LIPOID NEPHROSIS *

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Nephrosis is defined as a degenerative renal disease in which the lesions are restricted chiefly to the tubules. On the basis of etiology several types are distinguished:

1. Nephroses due to simple chemical poisons (*e. g.*, corrosive sublimate).
2. Nephroses due to poisons of metabolic origin (*e. g.*, bile acids).
3. Nephroses due to poisons of bacterial origin, as in pneumonia, diphtheria, abscess, etc.
4. Nephroses due to the toxemia of pregnancy.
5. Amyloid nephrosis.
6. Lipoid nephrosis.

This paper deals only with lipoid nephrosis — a type which has attracted much attention in recent years. The study has been directed chiefly toward the structural changes in the kidneys and the anatomical and clinical distinctions between lipoid nephrosis and glomerulonephritis. Some of the questions that have arisen in connection with the problem of lipoid nephrosis are: (1) Is lipoid nephrosis a renal disease or a general metabolic disorder? (2) Is it a distinct type of renal disease or merely a form of glomerulonephritis? (3) What is the nature of the mixed type — nephritis with nephrotic *Einschlag?* (4) Are all the non-contracted kidneys, associated with albuminuria and edema, instances of lipoid nephrosis? (5) Are there any certain clinical or anatomical distinctions between lipoid nephrosis and glomerulonephritis?

The authors chiefly responsible for the wide recognition of lipoid nephrosis as a distinct disease are Munk, Volhard and Fahr, and Epstein. Munk described it under the name of "lipoid nephrosis"; Volhard and Fahr, as "genuine nephrosis"; and Epstein, as "chronic nephrosis." The term suggested by Munk has been generally adopted since it refers to a striking characteristic of the disease.

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Lipoid nephrosis was defined anatomically by Volhard and Fahr under the designation of "genuine nephrosis." Nearly all subsequent contributors to this subject have accepted the criteria laid down by these authors. They described the kidneys as enlarged with smooth external surfaces and thickened cortices of yellowish color. The glomeruli appear normal or show only minor focal lesions. Large numbers of lipoid droplets are found in the convoluted tubules, and some may be seen in the interstitial cells and in the glomeruli. There is no tubular atrophy.

Clinically there is general agreement that the outstanding features are the presence of severe albuminuria and marked edema, and the absence of hypertension, cardiac hypertrophy, hematuria and uremia. There is a definite hypercholesterolemia and a decrease of the plasma proteins with reversal of the normal albumin:globulin ratio. Oliguria and decreased elimination of chlorides are frequently noted. The urine commonly contains doubly refractive droplets of lipoid (lipoiduria).

It is not known whether all kidneys with lipoid infiltration of the tubules are associated with the clinical phenomena of lipoid nephrosis. In the present state of our knowledge the diagnosis should not be made on the anatomical findings alone.

Some cases of chronic glomerulonephritis in the earlier stages present the clinical features of lipoid nephrosis, so that a diagnosis based on clinical data alone may be erroneous.

Frequently a renal disease is seen that presents all the clinical features of lipoid nephrosis except for the presence of hypertension or definite nitrogen retention. Epstein included cases of this type in his group of "chronic nephroses"; but they are usually considered a mixed form of nephritis and nephrosis. Fahr refers to this group as nephritis with nephrotic *Einschlag*, which may be translated as nephritis with a nephrotic tendency. The structural changes in the kidneys in this type will be described later.

Table I gives a résumé of all the available published reports in which the diagnosis was established by postmortem examination. The anatomical findings in these cases correspond with Volhard and Fahr's definition.

Table II gives a résumé of the published reports of living persons in which the clinical data seem to justify the diagnosis of lipoid nephrosis. Cases with high blood pressure have not been tabulated

since these are presumably not pure nephroses. When the blood pressure is not recorded the case is excluded because its exact nature is uncertain. Nephroses associated with chronic suppuration have also been omitted since they are presumably of the amyloid type.

In addition to the cases shown in the tables there are reports dealing with groups of patients without individual details. Clausen observed 23 cases of parenchymatous nephritis (nephroses) in children. There were ten deaths. Infection was the chief cause of death. In the single postmortem that was performed the glomeruli showed only a few polymorphonuclear leucocytes.

Schwarz and Kohn observed 17 cases of nephrosis in children. The diagnostic features were albuminuria and edema with hypercholesterolemia and reduced plasma proteins. Blood pressure and renal function are not mentioned. No postmortems were reported.

