THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME XIV NOVEMBER, 1938 NUMBER 6

A CLINICAL AND PATHOLOGICAL STUDY OF SUBACUTE AND CHRONIC GLOMERULONEPHRITIS, INCLUDING LIPOID NEPHROSIS *

E. T. BELL, M.D.

(From the Department of Pathology, University of Minnesota, Minneapolis, Minn.)

In a previous report [1] the various types of acute nephritis were described. This publication is based on a study of 181 cases which have been classified in accordance with certain clinical and pathological features as follows:

Group I. Subacute glomerulonephritis, 16 cases.

Group II. Chronic glomerulonephritis in which death was due to an intercurrent disease, 8 cases.

Group III. Advanced chronic glomerulonephritis of azotemic type, 117 cases.

A. With a history of acute glomerulonephritis, 30 cases.

B. No history of acute nephritis; kidneys weighing together 250 gm. or more, 33 cases.

C. No history of acute nephritis; kidneys weighing together less than 250 gm., 54 cases.

Group IV. Chronic glomerulonephritis of the hydropic type, 40 cases.

A. With the glomerular structure of chronic proliferative glomerulonephritis, 6 cases.

B. With a glomerular structure largely of membranous but partly of proliferative type, 9 cases.

C. With a normal glomerular structure or a membranous type of glomerulitis, 25 cases.

* Received for publication June 16, 1938.

The distribution of the cases by groups and by decades is shown in Table I. It is to be noted that this is the age at death and not the time of onset of the disease. When a complete history is available it is usually found that the disease has been present a number of years. In the 30 cases of the chronic azotemic type in which the complete course of the disease is known (Table IV) the average age of onset is 20 years and the average age at death 30 years. About two-thirds of the patients die between the ages of 20 and 50 years, and since most of them are under treatment only during the advanced stages, the grouping shown in Table I cor-

TABLE I

Frequency and Age Distribution of Nephritis

Age	Total number of autopsies	Groups				Total
		I	II	III	IV	
yrs.						
0–10	4,710	1	0	1	9	11
10–20	1,103	3	0	10	3	16
20–30	2,186	3	2	30	6	41
30–40	2,032	2	1	33	10	46
40–50	4,000	2	1	23	6	32
50–60	4,151	3	2	10	3	18
60–70	4,076	1	0	8	2	11
70–80	2,590	1	1	2	1	5
80–90	700	0	1	0	0	1
90–100	50	0	0	0	0	0
Total	25,598	16	8	117	40	181

responds fairly well with patients under observation. The disease is by no means limited to children and young adults, although it is probable that a majority of the cases have their onset during these periods. There are, however, instances in which the disease begins in middle life or later. In our experience about one-half of the cases of fatal nephritis in children under 10 years of age are the hydropic type (lipoid nephrosis).

Frequency: It appears in Table I that the forms of nephritis under discussion are relatively rare and comprise only about 0.7 per cent of the total mortality. Chronic Bright's disease, which includes hypertensive renal insufficiency as well as all forms of chronic glomerulonephritis, causes only a little over 1 per cent of all deaths. The high incidence of nephritis in vital statistics is

due to the inclusion of a large number of cases of primary hypertension with albuminuria and edema resulting from myocardial failure.

Sex: In the entire group studied there were 105 males and 76 females, but in the postmortem series there are approximately twice as many males as females over 30 years of age. When a correction is made for this factor there seems to be no predominance of either sex.

Group I. Subacute Glomerulonephritis (Table II).

This group blends on the one side with the acute and on the other with the chronic type, and the limitations are somewhat arbitrary. Clinically cases that terminate in uremia after a course of a few months duration are usually called subacute. Pathologically fairly definite diagnostic criteria have been established. The kidneys are not contracted; they are either of normal size or enlarged. Microscopically one finds a severe and uniform obstruction of all the glomeruli, but there are no hyaline glomeruli (Fig. 1). There is a moderate uniform atrophy of all the tubules. Subacute nephritis is distinguished from the acute form by the presence of moderate tubular atrophy; there is very little atrophy in the acute type. It is distinguished from chronic nephritis by the moderate uniform tubular atrophy and the absence of hyaline glomeruli; in the chronic form there are patches of extremely atrophic tubules associated with hyaline glomeruli (Fig. 5).

The 16 cases listed in Table II were identified by their pathological features but the clinical duration was known accurately in nearly all of them.

Example of Subacute Glomerulonephritis (Case 2, Table II)

Clinical History: A boy, 16 years of age, was admitted to the hospital Sept. 16, 1937. There was no history of scarlet fever. He had had occasional attacks of sore throat, but there had been no infection of any kind during the year preceding his present illness. In the latter part of June, 1937, he first noticed a slight swelling of the face and ankles, otherwise he was well at this time. About July 9th, he began to feel drowsy and weak; the swelling of his face and ankles had not increased. He consulted a physician who diagnosed nephritis. In August he spent 2 weeks in a hospital under the diagnosis of acute nephritis. About September 5th a generalized anasarca developed, with weakness, headache, vomiting and drowsiness. After September 11th he noted a disturbance of vision and oliguria.

TABLE II

Group I. Subacute Glomerulonephritis

Case No.	Autopsy No.	Age	Sex	Duration	Blood pressure	Albuminuria	Edema	Urea nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Epithelial crescents	Comment
		yrs.		*mos.*	*mm. Hg.*			*mg./100 cc.*	%	*gm.*	*gm.*		%		
1	25–798	8	F	2	—	—	2	—	—	149	224	0	—	4	
2	37–1830	16	M	3	192/112	4	3	77.8 (1 day)	—	360	710	0	50	2	Casts. Plasma proteins 4.2 gm. %
3	30–1567	16	M	7	180/114	4	3	116 (1 wk.)	0 (1 wk.)	320	285	0	45	1	Retinitis
4	31–1508	17	F	6	200/112	—	3	56.4 (1 mo.)	—	390	225	2	—	1	Retinal detachment
5	18–118	21	M	7	140/80	+	2	14 (6 mos.)	15 (6 mos.)	375	425	1—	—	3	
6	18–237	22	F	4	220/120 (1 wk.)	3	3	33 (12 days)	—	300	260	2	—	3	
7	13–8	26	F	3	—	+	1	—	—	Normal	Normal	0	—	4	Marked hematuria
8	12–131	33	M	3+	—	+	1	—	—	460	415	2	—	1	
9	16–368	39	M	5	—	3	3	104 (1 day)	0 (1 day)	375	280	0	35	2	
10	25–945	41	M	2	248/102	1 3	2	80 (7 wks.)	10 (7 wks.)	—	335	0	—	0	Embolic type
11	22–554	43	M	6	140/60 (1 day)	3	1	119 (1 day)	—	610	270	3	—	0	Embolic type, aortic endocarditis
12	15–253	51	M	4	172/100	2	3	—	—	375	500	—	—	0	
13	19–5	55	M	12	200/120	+	1 3	—	0 (1 day)	420	520	0	—	1	Retinitis
14	30–415	57	M	3	150/95 180/100	4	2 0	140 (6 wks.)	2 (10 wks.)	430	360	1	50	1	Retinitis
15	29–1799	62	M	1	190/110	4	1	190 (2 wks.)	—	—	550	0	48	1	Edema of retina
16	11–77	70	M	—	—	+	3	—	—	475	335	0	—	3	

The percentage of phenolsulphonephthalein excreted in 2 hours is shown. Numerals are used to indicate the intensity of albuminuria, edema, passive congestion of the liver and the extent of formation of epithelial crescents. The time before death is indicated in some of the observations. The — sign means no observation.

On admission, Sept. 16, 1937, a severe generalized anasarca was noted. There was dyspnea, with evidence of edema of the lungs and ascites. The temperature was subnormal and the heart rate was rapid and regular. The eyegrounds showed a grayish exudate but the retinal arteries appeared normal. The blood pressure was 192/112 mm. Hg. The total diuresis for 24 hours was only 45 cc. Death occurred on Sept. 18, 1937.

Laboratory Examinations: Hemoglobin 50 per cent; red cell count 2,700,000; leukocytes 12,900 — 84 per cent neutrophils; blood urea nitrogen, 77.8 mg. per cent; carbon dioxide combining power of the blood, 16 per cent. Plasma proteins: albumin 2.2, globulin 2 — total protein 4.2 gm. per cent.

In subacute glomerulonephritis the blood pressure usually rises steadily and is commonly very high in the advanced stages. Disturbances of vision from retinal edema or hemorrhages are frequent.

The urine contains abundant albumin and casts. The specific gravity often decreases, and oliguria is frequently a prominent feature. Hematuria is infrequent.

Edema is usually rather well marked and was not absent in any of our cases. The plasma proteins were determined in only 1 case (Case 2), and their low level is an ample explanation of the edema in this instance. Cardiac failure may have been a contributory cause of edema in Cases 4, 6, 8 and 11, since there was a definite chronic passive congestion of the liver in each of these. In Case 11 the associated heart disease was presumably the cause of the severe passive congestion of the liver. Probably the low level of the plasma proteins is the chief cause of edema, since edema was present in 9 cases in which there was no passive congestion of the liver. A high venous pressure is a more delicate indication of cardiac failure than passive congestion of the liver, but this observation was not available.

Renal insufficiency may always be demonstrated if tests are made in advanced stages of the disease. Death was apparently due to uremia in all of our cases. As in other forms of uremia, the hemoglobin decreases as renal insufficiency develops.

The heart is usually only moderately enlarged. Omitting the 8 year old child (Case 1) and the case of endocarditis (Case 11) the average weight of the heart was 389 gm. Apparently hypertension must be maintained at a high level for a long time before marked cardiac hypertrophy develops.

The kidneys are of normal size or moderately enlarged, but

occasionally they are very large (Case 2). The average combined weight of the kidneys in 15 cases is 380 gm., but if Case 2 be omitted the average weight of the remaining 14 cases is only 356 gm. The external surfaces are smooth and on section the cortices are of normal or increased width. Microscopically, as noted above, there is found a uniform diffuse tubular atrophy (Fig. 1). There are no islands of normal tubules, as in chronic nephritis, and the tubular atrophy is not extreme. Since all the tubules are involved it is obvious that the patient cannot survive to the point of extreme tubular atrophy such as one finds in parts of the cortex in chronic nephritis. The glomeruli are uniformly involved and severely obstructed. There are no solid hyaline glomeruli, since the process is too recent, but there may be small hyaline areas in the centers of some of the glomerular lobules. Epithelial crescents may play a rôle by compressing the glomeruli, but the most important cause of glomerular obstruction is endothelial proliferation.

There are different histological types. In the usual proliferative form the centers of the glomerular lobules consist of a dense mass formed by splitting and fusion of the central capillary basement membranes. This central mass may show beginning hyaline degeneration. The peripheral zones of the glomerular lobules contain narrow capillaries which are, however, insufficient in number and caliber to afford adequate filtration. Decreased glomerular filtration results in partial disuse atrophy of the tubules.

In Cases 1 and 7 the glomerular obstruction was due largely to epithelial crescents. In Cases 10 and 11 the lesions were all of embolic type, and in 1 of these, Case 10, no endocarditis was present. These 2 cases might also be classified as embolic glomerulonephritis, but lesions of embolic type frequently occur independently of endocarditis. Occasionally uremia is due in part to extensive tubular obstruction by casts as in Case 2.

Group II. Chronic Glomerulonephritis in which Death was due to an Intercurrent Disease (Table III)

The 8 cases listed in Table III are examples of chronic glomerulonephritis in which death was caused by another disease before marked renal insufficiency had developed. These cases are of particular interest since little is known of the structural changes

TABLE III

Group II. Chronic Glomerulonephritis in which Death was due to an Intercurrent Disease

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Blood pressure	Albuminuria	Edema	Urea nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Hyaline glomeruli	Tubular atrophy	Cause of death
		yrs.			*mm. Hg.*			*mg./100 cc.*	%	*gm.*	*gm.*		%	%		
17	24–807	20	F	7 mos.	138/86 158/98	2	1	49.4 (6 mos.) 15.5 (8 days)	47 (5 days)	400	465	—	40	0	0	Streptococcic bacteriemia
18	31–794	22	F	3 yrs.	140/90 (3 yrs.) 150/90 (5 days)	4	0	—	61 (3 yrs.)	—	Large	1—	—	10	1—	Tetanus following induced abortion
19	33–292	34	F	2 mos.+	170/90	4	1	28 (2 days)	—	420	462	3	70	10	1d	Ulcerative colitis, encephalomalacia
20	27–511	43	F	1 yr.	110/70	1—	1	—	—	538	304 (one)	1	—	0	0	Cardiac failure
21	25–146	51	F	4 yrs.	—	1	0	29.5 (2 wks.)	—	240	190	—	90	0	0	Bronchopneumonia
22	28–1110	58	F	4 yrs. (?)	—	1—	0 3 2	—	—	215	195	1—	40	0	0	Marked emaciation, ischiorectal abscess
23	31–748	70	F	4 mos.+	170/100	2	3	Normal (1 wk.)	—	606	438	2	34	20	1	Cardiac failure
24	34–1408	80	F	? yr.	138/60	1	1	15.6 (1 day)	—	450	250	0	58	5	1	Purulent bronchitis, pericarditis

Explanations as in Table II. 1_d = diffuse tubular atrophy of mild degree.

in the kidneys during the long interval between the primary acute attack and the terminal chronic stage.

