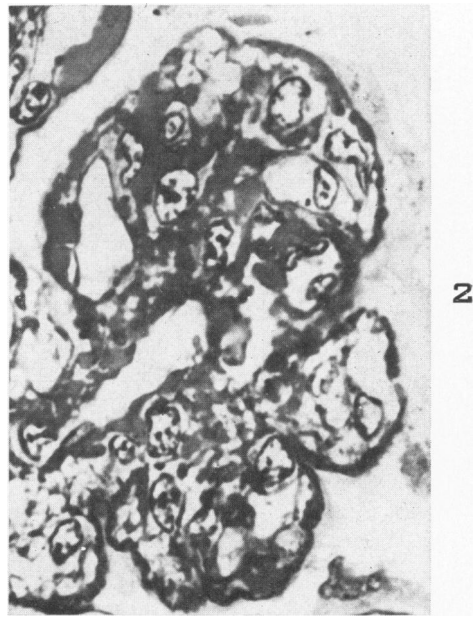

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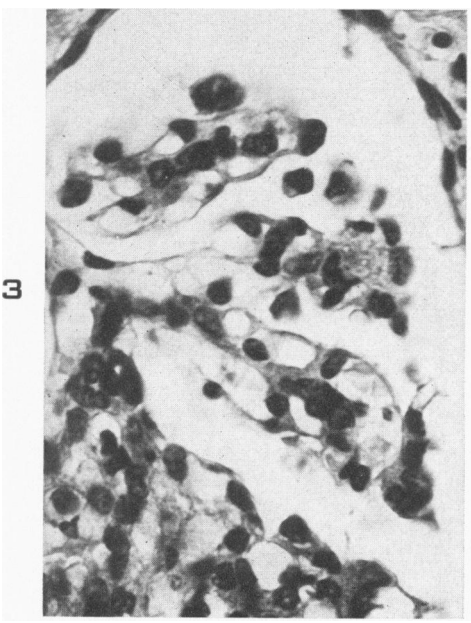

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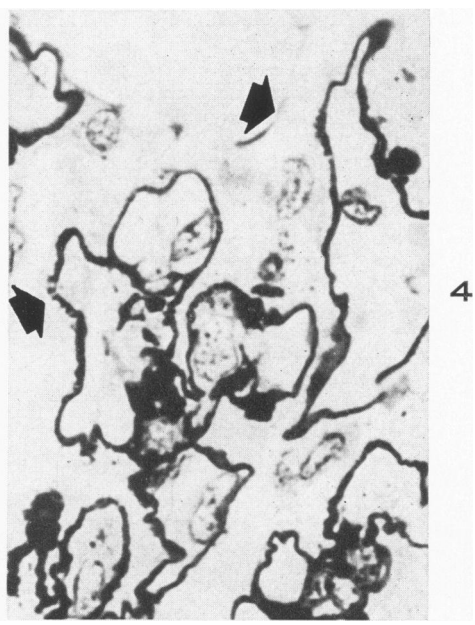

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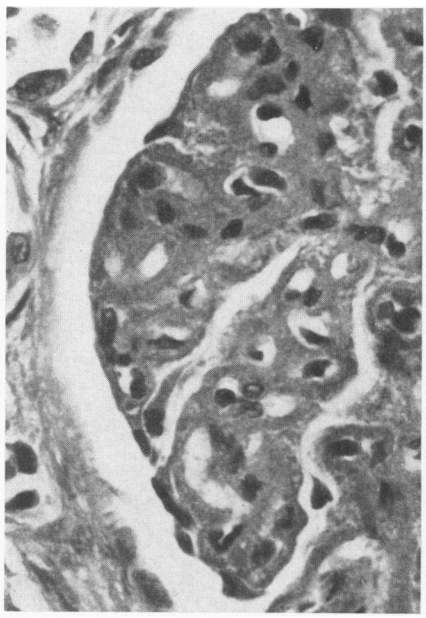
FIGS. 5 and 6. Case 20. Marked thickening of the capillary walls caused by advanced membranous transformation. Fig. 5. Standard section. Fig. 6. Thin section, PAS stain.

FIGS. 7 and 8. Case 4. Thickening of the capillary walls caused by splitting of the basement membranes. Cells can be seen between the split layers. Fig. 7. Standard section. Fig. 8. Thin section, PAS stain.