Bannick and Keith reported 25 chronic nephroses. Their criteria were: edema for several months without demonstrable vascular disease, a blood pressure not above 140/90, blood urea not above 40 mg. per 100 cc., hypercholesterolemia, decreased plasma proteins, no hematuria, no retinitis. There were two deaths but no postmortem reports were given.

Munk, in 1913, reported 5 cases of lipoid nephrosis with albuminuria, edema, lipoiduria and oliguria. Blood pressure was given in only one instance. Four of the patients had syphilis.

Among 300 cases of nephritis with edema, Schlayer found only 6 cases of pure lipoid nephrosis and some of these were uncertain.

Before discussing the several phenomena of lipoid nephrosis in detail, I shall give the results of my own studies on this subject.

Group I. Pure Lipoid Nephrosis

Case I. *Clinical History:* A–28–647. Male, 28 yrs. old. The patient stated that he developed a cold about April 3, 1928, and one week later noticed swelling of the legs and puffiness about the eyes. After a few days the swelling became more prominent and involved the skin of the chest and back. The only subjective symptom was weakness. The urine was dark brown in color and reduced in amount. He was admitted to the hospital April 17, complaining of weakness and edema. Physical findings were negative except for severe generalized edema and moderate tenderness over both kidney regions posteriorly. Hemoglobin was 97 per cent on admission and 81 per cent two weeks later. Erythrocytes were 4,970,000 on admission and 4,600,000 later. Leucocyte count April 17, 7150 with 66 per cent polymorphonuclears. There was a definite oliguria. The specific gravity of the urine was constantly high, 1021 to

TABLE I

Lipoid Nephroses in which the Diagnosis was Confirmed by Postmortem Study

Author	Age in yrs.	Sex	Duration	Outcome	Edema	Urine albumin gm. per 1000 cc.	Cholesterol mg. per 100 cc.	Serum albumin	Serum globulin	Total protein	Blood pressure	Urea nitrogen mg. per 100 cc.	N. P. nitrogen mg. per 100 cc.	Phenolsulphonephthalein	Urine amount in cc.	Wassermann	Basal metabolic rate	Peritonitis	Weight of kidneys in gm.	Lipoiduria
McElroy	17	M	2 mo.	D	3	4					115–75		77		360	—		+		
Kaufmann, Mason	29	M	7 mo.	D	3	5 to 8		Normal ratio			142–98 122–90	24 39		48	2030 0	— —		+ +	570	
Bock, Mayer	43	F	3 mo.	D	3	12					95– 100–85				1700 500			+ +		
Rigler, Rypins	2½	M	9 wk.	D	3	+++	366	3.08	3.39	6.47	100–80	10.3 20.0								
Murphy, Warfield	21	M	1 yr. +	D	3	++	500 700				118–70 125–65	Normal		60		— —	—10 —15		415	+ +
Fahr	19	M	6 wk.	D	3	16 to 60					120–		31							+
	38	F	10 mo.	D	+	22 to 60					132–		34		less					
	9	M	2½ mo.	D	3	15 to 25					108–							+		
	18	M	4 wk.	D	3	12 to 30					128–				less					
	7	M	9½ mo.	D	+	+									less					
	16	F	15 mo.	D	+													+		

Volhard, Fahr.....	15	M	15 mo.	D	+	5 to 51					120–58				200 2600		.	+		
	22	M	6 mo.	D	2	2 to 14					130–90		29 75		550 800			+	510	
Stepp, Petri.....	16	M	6 mo.	D	3	24	960				110– 120–		46		200					
Vandorfy.....	24	M	7 mo.	D	2	3 to 24					135–				800			+	large	
Stolz.....	3	M	1 mo.	D	3	6					80–							+	large	
	51	M	2 yr.	D	1,3	5					120– 105–75							+	large	–
Major, Helwig.....	34	M	10 mo.	D	3	+++		33%	66%		140–90	15		22	less		–31		430	
Löwenthal.....	8	M	2½ yr.	D	3	2 to 28					88–58 120–90	Normal			180 1450					+
	4½	F	17 mo.	D	3	0.5 to 20	400 770		50%	6.5	Normal				100 500					
	29	F	3 mo.	D	3	3 to 28	300				Normal				100 800	–				+
	21	M	4 mo.	D	3	1 to 45	420			3.9	Normal	Normal			300 2600	–			large	+
	16	F	14 mo.	D	3	8 to 12	306				Normal				300 800	–				+