The diagnosis of glomerulonephritis in this group is based entirely on the microscopic structure of the kidneys except in Cases 17 and 18 in which it was also established clinically. In the other 6 cases the renal symptoms were overshadowed by those of the major illness. In Case 19 the clinical picture was that of ulcerative colitis with severe albuminuria and mild edema. In Case 20 the clinical impression was cardiac failure. In Case 21 there was a history of dyspnea and palpitation for 4 years, and a general anasarca developed during the last month of life. In Case 22 there was an ischiorectal abscess of 4 years duration, as well as severe emaciation. There was only a trace of albumin in the urine and the edema developed terminally. Case 23 was a typical example of hypertension with cardiac failure.

There was a very slight elevation of the blood urea nitrogen in Cases 19 and 21, but there was no clinical or anatomical evidence of serious impairment of renal function in any instance.

The clinical history in Case 18 will be given in detail since this case is a good illustration of the group under discussion. I am indebted to Dr. George Fahr for the excellent clinical record which follows.

The patient, an unmarried woman, 19 years of age, was admitted to the hospital Feb. 15, 1928, complaining of a cold, sore throat, headache and swollen cervical lymph nodes. The diagnosis was acute tonsillitis. On February 27th the urine contained albumin ++++, the leukocyte count was 13,300, and the blood pressure was 140/90 mm. Hg. The 2 hour excretion of phenolsulphonephthalein was 61 per cent. There was no edema. The diagnosis was acute glomerulonephritis. The patient gradually improved. On March 1st, the leukocyte count was 8700 and the blood pressure on March 7 was 126/84 mm. Hg. Tonsillectomy was performed on March 13, 1928, and the patient was discharged on April 19, 1928.

She was readmitted on Oct. 8, 1928, with symptoms of sinusitis. The urine showed albumin ++; the leukocyte count was 9050; and a concentration-dilution test gave a range of specific gravity from 1005 to 1023. The clinical diagnosis was now chronic glomerulonephritis, which was regarded as the outcome of the attack of acute glomerulonephritis in the preceding February. The patient was discharged after a few days and continued her work as a nurse in apparently good health until the onset of her final illness on May 1, 1931.

She was readmitted to the hospital May 1, 1931, suffering from acute endometritis following an induced abortion. Tetanus developed and death occurred on May 6, 1931. There was albuminuria but no edema. The blood pressure was 150/90 mm. Hg. No functional studies were made at this time.

At postmortem the kidneys were found to be enlarged with smooth external surfaces. Microscopically about 10 per cent of the glomeruli are hyaline, and there is atrophy of their associated tubules. Practically all of the other glomeruli present a similar appearance. They are slightly enlarged and their lobulations are distinct (Fig. 2). Under higher magnification the lobules show solid central portions with small peripherally situated capillaries (Fig. 3). There is some increase of endothelial cells but the capillaries are not markedly constricted. The peripheral capillary basement membranes are not thickened. Glomerular filtration is evidently fairly good since there is no atrophy of the tubules associated with these glomeruli.

The structural changes in the kidneys of the other 7 cases in Group II correspond to the above description aside from minor variations. The kidneys are not contracted but are usually somewhat enlarged. In Case 19 there were some epithelial crescents, the capillary obstruction was more pronounced than is shown in Figures 2 and 3 and had resulted in a slight tubular atrophy. In Case 21 the glomerular lesions were less intense than in Case 18. In Case 23 an arteriolosclerosis was present which was responsible for most of the hyaline glomeruli.

We may now trace the pathogenesis of the glomerular lesion in chronic glomerulonephritis. The normal glomerular lobule is composed of capillaries with a distinct basement membrane in both inner and outer walls (compare Figs. 3 and 4, Plate 130, *Am. J. Path.*, 1936, **12**, 801–824). In acute glomerulitis there is an increase of endothelial cells and the central basement membranes of the capillaries are split into numerous irregular fragments which have been called intracapillary fibers. In severe glomerulitis the capillaries are completely obstructed, but in the less severe lesions (Fig. 4), from which the chronic forms probably develop, the capillaries are not closed completely. As the inflammation subsides the blood forces the intracapillary fibers to the center of the lobule where they become fused to form a central hyaline mass and the lobule then has the appearance shown in Figures 3 and 7. If the capillaries are completely closed during the acute attack the glomerulus becomes hyaline. The functioning glomeruli in chronic azotemic glomerulonephritis usually resemble those shown in Figures 2 and 3. The most important difference between the

early or mild lesions of Group II and those of advanced azotemic glomerulonephritis is that in the latter group nearly all the glomeruli have become hyaline; the persistent functioning glomeruli in the advanced stage are not notably different in structure from those of the early stage. One may well believe that the progress from the early to the advanced stage of chronic glomerulonephritis is due to repeated acute attacks which obstruct more and more of the glomerular circulation.

The only publication known to me which deals with the structure of chronic glomerulonephritis in the pre-uremic or latent chronic stage is one by Dorothy Russell [2] in 1934. She described a kidney removed under an erroneous diagnosis 16 years before death. The remaining kidney at autopsy showed a typical advanced chronic glomerulonephritis. The illustration of the kidney removed 16 years before death is shown only under low magnification but resembles those of Group II.

Group III. Advanced Chronic Glomerulonephritis of the Azotemic Type (Tables IV, V and VI)

This group, which comprises 117 cases, has been divided into 3 subgroups in accordance with certain clinical and pathological features. Subgroup A (Table IV) includes 30 cases in which there was a definite history of acute glomerulonephritis. Subgroups B and C (Tables V and VI) include 87 cases in which no history of an acute attack was obtained; in the former the kidneys weighed together 250 gm. or more, in the latter they weighed less than 250 gm. and showed varying degrees of contraction. It will appear that the separation of subgroups B and C has little clinical significance but it will serve to emphasize certain structural differences between large and small kidneys.

Considering Group III as a whole we may call attention to certain features.

Duration: The total course of the disease is known only in the 30 cases listed in Table IV. In this group the duration ranges from 18 months to 26 years. The average time between the acute attack and death is 10 years. The duration is as follows: under 5 years, 8 cases; 5 to 10 years, 9; 10 to 15 years, 5; 15 to 20 years, 5; 20 to 26 years, 3.

The acute attack is often followed by a latent period during

which the patient considers himself well, although it is probable that symptoms and signs of the disease could be detected by careful examination. As shown in the table, the latent period may last many years (Case 54, 24.5 years; Case 46, 23.5 years; Case 39, 14 years). However, the active chronic stage may begin immediately after the acute stage, *e.g.* Cases 29, 32 and 35.

The duration shown in Tables V and VI is merely the length of the active chronic stage in most of the cases. It is measured from the date of onset of symptoms as given by the patient except in a few cases in which it is dated from the finding of albuminuria in the course of an examination for life insurance. It is remarkable that 16 patients worked at their usual occupations and considered themselves in good health up to a period from 1 month to 3 months before death, although the kidneys at postmortem often showed a high degree of contraction indicating a duration of many years. It is clear that the duration of symptoms is far less than the total course of the disease. The average duration in the group in which the complete history is known (Table IV) is 10 years, while in those with no history of acute onset (Tables V and VI) it is only 3 years.

Frehse,[3] in a study of 248 cases of nephritis, found that 68 lasted over 5 years, 23 over 10 years, 19 over 15 years, 6 over 20 years, and 3 over 40 years.

The Acute Attack: In most instances the acute attack was typical and fairly severe, confining the patient to bed for a number of weeks, but in some cases it was mild and characterized only by headache with albuminuria or edema. It is easily possible that in the cases with no history of acute glomerulonephritis there was a mild attack that was not recognized as nephritis. For example, in Case 18 the condition following the attack of acute tonsillitis would not have been recognized as acute glomerulonephritis if a careful study had not been made. It is the usual experience that in a majority of the cases first seen in the active chronic stage careful inquiry does not reveal an illness which can be interpreted as acute glomerulonephritis. On the other hand, patients first seen in the acute stage and subsequently followed for a number of years show all the variations in the clinical course that appear in Table IV. Some of them pass directly into the active chronic stage and others remain in fairly good health for a number of years.

TABLE IV

Group III. Subgroup A. Chronic Azotemic Glomerulonephritis with a History of Acute Glomerulonephritis

Case No.	Autopsy No.	Age	Sex	Total duration	Duration of active chronic	Initial infection	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Edema	Retinitis	Epithelial crescents	Histological type	Comment
		yrs.		*yrs.*			*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%	*gm.*	*gm.*		%					
25	35–2064	15	M	4	4 yrs.	—	220/110	—	285 (1 day)	—	380	460	0	59	2 0	—	0	b_1	
26	36–2149	15	F	1.5	18 mos.	Tonsillitis	148/100 (18 mos.) 170/130	34 (18 mos.) 118 (1 day)	—	49 (18 mos.) 0 (1 day)	450	160	2	54 (18 mos.)	1 4	—	0	a	Plasma proteins 5.5 gm. %
27	25–246	16	F	4	16 mos.	Sore throat	180/130	70 (1 mo.)	—	0 (1 mo.)	400	163	1—	38	2 1	+	2	a	
28	23–846	18	M	2	1 mo.	—	200/134	181 (2 days)	—	—	475	245	1—	50	1	+	3	a_2	
29	31–1974	19	M	9	9 yrs.	Scarlet fever	180/110	110 (1 mo.) 238 (1 day)	—	—	550	200	0	28	1 0	—	1	a	
30	34–763	19	F	4	4 yrs.	Common cold	180/148 (5 mos.)	—	102 (1 wk.) 218 (1 day)	20 (5 mos.)	350	150	2	46	2 0	+	2	a	Exacerbations
31	36–1587	20	M	10	2 yrs.	Common cold	190/125 (1 mo.)	—	171 (1 mo.)	—	585	180	0	35	1 3	+	0	a	
32	33–1180	21	F	14	14 yrs.	Scarlet fever	160/100 (4 mos.)	—	327 (2 wks.)	2 (4 mos.)	325	100	1	35	2 1	0	3	a	
33	28–170	21	M	3	3 yrs.	—	230/160	28 (1 yr.) 119 (4 days)	—	2 (4 days)	420	174	1	50	2 0	—	1	a	
34	32–2024	24	F	8	5 yrs.	—	195/140	200 (2 days)	—	0 (6 wks.)	475	210	1—	40	2 0	+	0	a	Exacerbations
35	27–452	24	M	18	18 yrs.	—	158/80	97 (3 wks.)	—	0 (3 wks.)	320	135	—	16	0 1—	+	3	a	
36	23–48	25	M	9	9 yrs.	Measles	210/140	165 (4 days)	—	4 (1 mo.)	—	163	—	37	0	+	1	a	
37	17–62	27	F	8	8 yrs.	—	160/? (8 yrs.) 185/100 (2 wks.)	101 (2 wks.)	—	0 (2 wks.)	455	150	0	40	1 2	p_v	2	a	

38	19–264	29	M	6	2 mos.	Common cold	170/80	87 (1 mo.)	—	0 (1 mo.)	435	340	1	25	1	+	2	b_1	
39	36–2304	29	M	14	1 mo.	Scarlet fever	170/110	27 (1 mo.)	—	0 (1 mo.)	540	80 (one)	0	—	1 0	+	0	a	
40	27–261	31	M	3	3 yrs.	Sore throat	180/95 (3 yrs.) 180/90	260 (2 wks.)	—	—	420	175	1–	45	1 0	+	0	a	
41	30–1480	32	F	16	11 yrs.	—	142/82 (11 yrs.) 250/130	50 (1 wk.)	—	60 (10 yrs.) 0 (1 wk.)	350	100	0	75	2	—	0	a	
42	18–117	32	M	10	2 mos.	—	190/140	—	—	0 (2 wks.)	630	405	2	—	2 1	—	2	bd	
43	33–2022	33	M	12	3 mos.	—	220/130	280 (3 days)	—	—	550	180	1	—	1 0	+	0	a	
44	34–267	35	M	16	10 yrs.	Influenza	180/100	—	328 (3 wks.)	—	575	190	0	36	1	+	0	a	Exacerbations
45	27–49	35	F	6	5 yrs.	—	148/90 (3 days)	101 (1 day)	—	—	300	Small	0	30	3	0	2	a	
46	28–1249	36	M	24	5 mos.	—	236/160	152 (6 wks.)	—	0 (7 wks.)	420	90	0	26	3 1	—	1	a	
47	31–1746	37	M	15	12 yrs.	—	220/130	190 (10 days)	—	5 (2 wks.)	680	225	0	39	0	+	1	ad	
48	31–241	38	F	23	16 yrs.	Scarlet fever	225/135	80 (5 days)	—	4 (7 days)	430	220	1	63	1	0	0	ad	
49	35–562	40	M	9	—	—	134/80 (3 days)	279 (1 day)	—	—	546	177	0	36	0	0	2	a	
50	27–653	43	M	6	5.5 yrs.	Sore throat	128/80 (6 yrs.) 260/120 (1 mo.)	15 (6 yrs.) 150 (2 days)	—	—	700	195	1	—	2	p_v	0	a	
51	31–1146	44	F	4	4 yrs.	—	—	65 (5 days)	—	0 (5 days)	350	200	0	—	0 1	—	1	a	
52	37–1993	46	F	15	15 yrs.	—	140/90 (5 yrs.) 215/140 (3 mos.)	31 (5 yrs.) 191 (2 wks.)	—	62 (5 yrs.) 23 (3 mos.)	380	130	—	72	0 1	—	0	ad	Onset during pregnancy
53	33–867	53	F	5	5 yrs.	Common cold	182/106 (1 mo.)	—	163.8 (3 wks.)	—	450	140	0	54	2 0	0	2	a	
54	30–1826	52	M	26	1.5 yrs.	Tonsillitis	238/124	47.6 (6 mos.) 74 (2 days)	—	70 25 (2 mos.)	627	254	0	55	0 1	—	0	b_1	

Explanations as in Table II. P_V = poor vision.