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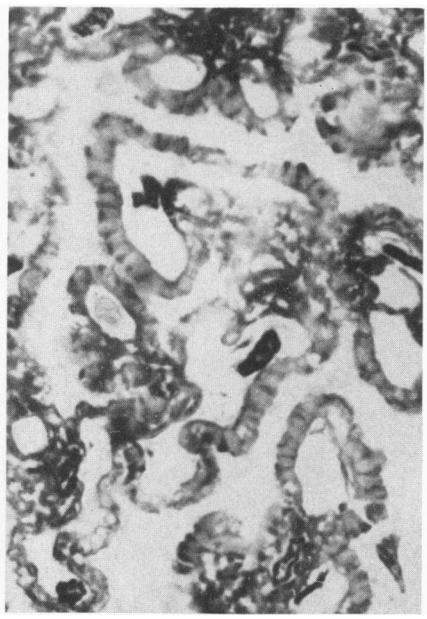

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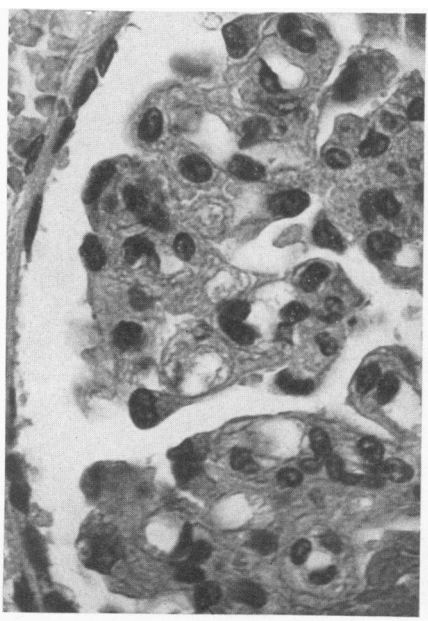

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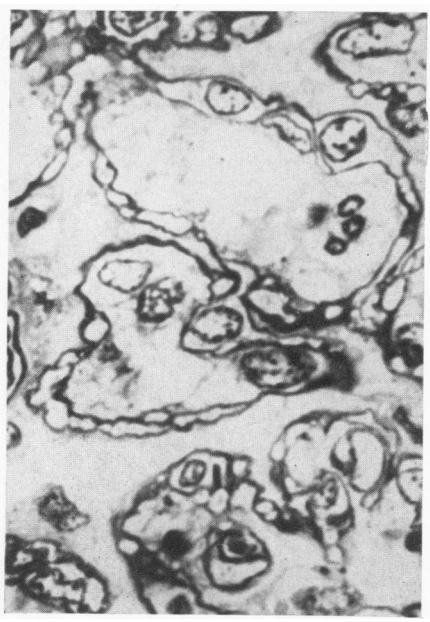

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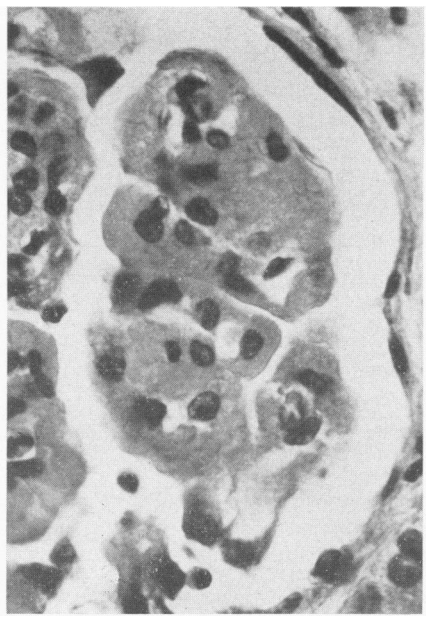
FIGS. 9 and 10. Case 12. "Wire-loop" thickening of the capillary walls is caused by deposition of hyalin between the split layers of basement membranes. In Figure 10 the "wire loops" can be seen along the periphery of the lobule (arrows); the widened intercapillary space in the center of the lobule also contains hyalin. Fig. 9. Standard section. Fig. 10. Thin section, PAS stain.

FIGS. 11 and 12. Case 26. In Figure 11 (section stained with PAS) capillary walls appear thick and homogeneous; in Figure 12 (stained with PA-SM) there is a thick deposit of weakly stained material, apparently between the basement membrane and the endothelium. Both figures, thin sections.



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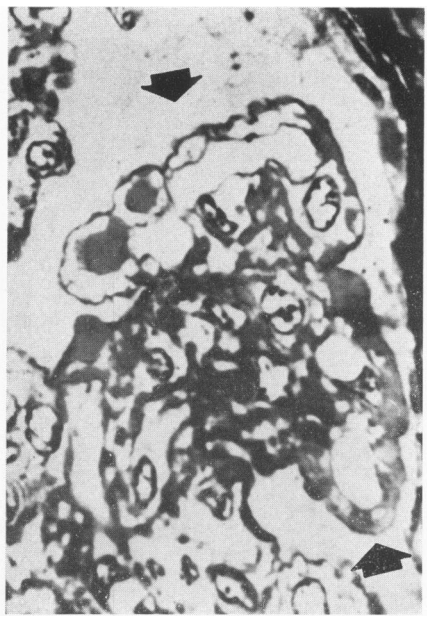