TABLE II

Lipoid Nephroses in which the Diagnosis is Based on Clinical Data

Author	Age in yrs.	Sex	Duration	Outcome	Edema	Urine albumin gm. per 1000 cc.	Cholesterol mg. per 100 cc.	Serum albumin	Serum globulin	Total protein	Blood pressure	Urea nitrogen mg. per 100 cc.	N. P. nitrogen mg. per 100 cc.	Phenolsulphonephthalein	Urine amount in cc.	Wassermann	Basal metabolic rate	Lipoiduria
Campanacci.....	3			Rec.	3	8					Normal							+
	48	F	3 yr.	Rec. alb. +	3	3 to 55					130–		42		600 800	–		+
	18	M		Rec.	2	5 to 6					120– 125–				500 600			±
Epstein, Lande ..	14	F	9 mo.	Imp. alb. +	3	+++	904				125–70	19.6		30			–18	
	27	F	2 yr. (?)	Imp. edema	3	+++	364				110–70	22.4		45		+	–15	
	33	F	7 mo.	Imp. alb. +	2	+++	375				95–60	14		35			–18	
	29	F	5 mo.	Recur	2	+++	508				110–70	18.2		30			–8	
	35	M	12 yr.	Imp. alb. +++	+++ to 0	+++	320			4.3	105–68	15.4					–15	
Rigler, Rypins...	21	F	8 mo.	Imp.	++	+++	330	2.19	5.03	7.2	115–65	9.8 16.0		55		–	–25	
	34	M	13 mo.		+++	+++	Milky	2.7	3.4	6.1	132–84	9.6 33.8		52		–	–12	

Bennett.....	22	M	18 mo.	Imp. alb. +	++	+++	117 528				140–90 100–70	Norm.				−	−19	
Grossman.....	27	M	6 mo.	Rec. alb. +	+++	12					120–		44		500 600			+
Murphy, Warfield	25	F	4 yr.	Not rec.	+++ to 0	++	266 388				128–80	16.8		65				+
	24	M	3 mo.	Not rec.	++ to 0		666 275				110–60 130–80	12 20		55 75			+10	
Epstein.....	28	M	5 mo.	Rec. alb. +	0	+++	300		50%	6.4	130–80		91	15	less			
	32	F	5 mo.	Rec.	+++	+++	840		74.5%	4.38	130–80		54.8	45	less			
Stepp.....	30	M			0	6 to 8	310				97–	Norm.			2000			
Fanconi.....	2	M	7 mo.	Rec.	+++	10	338			4.9 5.6	100–		32		less			
Karger, Ullmann.	7	F	6½ mo.	Imp. alb. +++	+++ to 0	+++	Milky				95– 110–		31 39					+
Oehlecker.....	15	M		Rec.	+	8 to 12	370 830				Normal				less			+

1058. A large amount of albumin was constantly present. There were some pus cells and many hyaline and granular casts in the sediment. The Wassermann reaction was negative. The basal metabolic rate was + 27 per cent. Blood cholesterol was found to be 372 mg., 383 mg., and 240 mg. on three separate examinations. Urea nitrogen was 13.5 mg. April 17, 16.7 mg. April 25, and 48.5 mg. May 6. The blood chlorides were 460 mg. April 17, 437 mg. one week later, and 435 mg. May 6. The first intravenous phenolsulphonephthalein test gave 14.6 per cent and the second 27 per cent. The serum proteins were approximately 4 gm., of which the globulin fraction was 97 per cent and the albumin fraction only 3 per cent. Repeated blood pressure determinations gave an average of 120/80. However one systolic reading of 140 mm. Hg. was recorded. A few days before death the patient developed fever with abdominal pain, tenderness and rigidity. A diagnosis of peritonitis was made. Death occurred May 7, twenty-eight days after the onset of the edema.

Postmortem: The necropsy reveals generalized anasarca and a diffuse fibrinopurulent peritonitis. Each pleural cavity contains about one liter of cloudy fluid with abundant fibrin on the surfaces. The heart weighs 315 gm., (body weight, 150 lbs.). There is moderate edema of the lungs. The heart and liver show cloudy swelling. The right kidney weighs 250 gm. and the left 260 gm. The capsules are not adherent. The external surfaces are smooth. The cortices are thicker than normal and pale yellow in color.