TABLE V

Group III. Subgroup B. Chronic Glomerulonephritis of the Azotemic Type. No History of Acute Glomerulonephritis. Kidneys Weighing Together 250 gm. or More

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Edema	Retinitis	Epithelial crescents	Hyaline glomeruli	Histological type	Comment
		yrs.			*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%	*gm.*	*gm.*		%				%		
55	33-1854	8	F	1 yr.	210/120	—	68 (8 days) 156 (1 day)	—	—	80	—	—	0	—	1	20	be	
56	33-855	17	M	8 yrs.	208/130	139 (2 days)	—	—	505	345	—	—	0	+	0	50	be	
57	34-2188	18	F	4 yrs.	140/100 (5 days)	39 (5 days)	—	—	275	300	0	—	1	—	0	40	b_1	
58	25-171	19	M	2 mos.	128/60 (5 days)	—	—	—	360	325	—	—	0	—	1	50	b	
59	22-118	20	F	3 yrs.	190/154	76.6 (6 days)	—	0 (6 days)	420	400	2	70	1 3	+	3	20	b_1	Exacerbations
60	36-2331	21	M	6 mos.+	200/130 (6 mos.) 235/130	—	—	—	525	325	1	—	0	+	0	90	b	Scarlet fever at age of 6 yrs.
61	34-2102	22	F	5 mos.+	—	17.4 (5 mos.)	—	20 (2 mos.)	—	300	0	70	1—	—	0	0	be	
62	35-1131	24	F	1 yr.	164/92	—	222 (3 days)	—	400	350	2	34	1—	—	1	60	b	
63	22-574	29	M	10 mos.	185/125	71 (2 wks.) 142 (2 days)	—	4 (2 wks.)	370	290	0	56	1 0	—	2	20	b_1	
64	14-192	30	M	—	192/?	—	—	—	490	360	—	—	1	—	1—	30	b_1	
65	33-5	30	M	10 yrs.	115/70 (3 yrs.) 170/110	—	176 (4 days)	0 (2 days)	550	400	0	60	0	+	1	70	b	
66	34-356	31	F	4 yrs.	170/90	—	267 (4 days)	—	570	280	1	94	0	+	2	70	b	
67	10-145	32	M	—	—	—	—	—	530	314	3	—	0 2	—	0	10	b_1	

68	15–67	35	F	3 yrs.+	–	–	–	–	400	Normal	0	–	1	–	1	30	b	
69	27–1200	36	M	7 yrs.	129/80 (1 yr.) 190/120	26 (10 mos.) 178 (3 days)	–	15 (3 days)	Large	Normal	1	53	1	+	1–	10	b_1	
70	17–108	39	M	3 yrs.	–	–	–	0	640	350	0	–	1	p_v	1	50	b_1	
71	19–220	43	M	1 yr.	140/60 (3 wks.)	125 (2 wks.)	–	0 (2 wks.)	Large	300	–	30	0	0	0	5	b_1	
72	11–76	44	F	15 yrs.	170/?	–	–	–	492	260	2	50	2	p_v	1	20	b	
73	33–1906	45	M	20 mos.	255/150	208 (4 days)	–	–	635	264	1–	40	1 3	–	1	60	b	
74	33–933	45	M	1 yr.+	160/120 (2 mos.) 192/140	90 (1 mo.) 245 (2 days)	–	–	380	260	1–	46	0	+	3	60	b	
75	34–1047	45	M	1 yr.+	160/110	40 (6 mos.)	–	–	610	310	1	–	0 3	–	0	50	b	
76	32–1498	47	M	5 yrs.+	224/?	180 (2 days)	–	–	450	360	0	–	1	+	4	40	b	
77	35–1770	48	M	–	High	48 (3 wks.)	87 (2 wks.)	–	400	250	1	–	0	+	3	60	b	
78	32–454	50	M	6 yrs.	225/125	81.9 (3 days)	–	5 (1 mo.)	600	455	2	49	1 3	+	0	15	b_1	Apoplexy
79	33–255	52	M	2.5 yrs.	134/90 (6 mos.)	59.5 (1 mo.)	–	–	519	482	0	–	1	–	3	50	b	Multiple myeloma
80	15–394	54	M	2 mos.	168/90	–	–	–	650	319	0	–	1 0	–	0	60	b	Old valve defect
81	36–2169	56	F	–	185/90	131 (5 days)	–	–	350	250	1	94	0	+	4	30	b_1d	
82	22–176	56	M	10 yrs.	184/100	–	–	–	500	475	1–	–	1	0	0	10	b_1	
83	31–465	60	F	9 mos.	220/120	44.5 (2 mos.)	–	–	427	312	0	50	1	–	2	30	bd	Diabetes
84	36–552	60	M	3 mos.	140/70 (3 mos.)	38.5 (6 wks.)	–	–	495	280	3	–	0 2	0	1	20	b_1	
85	16–119	63	M	–	–	–	–	–	400	300	0	–	0	–	3	30	b_1	
86	30–209	65	M	2 yrs.	156/82	79 (9 days) 167 (2 days)	–	10 (9 days)	500	250	0	68	0	–	3	50	b_1	
87	29–869	68	F	–	210/?	–	–	–	500	300	1	–	2	–	1	50	b_1d	Diabetes

Explanations as in Table II. Explanations of histological types in the text.

TABLE VI

Group III. Subgroup C. Chronic Glomerulonephritis of the Azotemic Type. Kidneys Weighing Together Less than 250 gm.

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Edema	Retinitis	Epithelial crescents	Histological type	Comment
		yrs.			*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%	*gm.*	*gm.*		%					
88	30–519	14	F	1 yr.+	—	176 (3 wks.)	—	—	170	185	0	43	1—	—	2	b_1	
89	15–373	23	M	3 mos.	180/115	—	—	11 (2 mos.)	557	Small	—	50	1	—	0	a	
90	16–384	24	M	3 mos.	170/90	131 (5 days)	—	0 (6 days)	415	205	0	20	1	—	2	b_1	
91	33–214	24	M	1 mo.	188/90	296 (1 day)	—	—	400	87	0	20	1	—	3	a	
92	32–947	25	M	—	150/70	240 (1 day)	—	—	380	140	0	54	0	—	0	a	
93	37–1501	25	M	6 wks.+	168/98	120	—	0 (2 wks.)	450	122	—	36	1	0	0	a	
94	27–1287	25	M	3 mos.	220/160	82 (2 wks.) 116 (1 day)	—	16 (2 wks.)	325	105	0	65	2	e_d	0	a	
95	19–2	25	M	9 mos.	210/118	72 (9 days)	—	0 (9 days)	500	195	—	—	0	+	1—	a	
96	26–286	26	F	4 yrs.	160/110 (3 yrs.) 210/130 (1 yr.)	72 (3 yrs.)	—	—	380	210	2	—	1 0	0	1	b_1	Exacerbations
97	22–47	27	M	2.5 yrs.	182/110	133	—	0	540	110	0	30	1 0	—	2	a	
98	24–697	27	M	—	122/44 (1 day)	—	—	—	200	52	0	—	0	—	0	a_1	
99	32–1935	27	M	10 yrs.	194/114	131 (3 wks.) 216 (3 days)	—	—	550	175	1—	—	0	+	4	a	

100	16–132	27	M	3 mos.	–	–	–	–	425	150	0	36	1	–	2	a	
101	36–12	28	M	7 yrs.	154/100 (9 mos.)	140 (5 days)	–	0 (5 days)	350	71	0	59	0	–	0	a	
102	36–1467	28	F	6 yrs.	185/80	–	–	–	325	50	1–	–	1	+	1	a	
103	28–1446	29	F	2 yrs.	114/94 (2 yrs.)	124	–	–	430	80	–	60	0 1–	–	2	a_1	
104	37–2199	29	F	10 yrs.	194/124 172/102 (2 yrs.)	80 (3 mos.)	–	–	425	113	–	36	1	+	0	a	
105	15–363	30	M	3 yrs.	190/110 –	203 –	–	0 (1 mo.)	575	155	–	–	0	–	1	a	
106	31–1247	31	F	5 yrs.+	190/110	–	–	–	275	95	0	–	3 1	–	0	a	Exacerbations
107	32–2089	32	F	–	130/60 (3 days)	–	214 (1 day)	–	–	50	–	–	1–	–	0	a	
108	34–673	32	F	4 yrs.	180/110 (2 yrs.) 230/160	48 (14 mos.) 157 (2 days)	–	–	518	81	0	35	0 2	+	2	a	
109	19–160	32	M	–	120/80 (3 days)	–	–	–	350	140	0	–	0	–	2	a	
110	28–1189	33	F	6 yrs.	210/?	60 (2 wks.)	–	–	350	120	0	45	0	–	2	a	
111	22–128	33	F	9 yrs.	154/92	29.6 (2 wks.)	–	–	360	230	0	70	1	–	0	b_1	
112	32–2005	34	M	3 yrs.+	180/120	60 (2 mos.)	184 (2 mos.)	4 (2 mos.)	360	95	0	–	0 1	+	4	a	
113	20–204	34	M	3 mos.	200/120	–	–	–	425	195	1–	–	1–	+	2	a	
114	13–145	35	M	4 mos.	132/? (4 mos.)	–	–	–	475	169	0	35	2	–	2	a	
115	23–267	35	F	9 mos.	140/90 (11 days)	–	–	0 (8 days)	375	135	2	–	2	–	3	a	

TABLE VI (*Continued*)

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Edema	Retinitis	Epithelial crescents	Histological type	Comment
		yrs.			*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%	*gm.*	*gm.*		%					
116	23–293	35	M	4 yrs.	142/100 (4 yrs.) 202/132	120 (2 days)	–	0 (3 wks.)	500	123	–	38	1 0	–	0	a	
117	26–251	35	F	–	250/160	169 (1 day)	–	–	370	200	1	67	0	+	1	ad	Diabetes
118	31–1197	37	F	3.5 yrs.	158/98 (3 yrs.) 200/120	Normal (3 yrs.) 110 (7 mos.)	–	40 (3 mos.)	350	140	0	74	0	e_d	0	a	
119	28–734	37	M	1 yr.	160/130	132 (6 days)	–	0 (6 days)	450	200	1	64	0 2	+	0	a	
120	35–360	37	F	7 yrs.	275/150	31.5 (2 yrs.) 119.7 (1 day)	–	–	544	155	0	47	1–	p_v	0	b	
121	28–347	39	F	–	–	37.8 (6 mos.)	–	–	370	226	1	55	1	–	3	b	
122	37–1290	40	M	–	–	62 (1 day)	132 (1 day)	–	300	60	0	–	0	–	0	a	
123	31–1063	40	F	4 yrs.	240/150	155 (2 mos.)	–	53 (2 yrs.) 1 (2 mos.)	520	140	–	44	2	–	2	a	
124	37–643	40	M	2 yrs.+	200/145	–	–	–	600	185	1	50	0 2	+	0	a	
125	30–1631	41	M	3 yrs.	220/150	–	90 (8 mos.)	–	550	210	–	–	0 2	+	1	a	
126	21–434	41	F	1 yr.	180/70	238 (6 days)	–	0 (11 days)	560	150	1–	–	1 3	p_v	1–	a	
127	23–604	41	F	7 mos.	210/140	196 (10 days)	–	10 (3 wks.)	385	110	1–	48	1	p_v	0	a	

128	23–635	41	F	4 yrs.	134/90 (3 yrs.) 185/130	34 (2 yrs.) 185 (2 days)	–	10 (2 yrs.) 0 (2 days)	365	63	0	54	0 1–	–	2	a	
129	22–619	46	F	9 wks.	120/88 (3 wks.)	56 (10 days)	–	10 (10 days)	380	165	0	44	2 0	–	4	a	
130	17–207	46	F	11 yrs.+	160/110 (3 days)	89 (3 days)	–	0 (3 days)	400	120	–	50	0 2	–	2	a	Exacerbations
131	28–1369	47	M	5 yrs.	110/70 (12 hrs.)	121.8 (1 day)	–	–	355	140	0	45	0	–	2	a	
132	32–1453	48	M	–	High	–	–	–	450	112	1–	55	0	–	1	a	
133	36–715	49	M	1 yr.	–	–	230 (2 wks.)	0 (2 wks.)	510	110	3	38	0	–	0	a	
134	18–94	50	M	6 yrs.	188/124	–	–	–	640	205	–	75	1	–	2	a	
135	34–2030	52	M	1 yr.	200/135	–	83.7 (1 yr.) 227 (12 days)	5 (3 wks.)	500	185	0	32	0	0	1	a	
136	26–459	56	M	–	180/100	–	–	–	400	135	0	28	1–	–	2	a	
137	30–473	62	M	1 yr.	194/110	82.6 (3 wks.) 183 (1 wk.)	–	1 (9 days)	450	200	0	–	1	–	1	a	
138	31–1817	62	F	2 yrs.	Normal	85 (5 mos.) 100 (6 wks.)	–	–	275	150	0	–	1	–	0	a	
139	17–73	65	F	8 yrs.	200/95	156 (1 day)	–	23 (3 yrs.) 10	435	190	–	50	0 2	+	3	ad	
140	21–437	71	M	–	192/64	–	–	–	625	210	–	–	1	–	0	a	Old valve defect
141	15–139	72	M	3 mos.	–	–	–	–	686	223	–	–	1	–	4	a	

Explanations as in Table II. Explanation of histological types in the text.

The symptoms in the active chronic stage vary in intensity in the different patients.

In 7 cases there was a history of repeated acute exacerbations during which all the symptoms, including edema, albuminuria and decreased renal function became more intense. After the subsidence of the acute exacerbations the symptoms return to their previous levels, but there is a tendency to progressive impairment of renal function. The active chronic stage is therefore characterized either by continuous symptoms of low intensity or by acute exacerbations separated by intervals of varying length during which the symptoms are of only moderate severity.