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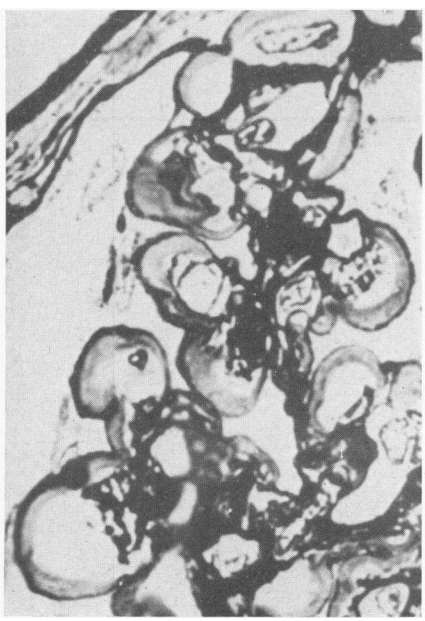

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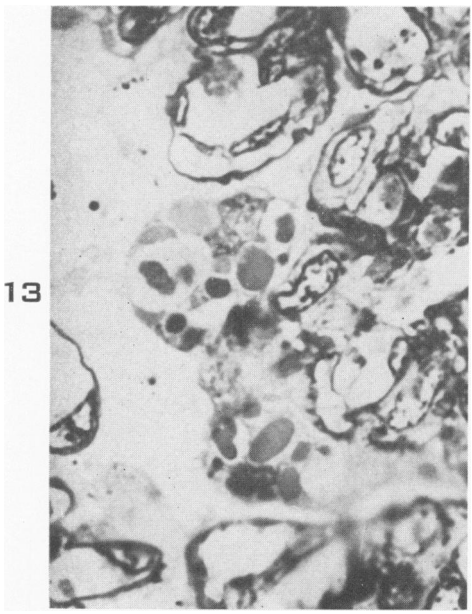
FIG. 13. Case 8. Hyaline droplets in visceral epithelial cells of the glomerulus (podocytes). Thin section, PAS stain.

FIG. 14. Case 16. Part of an epithelial crescent with pseudo-tubules, showing origin of "fibers" from the inner layer of Bowman's capsule (top). Capillary loops are in the right lower corner. Thin section, PAS stain.

FIG. 15. Case 11. Thickening and splitting of tubule basement membranes. Thin section, PAS stain.

FIG. 16. Case 8. Arteriole showing subintimal and medial deposits of hyalin. Thin section, PAS stain.



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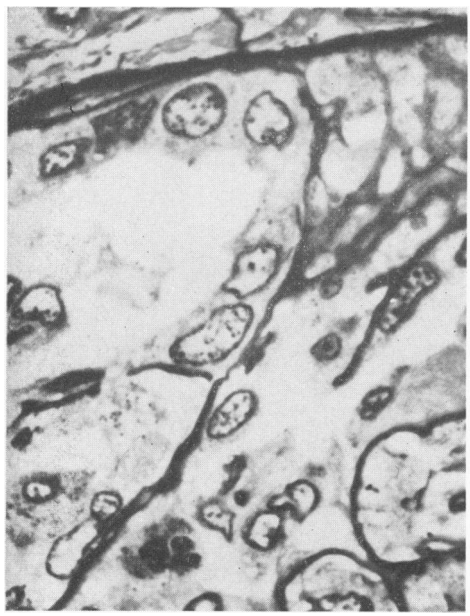

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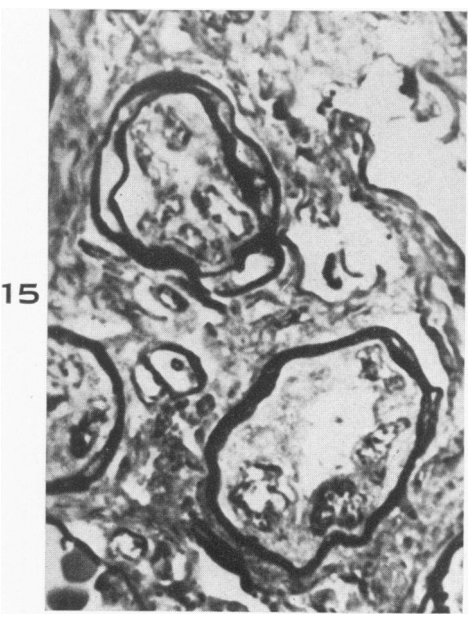

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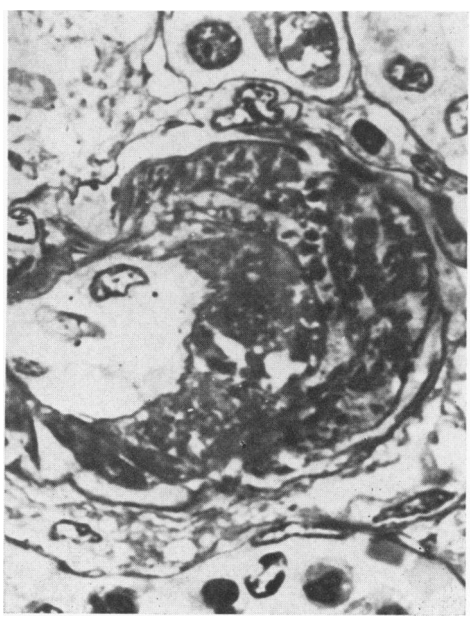

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