Microscopic Examination: Sections stained with hematoxylin and eosin show that there is no tubular atrophy and no disease of arteries or arterioles. Most of the convoluted tubules are dilated. There are no epithelial crescents. The glomeruli are enlarged, but they contain very few erythrocytes. The glomerular capillaries are dilated and under low magnification they appear to be empty, but careful study under high magnification shows that most of them are filled with mononuclear cells that have a very pale vacuolated cytoplasm (Fig. 1). Frozen sections stained with Sudan III show these cells filled with fat droplets. There are also some fat droplets in the epithelial cells of the glomeruli. The cells of the convoluted tubules are filled with fat droplets.

The structure of the glomerulus is seen much better in sections stained by Mallory's anilin blue connective tissue stain (Heidenhain, azan-carmine*) (Fig. 2). The cells that fill the capillaries are clearly seen to be of endothelial origin. They have a large amount of vacuolated cytoplasm, the vacuolization being due to fat droplets

* The reader is referred to McGregor's paper for details of the technique and for the histology of the glomeruli in glomerulonephritis.

that have been dissolved out. The majority of the endothelial cells are firmly attached to the basement membrane, but a few are partially or completely free. The basement membrane of the capillaries shows an uneven thickening. The structure differs from typical acute glomerulonephritis in the absence of hyaline fibers in the capillaries but resembles it in that the capillaries are filled with swollen endothelial cells. The capillaries are distended, but the obstruction is sufficient to interfere with renal function. In sections stained with hematoxylin and eosin the glomeruli were considered practically normal, since the extent of the capillary obstruction was not appreciated.

CASE II. *Clinical History:* A–28–5. Female, age 4 yrs. Admitted to the hospital June 21, 1927. The child had been well until about one week before admission when she developed a cold with a nasal discharge. Edema of the ankles appeared June 19, and no urine was passed during the 24 hrs. preceding admission. There was loss of appetite. The urine showed albumin ++++, and hyaline and granular casts. Leucocytes 11,900. Blood pressure 108/64. Temperature 99° F to 100° F. Profuse drainage from both ears. Maxillary sinuses cloudy on roentgenological examination. Blood urea nitrogen 24 mg. On June 25 both sinuses were drained, and the tonsils and adenoids were removed. Pus was found in the left sinus. Edema became very pronounced. July 5, blood pressure 118/80. No fever. General edema. Ascites. Edema varied from time to time and was not relieved by urea, ammonium chloride or thyroid extract. The blood pressure varied from 108/64 to 118/80. June 22, cholesterol 360 mg., blood urea nitrogen 24 mg., nonprotein nitrogen 50 mg.; June 24, urea nitrogen 20 mg., nonprotein nitrogen 62 mg.; June 30, cholesterol 284 mg., urea nitrogen 18 mg., nonprotein nitrogen 37 mg.; July 11, cholesterol 296 mg.; July 13, urea nitrogen 15 mg., nonprotein nitrogen 49 mg. Discharged Aug. 19, 1927, heavy albuminuria, slight edema.

Readmitted, Aug. 23, 1927, because of recurrence of edema. The edema disappeared on two or three occasions but soon reappeared. Albuminuria varied from + to ++++, and there were many pus cells in the urine. Temperature around 99° F. November 8, urea nitrogen 30.4 mg. November 18, total plasma protein 4.41 gm. Albumin:globulin ratio 1.47. December 10, irrigation of sphenoidal sinus, windows made in maxillary sinuses. Total plasma protein, 3.61 gm. Albumin:globulin ratio 1.11. December 13, hemoglobin 74 per cent, erythrocytes 3,890,000, leucocytes 16,050 — 65 per cent polymorphonuclears. December 30, hemoglobin 53 per cent, erythrocytes 3,130,000. Death Jan. 1, 1928, in convulsions and coma.

Postmortem: Emaciation. No edema. No fluid in serous cavities. Early bronchopneumonia. No peritonitis. Kidneys weigh 95 gm. and 105 gm. The capsules strip easily, and the external surfaces are smooth. The cortices are definitely yellowish in color.

Microscopic Examination: The convoluted tubules are moderately distended, and their cells are filled with fat droplets. There is no tubular atrophy, and the blood vessels are normal. There is very little blood in any of the capillaries. The glomeruli are small and bloodless. There are no epithelial crescents.