The Blood Pressure: In the tables the maximum blood pressure is recorded and this pertains to the terminal stages of the disease unless otherwise stated. In a few instances a blood pressure taken some months or years before death is recorded, the time prior to death being indicated in the table. There are 9 cases in which the maximum systolic blood pressure recorded was below 140 mm. Hg., *viz.*, Cases 49, 58, 79, 98, 107, 109, 114, 129 and 131. It is unlikely, however, that all of these cases represent chronic glomerulonephritis without hypertension. In Cases 49, 79 and 114 the marked enlargement of the heart is strong evidence that hypertension was present at some previous period, and in Cases 58, 98, 107, 109 and 131 the blood pressure was not recorded until shortly before death, a period during which terminal circulatory failure often develops. The period of observation in all of these cases is too short to justify the diagnosis of "chronic glomerulonephritis without hypertension." However, the small size of the heart in Cases 57, 98 and 138 suggests that hypertension did not play an important rôle in these instances. Cases have also been reported in which there was no elevation of blood pressure during a long period of observation (Bannick [4]).

In 88 cases with a maximum systolic pressure of 150 mm. Hg. or higher the distribution was as follows: 150 to 170 mm. Hg., 12 cases; 170 to 200 mm. Hg., 39 cases; over 200 mm. Hg., 37 cases. The large proportion of cases (30 per cent) with a systolic pressure above 200 mm. Hg. is surprising. In one instance a pressure of 275 mm. Hg. was recorded. This is conclusive evidence that a blood pressure above 200 mm. Hg. is not evidence against a diagnosis of chronic glomerulonephritis as is sometimes supposed.

The blood pressure usually tends to rise to higher levels as the renal disease progresses (note Cases 26, 41, 50, 52, 65, 69, 96, 103, 116, 118 and 128). Over a period of years it rises gradually to a maximum and usually does not decrease until a short time before death. The blood pressure rises as renal insufficiency increases. This phenomenon is in striking contrast with primary hypertension in which high levels of blood pressure are attained early in the disease.

The Weight of the Heart: The weight of the heart in 111 cases is as follows: 200 to 300 gm., 4 cases; 300 to 400 gm., 30 cases; 400 to 500 gm., 35 cases; 500 to 600 gm, 28 cases; and 600 to 700 gm., 13 cases. The average weight of 110 hearts is 456 gm. The hypertrophy in all instances is of left ventricular type. There is no obvious explanation of the great variation in the size of the heart. Apparently the weight of the heart is not directly related to the duration of the disease nor to the height of the recorded blood pressure. Perhaps we should not expect to find such a correlation since the work required of the left ventricle must depend upon the constancy as well as the degree of hypertension and the length of time involved. It often happens that the blood pressure is only moderately elevated for a number of years and becomes very high only in the terminal stages.

There is some relation between the size of the heart and the age of the patient. In 68 individuals under 40 years of age the average weight of the heart is 438 gm., while in 42 individuals over 40 years of age the average weight is 484 gm. Hearts weighing 500 gm. or more were found in 20 of 68 persons under 40 years of age (30 per cent), and in 20 of 42 over 40 years of age (48 per cent).

The average weight of 68 hearts from males is 489 gm., and of 42 hearts from females 403 gm. The normal heart averages about 50 gm. heavier in males than in females.

Judged by passive congestion of the liver there is some degree of heart failure in nearly one-half of the cases. As shown in Tables IV, V and VI, in 93 cases in which the liver was examined microscopically there were 51 cases with no passive congestion (0), 13 with very slight congestion (1–), 17 with definite but slight central atrophy (1), 9 with some central necrosis (2), and 3 with severe central necrosis (3) such as one finds in death from chronic myocardial failure.

In 1 of the 3 cases with severe passive congestion of the liver (Case 133) a high degree of renal insufficiency was established clinically and in the other 2 an anatomical diagnosis of uremia is justifiable. In 7 of the 9 cases with Grade 2 passive congestion of the liver, uremia was established clinically. We may conclude that heart failure of an appreciable degree may develop in chronic glomerulonephritis and that it may be exceptionally an important contributory cause of death, but uremia is practically always present at the time of death.

In striking contrast with primary hypertension a history of stroke was obtained in only 1 of the 117 patients (Case 78). There was only one typical example of coronary disease (Case 87, a woman 68 yrs. old). In 10 other cases there was complaint of precordial pain at times, but no severe coronary disease was found at postmortem.

Renal Function: It is noteworthy that the blood urea nitrogen seldom rises to high levels until a few weeks before death. Determinations made 6 months or more before death usually range from 25 to 50 mg. per cent. A very marked increase usually takes place during the last 1 or 2 days, and a striking increase is noted during the last 1 or 2 weeks. After the blood urea nitrogen has reached a level of 100 mg. per cent the patient seldom survives more than a few weeks. The marked variations in the terminal level of blood urea in different individuals may be due in part to differences in the amount of protein consumed. It is clear that extreme reduction of the number of functioning nephrons has usually taken place before the blood urea nitrogen rises above 40 mg. per cent. There is commonly a slowly progressive rise of blood urea until the terminal stages when a rapid increase occurs, but occasionally a patient will exhibit a marked elevation, due to an acute exacerbation of the nephritis, which returns to the previous level after the acute process has subsided.

Wakefield and Keith [5] reported a patient with a blood urea of 290 mg. per cent and a phenolsulphonephthalein output of 0, who recovered and was working in comfort 1 year later.

The phenolsulphonephthalein test gives about the same information as the determination of blood urea. With few exceptions the two tests run parallel, and the only advantage of doing both is the avoidance of possible errors.

Anemia: A hypochromic anemia of fairly severe degree is present in the terminal stages in the great majority of cases. The hemoglobin percentage was 50 or less in over two-thirds of the cases in which it was determined. In only 2 cases was there no anemia. In general the severity of the anemia increases as renal function decreases.

Retinitis: Retinitis, in the sense of retinal hemorrhages and exudates, was observed in 35 of the 46 cases in which the eyegrounds were examined (Table VII) and it was noted in 7 other cases that the patient had poor vision. The data on the caliber of the retinal arteries is too inadequate for discussion. It is well

TABLE VII

The Relation between Retinitis and the Level of the Systolic Blood Pressure. (The Eyegrounds Were Examined in Only 46 of the 103 Cases)

Blood pressure. Systolic mm. Hg.	Number	Retinitis +	Retinitis —
Below 140.....	8	0	1
140–150.....	7	0	3
150–170.....	12	2	2
170–200.....	39	16	2
Above 200	37	17	3
	103	35	11

recognized that retinitis is a result of hypertension. In Table VII it appears that retinitis was present in 33 of 38 patients with a systolic pressure above 170 mm. Hg. In the stage of uremia, primary hypertension and chronic glomerulonephritis usually cannot be distinguished by the appearance of the eyegrounds.

Edema: It is impossible to give a true picture of the degree and duration of edema by means of a summarizing table. In Tables IV, V and VI the numerals give only a rough estimate of the degree of edema during the period of observation. Edema is usually much more marked during acute exacerbations, and it varies greatly in intensity from time to time during the active chronic stage. It was not continuously severe in any of the cases in Group III (Cases 25 to 141). The cases in which edema was a constant and prominent feature are listed in Tables VII, VIII and IX. In 31 patients there was no edema at any time during the period of observation. Edema is often present early in the disease and absent in the

terminal stages, but frequently it is present only toward the end of the illness.

Edema is dependent upon several factors, the most important of which is probably the level of the plasma proteins, but the data in our records are inadequate for a discussion of this relationship. There is no evident relation between edema and the degree of contraction of the kidneys in Group III. Presumably increased venous pressure resulting from myocardial failure is often a factor of importance, but if passive congestion of the liver is taken as evidence of cardiac decompensation it may readily be seen from the tables that there is no close correspondence between edema and cardiac failure. However, there is a possible correlation between terminal edema and passive congestion of the liver. Congestion of the liver was present in 11 of 45 cases without terminal edema and in 18 of 49 cases with terminal edema.

The Relation between the Size of the Kidneys and the Clinical Features: For purposes of comparison the cases without a history of acute onset have been arranged in two groups, *viz.*, those with kidneys weighing 250 gm. or more (Table V), and those with definitely contracted kidneys weighing from 50 to 250 gm. (Table VI). The weights of the kidneys in the group with a history of acute onset (Table IV) may also be compared. It appears from these tables that it is not possible to predict the size of the kidneys from a study of the clinical history. One might expect that the cases of longer duration would show the greater degree of contraction of the kidneys, but this relationship does not obtain as may be seen by a study of Table IV. There is likewise no evident relation between the degree of contraction of the kidneys and the size of the heart, the level of the blood pressure or the prominence of edema. However, when edema is continuously severe, as in Group IV, one may predict that the kidneys will not be contracted.

The size of the kidneys in the azotemic and hydropic types is shown in Chart 1. It appears that the azotemic kidneys are usually much smaller than the hydropic but that some overlapping occurs. In the azotemic type (Group III) the combined weight of the kidneys is as follows: 50 to 99 gm., 13 cases, 11.5 per cent; 100 to 149 gm., 22 cases, 19.5 per cent; 150 to 199 gm., 26 cases, 23 per cent; 200 to 249 gm., 17 cases, 15 per cent; 250 to 299 gm., 10 cases, 8.8 per cent; 300 to 349 gm., 13 cases, 11.5 per cent;

350 to 399 gm., 4 cases, 3.5 per cent; 400 to 449 gm., 3 cases, 2.6 per cent; and 450 to 500 gm., 4 cases, 3.5 per cent. In the hydropic type (Group IV) the kidneys weighed over 300 gm. in 22 of 38 cases, as may be seen in Chart 1. In the azotemic group, in which uremia was always present at death, it may seem remarkable that uremia should develop in some instances when the kidneys are still of normal size and in others not until their weight is less than 100 gm., but these differences are explainable on the basis of the histological structure of the kidneys.

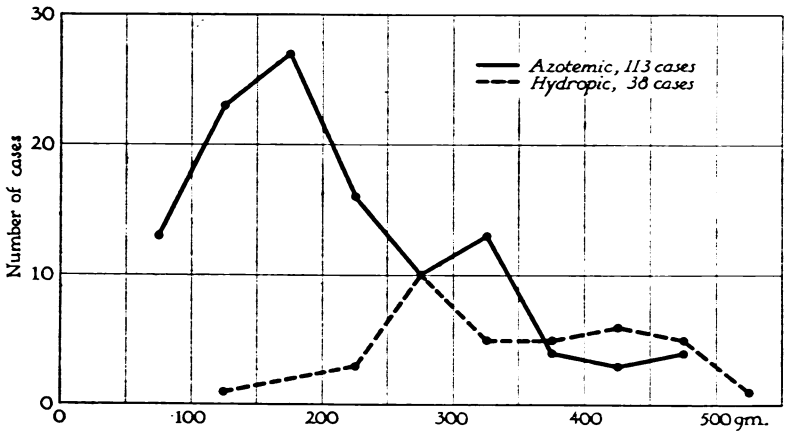


Chart 1. Size of the kidneys in azotemic and in hydropic glomerulonephritis.

The Structural Changes in the Kidneys

The variations in the size of the kidneys in the terminal stages of chronic glomerulonephritis are related to the structural changes that have taken place. These changes may be described as histological types and are so indicated in Tables IV, V and VI. From a study of the histological structure it may be determined why some kidneys are much smaller than others when the stage of uremia is reached.

As a result of acute glomerulitis the glomerular capillaries show a variety of effects ranging from no obstruction at all to complete obliteration. When the capillaries are normal, or only slightly narrowed, glomerular filtration continues and the tubules are unaffected, but when the capillaries are completely closed the glomerulus becomes hyaline and the tubules disappear entirely or

become small epithelial cords. Intermediate degrees of capillary obliteration, however, result in partial but not complete suppression of glomerular function and the associated tubule shows a degree of atrophy corresponding to the state of its glomerulus. Damaged glomeruli with partial tubular atrophy are a prominent feature of many kidneys (Fig. 6). When a large proportion of the glomeruli are of this type the kidneys may reach the stage of renal insufficiency without having undergone contraction. The varying sizes of the kidneys in the stage of uremia depend largely upon the proportion of glomeruli with partial tubular atrophy. In order to condense the histological descriptions the histological type of each kidney is given in the table. These types will be described and illustrated.

1. *Type a:* This is the most common form of chronic glomerulonephritis. The kidneys are small and contracted, the combined weight is usually less than 200 gm. and never over 250 gm. Sometimes they are extremely small (Cases 102, 107, 122 and 128). The cortices are thin. In microscopic sections (Fig. 5) it is noted that a large majority of the glomeruli are hyaline and that the tubules associated with these glomeruli have almost completely disappeared. A differential count usually shows that 80 to 90 per cent of the visible glomeruli are hyaline. The amount of destruction of the cortex is probably even greater than 80 or 90 per cent, since it is known that many hyaline glomeruli are ultimately removed by phagocytes (Moritz and Hayman [6]). Of the persistent glomeruli a few are normal with full sized tubules and some are partially obstructed with tubules showing corresponding stages of atrophy. The proportion of normal to partially obstructed glomeruli varies in different kidneys, sometimes the one predominating, sometimes the other.

Type a_1: This subgroup of Type *a* is represented by only 2 cases (Cases 98 and 103). In both of these the kidneys were very small but only a few hyaline glomeruli were to be seen. It is assumed that in these cases the hyaline glomeruli have been absorbed. One of these (Case 98) was a dwarf, weighing 80 pounds, and it is conceivable that this represents primary hypoplasia rather than atrophy.

Type a_2: This is represented by only 1 case (Case 28). There is a terminal acute glomerulonephritis superimposed on a chronic

glomerulonephritis. The persistent glomeruli show fresh epithelial crescents and other acute changes.

Type ad refers to Type *a* with an associated arteriolosclerosis. There are 8 cases with arteriolosclerosis (Types *ad* and *bd*) and all are characterized by very high blood pressure. The arteriolosclerosis is diffuse and severe. It is not uncommon to find an occasional hyaline arteriole in this disease but severe arteriolosclerosis is unusual.

Many investigators have apparently confused atrophy of small arteries and arterioles with true arteriolosclerosis. Segments of the cortex which contain nothing but hyaline glomeruli and atrophic tubules are functionless and require no blood. The arteries and arterioles supplying such scar-like areas undergo a disuse atrophy which may readily be confused with arteriolosclerosis, but the change is chiefly medial fibrosis and not intimal disease. Arteriolar disease, apart from atrophy, is so rare in chronic glomerulonephritis that it may be an accidental relationship. The structural changes in the arterioles in chronic glomerulonephritis do not support the argument that hypertension causes arteriolosclerosis.

2. *Type b* (*Fig. 6*): In this group the kidneys may show a slight reduction in size, a normal weight or even an enlargement. The size of the kidneys is not directly related to the duration of the disease. On microscopic examination it is found that the hyaline forms constitute less than one-half of the visible glomeruli. Frequently only 10 to 20 per cent of the glomeruli are hyaline, and rarely no hyaline glomeruli are to be seen. The most frequent type of nephron in these large kidneys is a damaged glomerulus with moderate atrophy of its tubule. With this type of lesion there is not much shrinkage of the renal cortex.

Type b_1 is a subgroup of Type *b* in which there are few or no normal glomeruli and tubules, the great majority of the nephrons being partially obstructed glomeruli with varying degrees of tubular atrophy (Fig. 7).

Type bd refers to Type *b* with an associated arteriolosclerosis; and Type *be* indicates Type *b* with extensive thrombosis of arterioles. There are 3 cases with widespread acute thrombosis of arterioles.

It is evident from the foregoing descriptions that small kidneys are those in which a large proportion of the nephrons have under-

gone complete atrophy because of complete closure of all the glomerular capillaries. In the small kidneys there are nearly always a few normal glomeruli with normal sized or hypertrophic tubules, and there are usually some partially closed glomeruli with tubules of diminished size. In the large kidneys normal and injured glomeruli outnumber the hyaline forms. Damaged glomeruli have a reduced functional capacity and one normal glomerulus is probably equivalent functionally to several injured forms. In a few instances nearly all the functioning glomeruli are of the damaged type (Type b_1). Uremia evidently may develop, as it does in the subacute type, before a large proportion of the glomeruli have become hyaline.

It is unlikely that the complex structure of the kidney seen at postmortem is the result of a single acute attack. In acute glomerulonephritis the intensity of the injury varies in different glomeruli — some escape with only minor injury, others suffer occlusion of a part of the glomerular circulation, and some exhibit complete capillary occlusion. In the healing stage after such an acute attack we would expect to see some normal glomeruli and tubules, some partially obstructed glomeruli with moderate atrophy of their tubules, and some hyaline glomeruli with disappearance of tubules. After the acute stage has subsided we would expect renal function to continue at a constant but reduced level. It is probable that repeated reinfections are responsible for the progressive failure of renal function in chronic nephritis.

Group IV. Chronic Glomerulonephritis of the Hydropic Type

In all the cases of this group edema was present during the greater part of the course of the disease and usually it was a very prominent feature. There were often one or more acute exacerbations during which albuminuria and edema were very severe, and remissions during which these features were much less intense. From the clinical standpoint all three subgroups of Group IV may be regarded as lipoid nephrosis in the sense in which this term is now generally used. There are no clinical features by which the three subgroups may be distinguished from one another, but there are histological differences in the structure of the glomeruli.

Subgroup A (Table VIII): In this group there are 6 cases that

TABLE VIII

Group IV. Subgroup A. Hydropic Type. Glomerular Structure of Proliferative Type

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Albuminuria	Edema	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Cholesterol	Plasma proteins	Weight of heart	Weight of kidneys	Hemoglobin	Passive congestion of liver	Hyaline glomeruli	Tubular atrophy	Basement membrane	Cause of death
		yrs.					*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%		*gm. %*	*gm.*	*gm.*	%		%			
142	37–524	16	F	14 mos.	4	4	145/90	15.4		44		4.54	498	340	46	0	10	1p	0	Hydro-thorax
							(1 yr.)	25.2	—	(1 yr.)	—	(1 yr.)								
							220/150	(1 mo.)		12		1.76								
										(1 wk.)		(1 mo.)								
143	34–2212	21	F	9 mos.	1	4	140/86	22.4	—	17	—	—	358	402	50	—	0	0	0	Parotitis
					2		(4 mos.)	(3 wks.)		(2 wks.)										
							120/70													
							(3 wks.)													
144	34–1543	41	M	7 yrs.	4	4	190/130	—	—	—	—	—	325	435	—	0	10	1p	0	Hydrotho-rax and ascites
145	24–580	68	M	4 mos.	2	3	200/115	41.5	—	—	—	—	350	275	—	1	0	0	1p	Lobar pneumonia
					4			(1 mo.)												
146	28–906	37	F	3.5 yrs.	3	1	142/104	38.5	—	—	—	—	340	136	54	3	50	2	2p	Mitral stenosis
						4	162/114	(3 mos.)												
147	34–633	76	F	3 mos.	1	4	—	—	—	—	—	—	375	240	20	1—	0	0	2p	Severe anemia

correspond clinically to lipoid nephrosis but belong anatomically with proliferative glomerulonephritis. A representative case of this group is reported fully:

CASE 142. *Clinical History:* A white female, 16 years old, was first admitted to the hospital Jan. 25, 1936. On Dec. 24, 1935, she had had several short attacks of pain in the right upper quadrant associated with flatulence and belching. During the next few days there were repeated attacks of vomiting but no pain. About Jan. 2, 1936, she first noticed swelling of the face, feet and ankles. The edema disappeared after a few days in bed. She had had scarlet fever about 1 year before the onset of the present illness and an occasional attack of sore throat during the previous 2 years.

On admission, Jan. 25, 1936, there was a marked edema of the face and the extremities. The systolic blood pressure was 145 and the diastolic 90 mm. Hg. Rales were heard in the bases of both lungs. The fundi were normal. Repeated examinations of the urine showed a specific gravity from 1017 to 1031, albumin ++++, and many casts and erythrocytes in all specimens. The 24 hour diuresis varied from 200 cc. to 1700 cc., being usually about 700 cc. The fluid intake was about 1200 cc.

The hemoglobin fell from 66 per cent on admission to 46 per cent shortly before death, and the erythrocytes from 3,660,000 to 1,800,000. The 2-hour excretion of phenolsulphonephthalein was 44 per cent (February 1936), 12 per cent (March 1936), and 26 per cent (October 1936). The blood urea nitrogen varied from 15.4 to 25.2 mg. per cent, creatinin from 1.5 to 2 mg. per cent. The total plasma proteins were 4.54 gm. per cent (April 1936), 6.27 gm. (May 1936) and 1.76 gm. (February 4, 1937).

The blood pressure varied from 145/90 on admission to 220/150 in November 1936. The edema varied in intensity from time to time but was usually quite pronounced. Dyspnea was usually a prominent symptom and headache was often severe. Death occurred on March 3, 1937. The clinical diagnosis was lipoid nephrosis.

At postmortem there was extreme anasarca. The peritoneal cavity contained about 1000 cc. of clear fluid, the right pleural cavity 500 cc., the left pleural cavity 800 cc., and the pericardial cavity 300 cc. There was also marked edema of the lungs. Death was apparently due largely to edema of the lungs and hydrothorax.

The heart weighed 498 gm. and showed left ventricular hypertrophy. There was no passive congestion of the liver.

The kidneys weighed 340 gm. and showed smooth external surfaces. On section a yellowish tinge was noted. On microscopic examination only an occasional hyaline glomerulus is noted, and there is a very little patchy tubular atrophy. All the glomeruli are moderately enlarged and uniformly involved. Lobulation is distinct. The lobules show central masses of hyaline of varying amount, formed by thickening and fusion of the centrally placed

capillary basement membranes (Fig. 8). The glomerular structure corresponds entirely to that of chronic proliferative glomerulonephritis, but death occurred from edema before any appreciable atrophy of parenchyma had taken place. The structure is therefore quite different from that of the great majority of cases in which death is due to uremia and the kidneys are atrophic. There is no diffuse thickening of the capillary basement membranes which characterizes most cases of lipoid nephrosis.

The other 5 cases of Subgroup A are similarly examples of chronic proliferative glomerulonephritis in which death occurred in a comparatively early stage of the disease. It may be said therefore that chronic proliferative glomerulonephritis may in unusual instances completely reproduce the clinical syndrome which we are accustomed to call "lipoid nephrosis."

Subgroup B (Table IX): This group includes 9 cases in which the clinical diagnosis was lipoid nephrosis. On the basis of the data presented a few of these cases may be considered examples of pure lipoid nephrosis in the broad sense but there was in most instances a little hypertension, some azotemia or a reduced output of phenolsulphonephthalein. There was only one death from uremia. In one instance, Case 156, edema was not very prominent and the case was classified in this group because of the thick capillary basement membranes. In Case 148 there was marked cardiac hypertrophy and hypertension. The plasma proteins were very low in the 2 cases in which they were determined, Cases 149 and 150. There is no evidence in any case that edema was of cardiac origin.

The most interesting feature of this group is the glomerular lesion. In only one instance, Case 148, is there any large proportion of hyaline glomeruli, and in 2 cases there are none. Aside from the hyaline forms the glomeruli are nearly all large with many permeable capillaries.

The glomerular lesions are partly of membranous and partly of proliferative type. In Cases 150 and 156 the glomeruli resemble those shown in Figures 2 and 3 except that the basement membranes are much thicker. Case 154 differs from these only in the presence of many fresh epithelial crescents. Case 149 is a typical membranous type except for a few glomeruli of the proliferative form. Cases 148, 151, 152, 153 and 155 show only occasional

TABLE IX

Group IV. Subgroup B. Hydropic Type. Thick Basement Membranes, but many Glomeruli of Proliferative Type

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Albuminuria	Edema	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Cholesterol	Plasma proteins	Weight of heart	Weight of kidneys	Hemoglobin	Passive congestion of liver	Hyaline glomeruli	Tubular atrophy	Basement membrane	Cause of death
		yrs.					*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%		*gm. %*	*gm.*	*gm.*	%		%			
148	35–1222	24	F	17 mos.	3	3	194/130 (2 days)	—	87.6 (2 days)	—	—	—	550	230	48	—	70	3	4	Hydrothorax
149	37–271	27	F	4 mos.	3	2 1	136/80 (2 mos.)	—	12.6 (2 mos.) 46 (2 wks.)	70 (2 wks.)	—	4.2	310	475	42	0	5	0	4	Lobar pneumonia
150	29–1880	27	M	3 yrs.	3	3	160/100	9 (1 mo.)	36 (1 mo.)	65 (1 mo.)	—	a, 0.69 g, 3.26	—	—	74	0	10	1—	3	Peritonitis
151	31–1672	37	M	16 mos.+	3	3	150/90	—	—	—	—	—	325	435	—	0	5	0	3	Hydrothorax and ascites
152	20–43	38	M	5 yrs.	3	3	122/84 (1 mo.)	16.4 (1 mo.)	—	30 (1 mo.)	—	—	325	390	52	0	10	1—	2	Pneumonia
153	27–925	39	F	8 yrs.	—	2 4	—	—	—	—	—	—	264	267	20	0	0	0	2	Severe anemia
154	17–230	45	M	1 yr.	2	1 4	140/70	24 (9 days)	—	30 (1 mo.)	—	—	400	360	—	0	0	2	2	Lobar pneumonia
155	33–574	45	M	—	4	4 0	128/70 165/80 (3 wks.)	22 (3 wks.)	42 (3 wks.)	65 (3 wks.)	—	—	425	400	—	0	10	1—	3	
156	27–305	52	F	2 yrs.	+	1	—	—	—	—	—	—	315	350	80	0	10	1	3	Peritonitis from perforated ulcer

Under plasma proteins, a = albumin, g = globulin.

glomerular lobules of proliferative type, all the others being membranous.

The glomerular structure in Subgroup B is therefore a blending of proliferative and membranous lesions with a predominance of the latter. There is a much closer resemblance to lipoid nephrosis than to azotemic glomerulonephritis.

Subgroup C (Table X): In the 25 cases in this group the clinical diagnosis was lipoid nephrosis and the glomeruli show no evidence of proliferative glomerulitis. Six of the 25 cases show no visible alterations in the glomeruli. It is certain that these 6 cases correspond to what others have called pure nephrosis but none of them satisfies the arbitrary definition laid down by Leiter that there shall be no elevation of blood pressure or decrease in renal function. However, they satisfy the criteria suggested by Blackman in that there is no progressive hypertension or renal insufficiency. Clinically there are no distinctions between those with no changes in the basement membranes (Cases 157, 158, 159, 160, 162 and 163), those with patchy membrane thickening (Cases 161, 164, 165 and 173) and 2 of those with pronounced thickening of the basement membranes (Cases 166 and 167). The great majority of those with thick basement membranes show hypertension.

It is noteworthy that in the 11 children (Cases 157 to 167) the structural changes in the glomeruli were much less pronounced than in the adults. Thirteen of the 14 adults but only 2 of the 11 children showed a diffuse thickening of the basement membranes.