The modified Mallory stain (Fig. 3) shows many more endothelial nuclei than are visible in the normal glomerulus. In one area a swollen endothelial cell is seen completely filling a capillary. There is no increase of epithelial cells. Very few leucocytes are found in the capillaries. The basement membrane is uniformly thickened and multilayered, and in several areas it shows a very marked thickening. Some of the capillaries are partially or completely obstructed by swollen endothelium or by the thickened basement membrane. The lesion resembles glomerulonephritis to the extent that there is enlargement and increase in number of endothelial cells.

CASE III. *Clinical History:* A–26–625. Female 6 yrs. old. In December 1925 the patient had a mild cold with some fever and malaise which confined her to bed for a few days. She recovered completely and was well until the middle of January 1926, when her eyelids became puffy and her feet and legs became swollen. This edema persisted. About the middle of March 1926 she was very ill for several days with an infection that was called influenza. The temperature was 102° F. Shortly afterward her abdomen became greatly distended. This distention also persisted. She was admitted to the hospital May 18, 1926. There was severe generalized pitting edema and ascites. The urine showed a heavy cloud of albumin with clumps of pus cells and hyaline and granular casts. May 18, urea nitrogen 27 mg., creatinin 1.5 mg., sugar 0.15 per cent. May 19, phenolsulphonephthalein 10 per cent for 2 hrs. (subcutaneous). June 3, urea nitrogen 19 mg., creatinin 1.4 mg., sugar 0.13 per cent. Phenolsulphonephthalein, 15 per cent for 2 hrs. Hemoglobin 68 per cent, red cells 3,680,000. Leucocytes, 16,800 with 56 per cent polymorphonuclears and 42 per cent lymphocytes. Temperature varied from 99.5° F to 101° F. Pulse 100 to 130. June 22, 1000 cc. of clear fluid removed from the abdomen. The patient gradually grew worse and died on July 3, 1926.

Postmortem: The postmortem reveals a generalized purulent peritonitis, a purulent left hydrothorax and early bronchopneumonia. The heart weighs 60 gm. The kidneys weigh together 275 gm. The external surfaces are smooth, and the cortices are of pale color and somewhat thicker than normal.

Microscopic Examination: Marked distention of many of the convoluted tubules. No material was available for fat or other special stains, but the vacuolated cells indicate strongly that abundant fat

was present. No disease of the blood vessels. No tubular atrophy. The glomeruli are small and bloodless. The capillaries are filled with large endothelial cells as in glomerulonephritis.

CASE IV. *Clinical History:* Male 17 yrs. old. Admitted April 8. The chief complaint was a progressive swelling of the legs of about one months duration, and occasional vomiting. No history of an infection of any kind. The physical findings were negative except for marked edema of the legs and moderate ascites. The urine showed albumin ++++. Blood pressure 120/70. The edema subsided somewhat under hospital care, but on April 24 the patient developed the physical signs and symptoms of generalized peritonitis. The edema increased. April 27, blood urea 106 mg. Blood pressure 120/90. April 30, blood urea 144 mg. Leucocytes 21,400. Death May 6.

Postmortem: Generalized purulent peritonitis. Kidneys 415 gm. and 428 gm. The external surfaces are smooth, and the cortices are very cloudy.

Microscopic Examination: No disease of arteries or arterioles. No hyaline glomeruli. No atrophied tubules. A small amount of fat in the convoluted tubules. Moderate dilatation of the convoluted tubules, and marked distention of the capsular spaces. The glomeruli are not enlarged. The capillary lumina appear to be definitely narrowed or collapsed. The anilin blue stain shows an uneven thickening of the basement membrane which has resulted in narrowing of many capillaries and occlusion of a few. There are only a few endothelial cells in the capillaries, and there are no hyaline fibers.

GROUP II. TRANSITION TYPE — NEPHRITIS WITH NEPHROTIC TENDENCY

CASE V. *Clinical History:* A–28–193. Female 18 yrs. old. Patient was a sex delinquent. Chancre was diagnosed Jan. 1, 1926. Intense antisyphilitic treatment was given (neosalvarsan and mercury) from April to July 1927. Sudden onset of edema July 18, 1927. Antisyphilitic treatment was then discontinued. For the next few days she had oliguria and severe pain over the kidneys. Urine contained albumin +++ at this time. She was kept in bed four months on a liquid diet which contained neither salt nor meat. The edema was generalized and did not decrease appreciably under this treatment. The urinary output was small except when she drank large quantities of water. Albumin decreased to +. In October 1927 she was allowed to get up and was given a general diet. However she soon became troubled with nausea and vomiting, and albumin became +++ again. She had frequent attacks of headache throughout her illness. Wassermann reaction positive June 28, 1926, negative October 1, December 6, 1926, and April 1, 1927. Admitted Nov. 22, 1927, to the hospital. Urine at all times showed a large amount of albumin, doubly refractive lipoids,