The plasma proteins were markedly reduced in 12 of the 13 cases in which they were determined. Cardiac failure plays no rôle in causing edema since passive congestion of the liver was present only in the 1 case with death from endocarditis.

There were 4 deaths from uremia and 17 from infectious processes. Twelve of the 17 infections were peritonitis, of which 5 were streptococcic, 2 pneumococcic and the others undetermined. An incomplete survey of the literature shows that peritonitis was assigned as the cause of death in 42 of 53 cases. Of these, 23 were pneumococcus infections, 10 streptococcic and 9 not specified.

The clinical course of the disease was usually characterized by alternating exacerbations and remissions, the symptoms being intense during the former and mild during the latter. In Case 159

TABLE X

Group IV. Subgroup C. Hydropic Type without Proliferative Glomerulitis. Thickened or Normal Capillary Basement Membranes

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Albuminuria	Edema	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Cholesterol	Plasma proteins	Weight of heart	Weight of kidneys	Hemoglobin	Passive congestion of liver	Hyaline glomeruli	Tubular atrophy	Basement membrane	Cause of death	Comment
		yrs.					*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%		*gm. %*	*gm.*	*gm.*	%		%				
157	34-383	1.5	M	6 wks.	4	3	114/70	—	—	—	—	—	—	300	—	0	0	0	0	Peritonitis	
158	31-886	3	F	7 mos.	4	4	90/50	31.5 (6 mos.) 10.7 (2 mos.)	—	33 (2 mos.)	240	—	65	190	50	0	0	0	0	Pneumococcic peritonitis	Onset with sore throat
159	35-461	4	M	16 mos.	4 0	4 0	110/68	21 (1 yr.) 58 (p. m.)	—	—	251	a, 1.07 g, 5.97 f, 0.8	75	250	82	0	0	0	0	Str. viridans peritonitis	Repeated attacks of peritonitis
160	35-242	5	F	15 mos.	1 4	3	94/68	13 (1 yr.)	71 (1 day)	—	244	a, 2.0 g, 2.2 f, 0.8	—	250	75	0	0	0	0	Peritonitis	Followed a cold
161	33-1579	5	M	2.5 yrs.	1 4	4	95/60 110/70	10.5 (1 mo.)	45 (1 mo.) 27.6 (3 wks.)	30 (1 mo.)	215	a, 1.65 g, 2.11	75	290	70	0	5	1p	3p	Streptococcic peritonitis	Followed pneumonia
162	26-625	6	F	6 mos.	3	4	—	27 (6 wks.) 19 (1 mo.)	—	15 (2 wks.)	—	—	60	275	68	—	5	1p	0	Peritonitis	
163	33-1472	7	M	13 mos.	4	3	96/66	11.7 (9 mos.) 29 (1 day)	45.8 (10 mos.) 75.8 (1 day)	40 (9 mos.) 74 (1 mo.)	—	a, 1.8 g, 2.8 f, 0.4	290	267	—	0	0	0	0	Peritonitis	
164	36-472	7	M	5 mos.	4	2	—	—	22 (3 wks.)	—	452 1025	a, 1.33 g, 3.56	175	310	—	0	0	0	1p	Erysipelas	
165	32-1297	9	F	2 yrs.	0 4	4 0	108/88	15.4 (2 yrs.)	48 (2 yrs.) 99.8 (2 wks.)	—	—	a, 0.6 g, 3.16	180	455	56	0	0	0	1p	Streptococcic peritonitis	
166	30-159	12	F	7 mos.	3	4	110/80	10.3 (7 mos.) 61.2 (1 day)	—	67 (7 mos.) 42 (1 mo.)	—	—	130	460	45	0	0	2	3	Streptococcic peritonitis	Hematuria crescents
167	0-38-820	13	F	5 mos.	2 4	4	116/82	—	—	—	609	2.71 4.2	170	425	—	—	0	0	2	Pneumococcic peritonitis	

168	30–1856	20	F	22 mos.	1 4	2 4	140/70 (22 mos.) 222/134 (4 mos.)	77 (22 mos.) 102 (1 day)	—	54 (22 mos.)	—	—	484	254	45	0	10	2	3	Uremia, pneumococcic bacteriemia	Followed sore throat
169	30–768	21	M	—	3	4	180/100 (1 wk.)	53.9 (9 days)	—	—	—	—	387	549	—	0	0	2	2	Peritonitis	
170	32–1080	31	M	6 yrs.	1 4	2	158/96 (6 mos.) 236/176	—	41.4 (6 mos.) 166.5	65 (6 mos.) 5	—	a, 0.9 g, 2.6	525	400	69	0	10	3	3	Uremia	Retinitis
171	34–1536	32	F	2 yrs.	4	3 0	130/98 (2 yrs.) 190/112	31.2 (2 yrs.) 120.4	—	50 (2 yrs.) 0	230	a, 1.49 g, 1.09 f, 0.66	440	170	44	0	70	3	3	Uremia	
172	28–183	34	F	7 mos.	3	3 0	200/140 (1 mo.)	47 (1 wk.)	—	0 (1 wk.)	—	—	300	300 (one)	48	—	0	1	2	Broncho-pneumonia	
173	35–654	36	M	5 wks.	4	3	108/74	—	38 (2 wks.)	—	—	a, 1.0 g, 0.9 f, 0.7	280	365	73	—	0	0	1p	Accident	
174	37–2146	36	M	1 yr.	3	3	130/90 (2 mos.) 160/120	28.7 (2 mos.)	—	15	423	a, 2.97 g, 1.83 f, 0.33	340	420	70	—	0	0	1		
175	25–636	37	M	5 yrs.+	2	2 1	150/120 170/120 (2 mos.)	31 (2 mos.) 159 (5 days)	—	—	—	—	450	375	—	1	50	3p	3	Uremia	
176	35–961	40	M	9 mos.	3	4	130/90 (8 mos.) 114/74	18 (8 mos.)	36 (8 mos.)	65 (8 mos.)	258	a, 1.76 g. 1.68 f, 0.46	325	485	—	1	0	0	2	Bacterial endocarditis	Followed sore throat
177	32–1127	43	M	7 yrs.	4	4	Normal to 250/?	Normal to very high	—	—	—	—	500	225	—	0	90	4	3	Uremia	5 yrs. as pure type
178	31–1408	48	M	4 mos.	4	2 4	148/102 (4 mos.) 162/104 (1 mo.)	—	77 (4 mos.) 95 (1 day)	55 (4 mos.)	—	—	Normal	305	—	0	10	2	3	Inanition	
179	17–145	54	M	1 yr.	2	4	155/80 190/95	13 (10 mos.) 23 (10 days)	—	72 (10 mos.)	—	—	320	450	—	—	10	1p	2	Purulent bronchitis	
180	35–114	58	M	3.5 mos.	3	3	140/90	15.9 (2 wks.)	—	44 (2 wks.)	—	a, 1.91 g, 2.62	250	270	56	0	0	0	2	Streptococcic peritonitis	
181	26–827	62	F	15 yrs.	3	3	134/82 (2 days)	25 (1 day)	—	—	—	—	330	260	40	0	0	0	4	Severe anemia	

Under plasma proteins, a = albumin, b = globulin, f = fibrinogen.

there were repeated attacks of peritonitis. The exacerbations often followed an upper respiratory infection. The duration of symptoms was only 5 and 6 weeks in Cases 173 and 157, and these might appropriately be classified as acute, but the duration in the other cases warrants the diagnosis of subacute or chronic.

Cardiac hypertrophy was found in those who died of uremia.

The Structural Alterations in the Kidneys: The convoluted tubules often contain numerous droplets of lipoid, but they never show primary degeneration or necrosis. Atrophy of the tubule occurs only when the capillaries of its associated glomerulus become obstructed; there is no primary tubular atrophy. Lipoid nephrosis is not a primary tubular disease.

In 6 instances there were no visible changes in the capillary basement membranes. Cases of this type have been reported by several writers and have given rise to the widespread belief that in lipoid nephrosis the glomeruli are normal. It appears from our study (Table X) that in young children the basement membranes either show no thickening at all (Fig. 9) or only focal areas of thickening (1p, in Table X), while in older children and adults thickening of the basement membranes is nearly always pronounced. The absence of thickening is not due entirely to a short duration of the disease, since in 3 cases without thickening the duration was 13 mos., 15 mos. and 16 mos. respectively. It seems highly improbable that these cases with normal appearing capillaries represent a different disease from those with thick membranes, since the clinical features of the two groups are almost identical and there are numerous gradations from normal membranes to those that are very thick. In view of the remarkable permeability of the capillaries to the plasma proteins one must believe that the capillary walls, *i.e.* the basement membranes, are injured even though they show no structural changes. The capacity of the membrane to thicken in response to the injury is in some way related to age.

In Cases 164, 165 and 173 there were individual glomerular lobules here and there with thick basement membranes, and in Case 161 there were a few glomeruli with marked diffuse thickening of the basement membranes (Fig. 10). Blackman noted a few hyaline glomeruli in several of his cases, but explained them as a result of focal glomerulonephritis. However, these individual glo-

meruli show the same thickening of the basement membranes as is found in the diffuse form.

Tubular atrophy occurs when the thickened basement membranes have produced marked narrowing or closure of the glomerular capillaries. Complete closure of the capillaries results in hyalinization of the glomerulus and extreme atrophy of its tubule. When a large proportion of the glomeruli have become hyaline the kidneys may shrink in size and uremia develops (Cases 171, 175 and 177) (Fig. 11). It is to be noted that the contracted kidneys of lipoid nephrosis are due to primary glomerular disease with secondary tubular atrophy and not to primary tubular degeneration as Th. Fahr maintained. When a small proportion of the glomeruli are hyaline (Cases 178, 179) a patchy type of atrophy develops. A diffuse tubular atrophy of moderate degree develops when all the glomerular capillaries are narrowed but not completely closed (Cases 166, 168, 169, 170, 171) (Fig. 12). Uremia may develop in this way before any large proportion of the glomeruli have become hyaline (Case 170).

The Relation of Hydropic Glomerulonephritis (Lipoid Nephrosis) to the Azotemic Type

In the foregoing discussion we have presented clinical and anatomical evidence that lipoid nephrosis is a glomerular and not a tubular disease, but since this view is not widely accepted at present a brief historical résumé of the subject may be helpful.

Prior to 1914 lipoid nephrosis was known as parenchymatous nephritis. It was well known that edema and albuminuria were outstanding features, that uremia seldom developed, and that the kidneys were usually large. At that time azotemic glomerulonephritis and the hypertensive kidney were regarded as disease of the interstitial tissue, "interstitial nephritis" in contrast with the "parenchymatous" type which was vaguely considered tubular disease.

The identification of glomerulonephritis by Langhans and Löhlein and of vascular disease by Ziegler initiated the modern period of renal investigation. The popular monograph by Volhard and Fahr in 1914 [7] created widespread interest in nephritis, but their effort to establish "nephrosis" as an entity has retarded progress. These writers classed as nephroses all renal diseases which

they considered degenerative in nature, such as the effects of chemical and bacterial poisons, amyloid disease, eclampsia and genuine or lipoid nephrosis. These diseases have little in common either clinically or pathologically and nothing is to be gained by placing them in one group. In recent years "nephrosis" has been restricted by most writers to lipoid nephrosis.

Volhard and Fahr distinguished two forms of lipoid nephrosis — pure nephrosis and nephrosis with a nephritic component. They believed that nephrosis and nephritis are distinct diseases, the former being degenerative in character, the latter inflammatory. When a patient with the nephrotic syndrome (albuminuria, edema, and so on) developed hypertension or uremia, they believed that nephritis had been superimposed on nephrosis. They stated that pure nephrosis shows only tubular degeneration and that nephritis shows inflammation in the glomeruli. These ideas are still widely supported by clinicians and pathologists.

Another theory of lipoid nephrosis that has many adherents is that it is a general metabolic disorder with secondary renal changes. This view was supported by Epstein [8] who wrote of "albuminuric diabetes." Diebold,[9] Wolbach and Blackfan [10] and others do not believe that the renal lesions are responsible for the symptoms.

It is customary to describe two forms of lipoid nephrosis — the pure type and the mixed type. There are many who believe that these forms are distinct and that the mixed type is a form of glomerulonephritis; others regard the mixed type as a mixture of nephrosis and nephritis, and a few believe that nephrosis is merely a variety of glomerulonephritis.

(*A*) *Pure Lipoid Nephrosis:* This disease is characterized clinically by the presence of marked edema, albuminuria, hypercholesterolemia and low plasma proteins, and by the absence of hypertension, hematuria and renal insufficiency. Pathologically the usual descriptions emphasize the presence of abundant lipoid in the renal tubules and the absence of glomerular disease.

There is disagreement in the literature as to the clinical limitations of the disease. The most rigid definition is given by Leiter [11] who excludes from this group every case in which there is hematuria, any elevation of blood pressure or any renal insufficiency. Volhard [12] apparently holds a somewhat similar view. But the

majority of writers adopt a more elastic definition. Gainsborough [13] found hematuria at the onset of the illness in 6 of 10 cases, and several other writers mention hematuria in an occasional case. One of our cases, Case 168, showed hematuria. Blackman [14] does not exclude cases that show transitory hypertension or increases of non-protein nitrogen, but he would reject any case with a constant or progressive increase of non-protein nitrogen or of blood pressure. He would also reject those with gross hematuria. Many of our cases in Table IX would be admitted by Blackman's definition but would be excluded by Leiter's. When the patient is studied thoroughly with repeated and varied functional tests some degree of nitrogen retention will usually be found at times. The blood urea may be somewhat elevated early in the disease but normal later on (Cases 158 and 162). These variations are probably due to extrarenal influences.