many hyaline casts and pus cells and occasional red cells. Hemoglobin 99 per cent. Erythrocytes 5,060,000. Leucocytes 11,400 on admission — differential normal. Phenolsulphonephthalein 70 per cent. Blood urea nitrogen varied from 14.9 to 19 mg. The blood pressure was 160/100 for about three weeks during her stay in the hospital. It was normal on admission and shortly before death. Heart normal. Lungs showed signs of congestion. Septic temperature. Death, Feb. 7, 1928.

Postmortem: Massive anasarca. Acute fibrinopurulent peritonitis. Hydrothorax (1200 cc. right, 700 cc. left). Heart 285 gm. Kidneys together 335 gm., surfaces smooth, cortices yellowish.

Microscopic Examination: No atrophy or dilatation of tubules. Extensive hyaline granular degeneration of many convoluted tubules. Abundant fat in all the convoluted tubules. No disease of arteries or arterioles. The glomeruli are of normal size and contain a relatively small amount of blood so that there appears to be an increase of cells at the expense of the lumina of the capillaries. The anilin blue stain (Fig. 4) shows that most of the nuclei belong to enlarged epithelial cells which compress the capillaries, but there is a definite increase in the number of endothelial nuclei. The basement membrane is definitely thicker than normal. The glomerular lesion consists chiefly in enlargement of the epithelial cells and thickening of the basement membrane with resulting narrowing of the capillaries.

The only clinical distinction from pure lipoid nephrosis is the presence of hypertension.

CASE VI. *Clinical History:* A–28–183. Female, 34 yrs. old. Well until June 1, 1927, when she first noticed unusual fatigue and drowsiness. On June 15 she noticed swelling of the ankles, and the next day her legs were swollen also. In the latter part of July she developed an acute respiratory infection and was very ill with general anasarca, vomiting and suppression of urine. She was told at this time that there was albumin and pus in the urine. Hospitalized for two months. Repeated abdominal paracentesis. Admitted to our service Jan. 4, 1928, complaining of fatigue, drowsiness, anasarca, vomiting and headache. Blood pressure 182/130. Distended abdomen (fluid). Albuminuria with casts. Hemoglobin 48 per cent. Erythrocytes 2,690,000. Leucocytes 9,300. Eyegrounds negative at first but a retinal hemorrhage was observed three weeks later. January 5, urea nitrogen 24.2 mg., creatinin 2.2 mg.; January 9, urea nitrogen 26 mg., creatinin 2.6 mg.; January 18, urea nitrogen 31.2 mg., creatinin 3 mg.; January 30, urea nitrogen 47 mg., creatinin 7.2 mg. Blood pressure January 9, 200/140; January 12, 204/140; January 18, 208/140. The edema gradually decreased under diuretics and low fluid intake, but death occurred on Feb. 6, 1928.

Postmortem: Edema of face, none elsewhere. Ascites. Heart 300 gm. Early bronchopneumonia. Acute rheumatic mitral endocarditis. Left kidney absent. Right kidney 300 gm., external surface smooth, cortex pale.

Microscopic Examination: Moderate diffuse tubular atrophy (Fig. 5). No hyaline glomeruli. No disease of arteries or arterioles. Moderate amount of fat in the convoluted tubules. Dilatation of some of the tubules. The glomeruli are not enlarged, but there is evidently an increased number of nuclei. The anilin blue stain (Fig. 6) shows a great many capillaries partly occluded by large endothelial cells and polymorphonuclear leucocytes. The most striking change is a marked, irregular thickening of the basement membrane, which causes narrowing and sometimes complete occlusion of the capillaries. There is no change in the epithelial cells of the glomerulus. The extensive narrowing and occlusion of the glomerular capillaries are responsible for the tubular atrophy. The obstruction in the glomerular circulation is fairly uniform but none of the glomeruli are completely occluded. The result is a moderate diffuse tubular atrophy with no hyaline glomeruli and no completely atrophied tubules. One enlarged glomerulus was found which showed complete occlusion of all the capillaries by endothelial cells and hyaline fibers, such as is found in typical glomerulonephritis.