With regard to the pathological changes in the kidneys the great majority of authors find the glomeruli normal. Blackman found a few hyaline glomeruli with atrophic tubules in several of his cases. There were focal thickenings of the basement membranes in 4 of our cases (Cases 161, 164, 165 and 173). In Case 166 there was a marked diffuse thickening of all the basement membranes with a beginning diffuse tubular atrophy, but some would reject this case because of the high urea nitrogen on the day of death.

(*B*) *The Mixed Type of Lipoid Nephrosis:* As noted above, this disease has all the positive features of the pure type but has in addition either azotemia or hypertension, or both conditions. In the literature there are three theories in regard to the nature of this disease: (1) that it is a form of glomerulonephritis entirely distinct from pure lipoid nephrosis; (2) that it is a nephrosis with a superimposed nephritis, or *vice versa*; and (3) that it is a variety of glomerulonephritis closely related to pure lipoid nephrosis and that its special symptomatology is due to the anatomical nature of its glomerular lesions.

Many writers discuss the "nephrotic syndrome" or nephrosis including cases of both the pure and the mixed types, and do not concern themselves with the anatomical nature of the lesion.

(1) The view that pure nephrosis is different from the mixed type is supported by many writers on the basis of their experience. They have observed cases of nephrosis without persistent hyper-

tension or azotemia where the individual either recovered entirely or died of an infection, usually peritonitis. At postmortem no proliferative glomerulitis was found. But these writers offer no explanation for the cases that exhibit the symptoms of pure lipoid nephrosis for some years and then develop hypertension and uremia. Several such cases are now on record. Volhard [12] mentioned a case of nephrosis in a boy 7 years of age, who developed clinical evidence of a nephrotic contracted kidney. Débre and Marie [15] reported the case of a child 5 years of age who died in uremic coma after a period of 3 years of pure lipoid nephrosis. Gainsborough [13] reported that one of his patients had nephrosis for 8 years and developed slight hypertension and nitrogen retention during the last few months of life. A remarkable case was reported by George Fahr [16] (Case 177). The patient, a physician, was 36 years of age at the onset of his illness. For 5 years he had a typical picture of pure lipoid nephrosis and was studied carefully in several prominent clinics. During the last 2 years of his life he gradually developed hypertension and azotemia, and died with a very high blood pressure and a marked elevation of blood urea.

It is, therefore, well established that pure lipoid nephrosis may pass gradually into the mixed type, developing hypertension and uremia. Those who insist on the separate identity of the pure and mixed types can only suppose that nephritis has been superimposed on the nephrosis, but as we shall show presently no new disease has been introduced but the glomerular capillaries have been progressively narrowed and closed by thickening of the basement membranes.

(2) The second view is that the mixed type is a mixture of two diseases, *i.e.* nephrosis and nephritis. This view was first promulgated by Volhard and Fahr who used the expression "nephritis with a nephrotic Einschlag." It is not entirely clear what these authors meant by a "nephrotic Einschlag." Volhard explained some years later that he meant nephritis with a tendency to edema, but Fahr has stated definitely that nephrosis is something quite distinct from nephritis.

The erroneous view has been widely accepted that albuminuria and edema indicate nephrosis and that hypertension and azotemia mean nephritis. But albuminuria and edema occur also in nephritis although usually in lesser intensity, and consistency re-

quires the advocates of this theory to admit some nephrotic component in most cases of nephritis. There is no feature of nephrosis that does not occur also in some cases of nephritis. Furthermore it has been clearly established that albuminuria and edema are due to glomerular and not to tubular disease.

(3) The third theory postulates that the mixed type of lipoid nephrosis is a variety of glomerulonephritis closely related to pure lipoid nephrosis, and that its symptoms may be explained by the nature of the glomerular lesions. We have advocated this interpretation for several years.

Résumé of the Pathology of Hydropic Glomerulonephritis (Lipoid Nephrosis): The clinical syndrome, commonly called lipoid nephrosis, is not associated with a uniform type of glomerular lesion. In 6 of our 40 cases there was a proliferative glomerulonephritis but most of the glomerular capillaries were patent, allowing the escape of serum proteins into the urine and thus favoring the development of edema.

In 6 young children there were no visible changes in the glomeruli. In 3 children and 1 adult individual glomeruli or individual glomerular lobules showed thickening of the capillary basement membranes. In the other 24 cases there was a definite diffuse thickening of the membranes. Two children, aged 12 years and 13 years respectively, showed this membranous change as strikingly as the adults. In nine adults (Table IX) some glomerular lobules showed proliferative changes. In 3 of the 4 cases with death from uremia a large proportion of the glomeruli were hyaline.

Apart from the 6 cases of proliferative glomerulonephritis mentioned above, lipoid nephrosis was associated with a membranous type of glomerulitis when any lesions were visible. There were no clinical distinctions between the 2 cases in children (Cases 166 and 167) with thick membranes and those with normal membranes. In those with diffuse thickening of the basement membranes hypertension was present in 14 and absent in 8 cases.

A moderate tubular atrophy develops when the glomerular capillaries become so narrow that they transmit a decreased amount of blood (Cases 166, 169 and 178), and the tubules disappear almost completely after the glomeruli become hyaline. The glomeruli are obliterated by progressive thickening of the

basement membranes. In the cases with death from uremia tubular atrophy is very pronounced. The atrophy of the tubules is not due to primary tubular disease but is secondary to the closure of the glomeruli. The "nephrotic contracted kidney" results from membranous glomerulonephritis.

Discussion

In the various forms of glomerulonephritis the symptoms and the clinical course are closely dependent upon the character and the extent of the glomerular lesions. If the initial acute attack results in widespread severe capillary obstruction renal insufficiency soon develops. Those cases that terminate in uremia within a few months are called acute, while those that survive from 4 or 5 months to 1 year are usually called subacute. When the initial glomerular injury is less intense so that a majority of the capillaries remain more or less permeable a chronic nephritis develops. Complete anatomical recovery evidently takes place after mild acute glomerulonephritis. The initial lesions are less severe and extensive in the cases that become chronic than in those that follow a subacute course.

The initial glomerular lesion consists of an increase of endothelial cells and splitting and fragmentation of the central capillary basement membranes in the interior of the lobules (Fig. 4). If the capillaries become completely occluded the glomerulus becomes hyaline; if partially occluded a peripheral circulation develops in the lobule and the hyaline fibers, derivatives of the central membranes, become fused into a hyaline mass at the center of the lobule (Figs. 3 and 7). The glomeruli shown in Figures 2, 3 and 7 represent the usual structure of functioning glomeruli in chronic azotemic glomerulonephritis. Their structure is definitely altered but evidently glomerular filtration is not notably reduced since the associated tubules are not atrophic.

In latent chronic glomerulonephritis nearly all of the glomeruli have a structure similar to that shown in Figures 2 and 3. If the lesion does not progress beyond this stage renal function remains adequate. In advanced chronic glomerulonephritis many of the persistent glomeruli have a structure similar to those of the latent stage. The chief difference between the latent and advanced stages is that in the latter most of the glomeruli are either hyaline

or markedly obstructed. Azotemic glomerulonephritis is characterized by obstruction of the glomerular capillaries.

In hydropic glomerulonephritis the capillary walls are injured but the lumens remain open. This type of lesion seldom occurs in proliferative glomerulitis but it is characteristic of membranous glomerulitis. It is not known whether or not membranous glomerulitis has a different etiology from the proliferative form; we know only that in the proliferative type the capillaries become obstructed, while in the membranous form the capillary walls are injured and become permeable to the plasma proteins. The marked permeability of the capillaries to proteins causes edema, which is the outstanding feature of the disease. Hypertension does not develop until the thickened membranes have produced a definite narrowing of the capillalry lumens. Extreme thickening of the membranes may result in extensive hyalinization of the glomeruli and renal insufficiency. For some unknown reason hydropic glomerulonephritis in young children seldom shows extensive thickening of the basement membranes.

Azotemic nephritis is due to capillary obstruction and hydropic nephritis results from increased permeability of the capillaries to proteins. Azotemia develops regularly in proliferative glomerulitis but infrequently in the hydropic form. Hydropic glomerulonephritis is usually due to membranous glomerulitis, occasionally to the proliferative form.

Summary

Of 181 cases of glomerulonephritis, 16 were classified as subacute, 8 as latent chronic, 117 as chronic azotemic and 40 as chronic hydropic.

In subacute glomerulonephritis the kidneys are not contracted. There is widespread severe glomerular obstruction with well advanced uniform tubular atrophy. There are few hyaline glomeruli.

There are 125 cases of chronic azotemic glomerulonephritis. Eight cases of latent chronic glomerulonephritis are described in which death was due to an intercurrent disease. Only 1 such case has been reported previously. There are only a few hyaline glomeruli and there is little or no tubular atrophy. The glomeruli are all damaged to some degree, their lobules showing hyaline central portions and peripheral capillaries.

Thirty cases of chronic azotemic glomerulonephritis are reported in which there is a history of an initial acute attack. The total duration varied from 1.5 years to 26 years, with an average duration of 10 years. In 15 of the 30 cases the acute attack was followed by a latent chronic stage varying from 1 year to 24.5 years in length; in the remaining 15 cases the acute stage passed directly into active chronic nephritis.

In 30 per cent of the cases the systolic blood pressure was 200 mm. Hg. or higher.

There is some degree of chronic passive congestion of the liver in nearly one-half of the cases, indicating some degree of heart failure, but there is no evidence that heart failure is ever more than a contributing cause of death since all of the patients had uremia. Heart failure may occasionally be a contributory cause of edema. Only one patient had a history of apoplexy and only one had an attack of coronary sclerosis.

Retinitis was found in 35 of 46 cases in which the eyegrounds were examined. There is a definite relation between high blood pressure and retinitis.

There is no relation between the weight of the kidneys and the duration of the disease or the height of the recorded blood pressure. The kidneys are occasionally of normal size or even enlarged in the terminal stages. Large kidneys contain a high proportion of injured glomeruli with moderately atrophic tubules, while small kidneys consist largely of hyaline glomeruli with extremely atrophic tubules.

Forty cases of hydropic glomerulonephritis (lipoid nephrosis) are reported. In 6 of these the glomerular structure was that of chronic proliferative glomerulonephritis, and in 9 others there was a mixture of proliferative and membranous glomerular lesions with the latter in great preponderance. In the remaining 25 cases there were no proliferative lesions.

In 6 cases in young children there were no visible changes in the glomerular capillaries, and in 3 other children there were only focal membranous lesions.

With one exception diffuse thickening of the basement membranes was present in all persons over 12 years of age.

In 4 cases membranous glomerulitis produced such an extensive narrowing of the glomerular capillaries that uremia developed.

When a patient with pure lipoid nephrosis develops hypertension and uremia no new disease is superimposed — there is merely progressive thickening of the basement membranes.

Nephrosis is a form of glomerulonephritis in which the glomerular capillaries remain open and allow the blood proteins to escape into the urine. In proliferative glomerulonephritis the capillary lesions are nearly always of obstructive type.

REFERENCES

1. Bell, E. T. The pathology and pathogenesis of clinical acute nephritis. *Am. J. Path.*, 1937, **13**, 497–552.
2. Russell, Dorothy S. An early stage of nephritis repens. *J. Path. & Bact.*, 1934, **38**, 179–186.
3. Frehse, Karl. Ueber die Dauer der chronischen Nephritis. *Deutsche med. Wchnschr.*, 1922, **48**, 1543–1545.
4. Bannick, Edwin G. Severe chronic glomerular nephritis without hypertension, cardiac hypertrophy or retinal changes; report of two cases. *Arch. Int. Med.*, 1927, **39**, 741–747.
5. Wakefield, E. G., and Keith, Norman M. Severe renal insufficiency; untoward effects of intravenous administration of solution of sodium chloride. *Arch. Int. Med.*, 1932, **49**, 165–170.
6. Moritz, Alan R., and Hayman, J. M., Jr. The disappearance of glomeruli in chronic kidney disease. *Am. J. Path.*, 1934, **10**, 505–518.
7. Volhard, F., and Fahr, Th. Die Brightsche Nierenkrankheit. Julius Springer, Berlin, 1914.
8. Epstein, Albert A. Further observations on the nature and treatment of chronic nephrosis. *Am. J. M. Sc.*, 1922, **163**, 167–186.
9. Diebold, Otto. Zur Frage der Lipoidnephrose. *Deutsche med. Wchnschr.*, 1929, **55**, 1550–1553.
10. Wolbach, S. Burt, and Blackfan, Kenneth D. Clinical and pathological studies on so-called tubular nephritis (nephrosis). *Am. J. M. Sc.*, 1930, **180**, 453–476.
11. Leiter, Louis. Nephrosis. *Medicine*, 1931, **10**, 135–242.
12. Volhard, F. Die Nephrosen. Handbuch der inneren Medizin, von Bergmann, G., and Staehelien, R. Julius Springer, Berlin, 1931, **6**, 1025–1178.
13. Gainsborough, Hugh. A study of so-called lipoid nephrosis. *Quart. J. Med.*, 1929, **23**, 101–127.
14. Blackman, S. S., Jr. Pneumococcal lipoid nephrosis and the relation between nephrosis and nephritis. *Bull. Johns Hopkins Hosp.*, 1934, **55**, 1–56.

15. Debré, Robert, and Marie, Julien. Sur le syndrome de néphrose lipoïdique dans l'enfance. *Rev. franç. de pédiat.*, 1931, 7, 121–142.

16. Fahr, George. What is lipemic nephrosis? *Am. J. M. Sc.*, 1937, **194**, 449–463.

DESCRIPTION OF PLATES

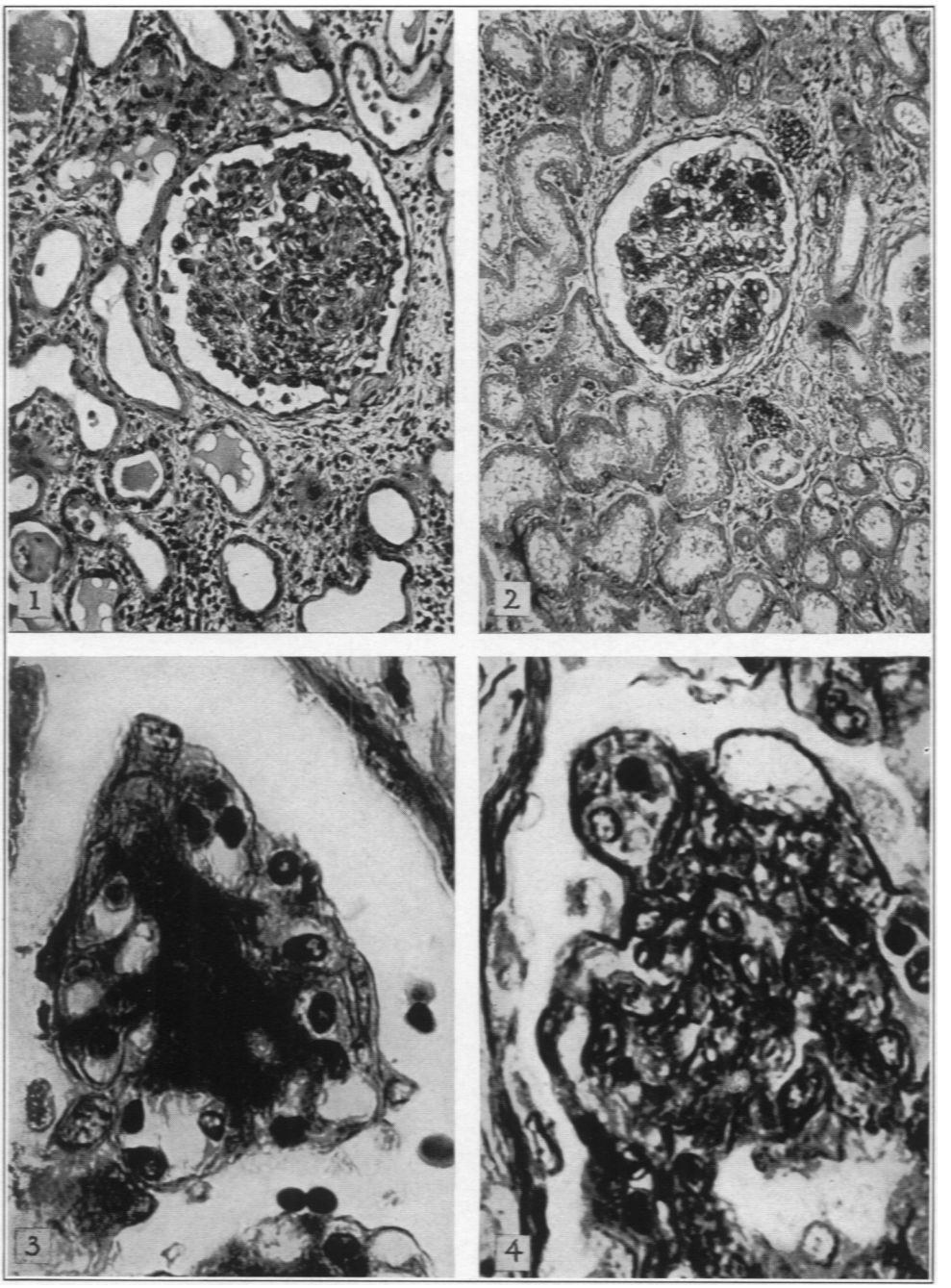
PLATE 142

FIG. 1. Case 2. Subacute glomerulonephritis. Note obstruction of glomerular capillaries and moderate tubular atrophy. × 200.

FIG. 2. Case 18. Latent chronic nephritis. Note absence of tubular atrophy. The glomerular lobules show solid central portions with peripheral capillaries. × 200.

FIG. 3. Case 18. Latent chronic nephritis. Detailed structure of glomerular lobule. Note hyaline central portions of lobule and peripheral capillaries. × 850.

FIG. 4. Glomerular lobule from mild acute glomerulonephritis. Note fragmentation of the central capillary basement membranes and partial permeability of capillaries. This is probably the type of lesion that becomes chronic. × 850.



Bell Subacute and Chronic Glomerulonephritis

PLATE 143

FIG. 5. Case 93. Chronic azotemic glomerulonephritis with contracted kidneys. Histological type *a*. Note large proportion of hyaline glomeruli. × 80.

FIG. 6. Case 25. Chronic azotemic glomerulonephritis with uremia. Weight of kidneys 460 gm. Duration 4 years. Histological type b_1. Partially obstructed glomeruli with well advanced tubular atrophy. × 200.

FIG. 7. Case 57. Chronic azotemic glomerulonephritis with uremia. Histological type b_1. Lobule of a glomerulus showing central hyaline mass and peripheral capillaries. × 850.

FIG. 8. Case 142. Group IV. A. Chronic hydropic glomerulonephritis with the microscopic structure of proliferative glomerulonephritis. × 200.

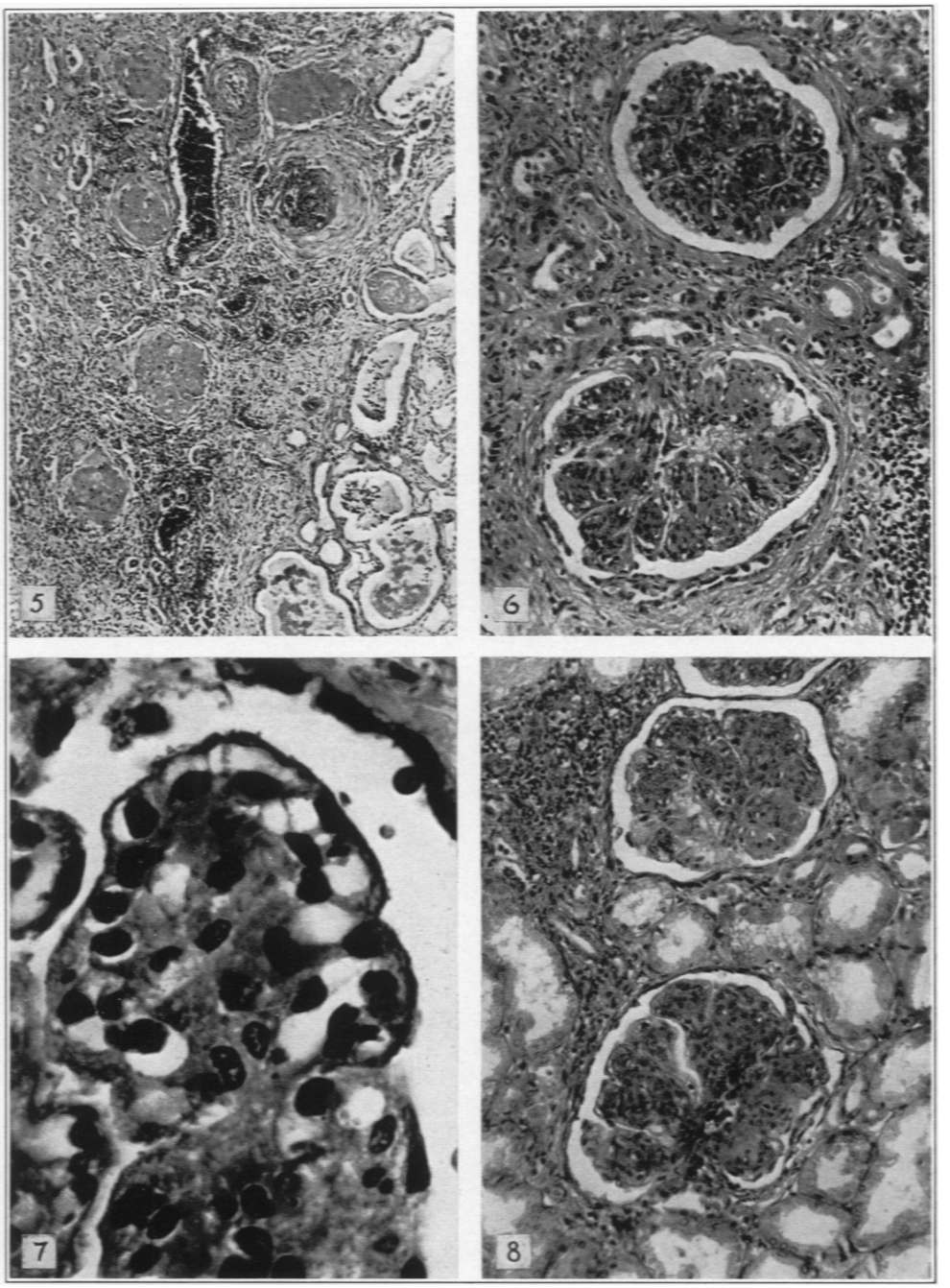

5
6
7
8

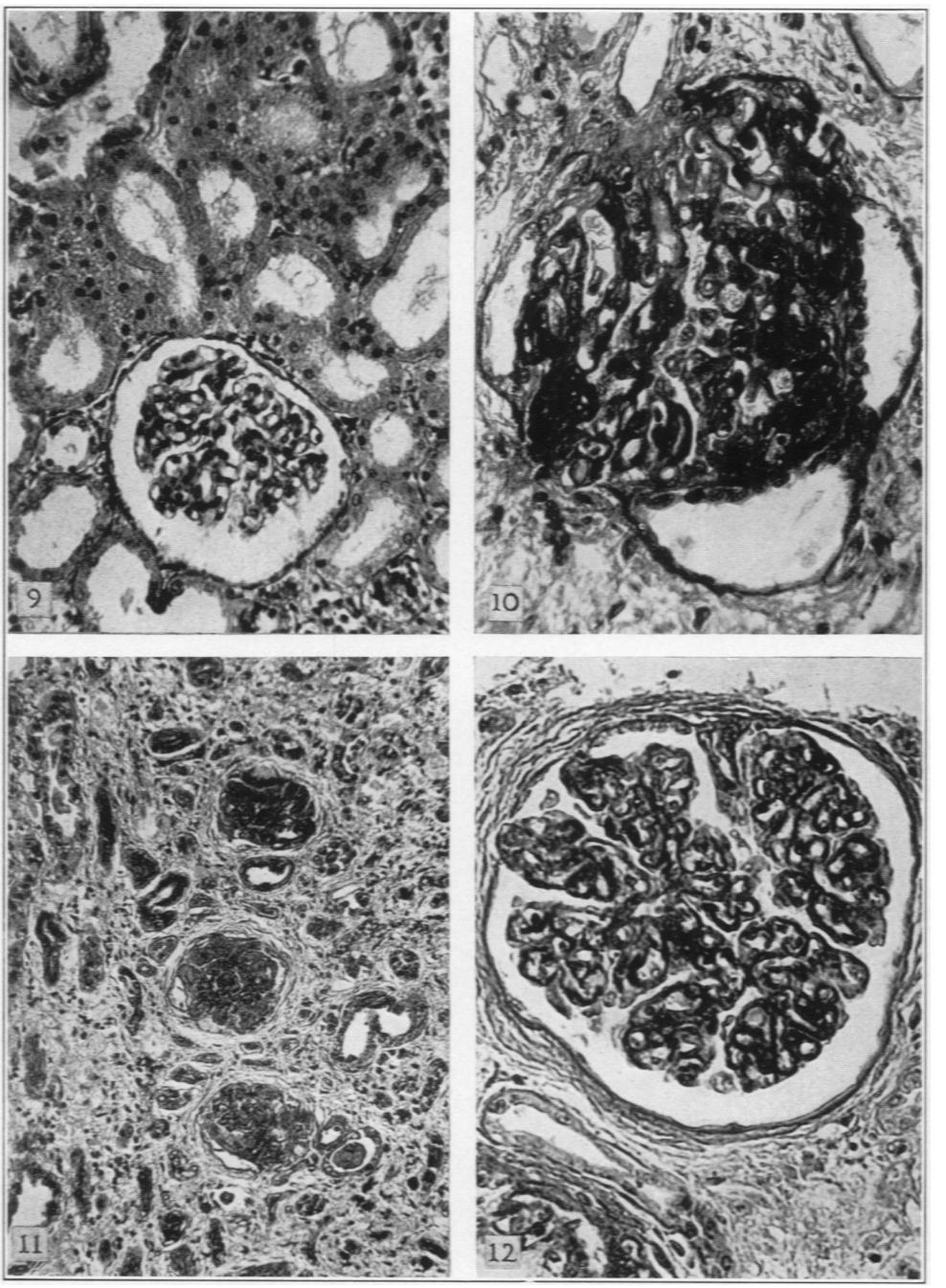
PLATE 144

FIG. 9. Case 164. Hydropic glomerulonephritis in a child 7 years of age. There are no structural changes in the glomeruli. × 200.

FIG. 10. Case 161. Hydropic glomerulonephritis in a child 5 years of age. A majority of the glomeruli show no changes. The illustration shows an individual glomerulus with diffuse thickening of the basement membranes. Mallory-Heidenhain stain. × 400.

FIG. 11. Case 171. Chronic hydropic glomerulonephritis with contracted kidneys and uremia. Note small hyaline glomeruli and atrophic tubules. × 150.

FIG. 12. Case 168. Chronic hydropic glomerulonephritis. A glomerulus stained by the Mallory-Heidenhain method. Ninety per cent of the glomeruli were of this structure. Note the thick basement membranes. × 400.



Bell Subacute and Chronic Glomerulonephritis