CASE VII. *Clinical History:* A–17–145. Male 54 yrs. On the night of Aug. 19, 1916, after working in a cold damp place he suddenly developed edema of the feet. He continued to work, but the swelling grew worse. On September 7 he first noticed edema of both lower eyelids. Admission, Sept. 14, 1916. The urine showed albumin ++, hyaline and granular casts. Hemoglobin 75 per cent, erythrocytes 5,800,000, leucocytes 8000. Blood pressure 155/80. Wassermann reaction negative. Phenolsulphonephthalein, September 15, 72 per cent; September 29, 52 per cent. September 15, urea nitrogen 13 mg., creatinin 4 mg., sugar 0.16 per cent. Discharged Nov. 25, 1916. Readmitted May 17, 1917. On the second admission he complained of marked swelling of the feet and back, severe dyspnea, and gastric distress. He stated that he had felt drowsy and tired most of the time since he left the hospital. Urine: albumin ++, granular and hyaline casts. Hemoglobin 75 per cent, erythrocytes 4,000,000, leucocytes 8000. Blood pressure 190/95; 175/95. July 16, blood pressure 125/95. Wassermann reaction negative. Phenolsulphonephthalein May 19, 35 per cent; July 7, 20 per cent. Urea nitrogen, June 11, 23.7 mg., creatinin 3.2 mg., sugar 0.11 per cent. Death July 21, 1917.

Postmortem: Severe general anasarca, marked ascites and hydrothorax. Edema of lungs, purulent bronchitis and atelectasis. Heart

320 gm. Kidneys together weigh 450 gm., smooth external surfaces, thickened yellowish cortices.

Microscopic Examination: There are a few hyaline glomeruli with atrophic tubules. Many of the convoluted tubules are dilated, and all of them contain fat droplets. There is no disease of arteries or arterioles. The glomeruli are of normal size and contain only a few erythrocytes. Many of them show adhesions to the capsule (Fig. 7). The anilin blue stain shows a general narrowing of the capillaries due chiefly to enlargement of the epithelial cells and thickening of the basement membrane. There are some swollen endothelial cells in the capillaries. The structure is about the same as is shown in Fig. 4. At the site of the adhesions a few capillaries contain hyaline fibers and swollen endothelium as in typical glomerulonephritis.

Group III. Non-Contracted Kidneys of Uncertain Type

These probably belong with the lipoid nephroses, but the available clinical data are insufficient for a definite diagnosis.

Case VIII. *Clinical History:* A–27–511. Female, 43 yrs. old. Present illness began 1 yr. ago with pain in the right upper quadrant and vomiting. Since that time she has had repeated attacks of dyspnea and edema of the ankles. No other past history available. Admitted to the hospital May 6, 1927, 12 hrs. before death, in coma. Severe dyspnea. Slight edema of the ankles. No cardiac murmurs. Blood pressure 110/70. Urine: trace of albumin, no sugar, occasional hyaline casts.

Postmortem: Heart weighs 538 gm., left ventricular hypertrophy, no valvular lesions. No fluid in the serous cavities. Marked edema and congestion of lungs. Liver weighs 2730 gm. and shows moderate fatty metamorphosis. The left kidney weighs 304 gm. The capsule strips easily. The external surface is smooth. The cortex is of grayish yellow color. (No note was made on the right kidney.)

Microscopic Examination: No tubular atrophy. No hyaline glomeruli. Small arteries show a marked increase of elastic tissue. No hyalin in the arterioles. Moderate dilatation of all convoluted tubules A small amount of fat in the convoluted tubules. The glomeruli are large and anemic and show a great decrease in the capillary bed (Fig. 8). The anilin blue stain (Fig. 9) shows a marked irregular thickening of the basement membrane which has resulted

in narrowing of all the capillaries and complete closure of a few. There is a notable increase in the number of endothelial nuclei. Epithelial cells are inconspicuous.

The marked left ventricular hypertrophy indicates that hypertension was present for a long time. The low blood pressure found shortly before death does not exclude a previous hypertension. The possibility that this is a primary hypertension must be considered, but none of the known cases of this disease shows such striking glomerular lesions in the absence of arteriolar disease. The glomerular lesions have some resemblance to advanced chronic glomerulonephritis.

CASE IX. *Clinical History:* A–26–827. Female 62 yrs. old. Admitted Sept. 11, 1926, complaining of generalized edema and dyspnea. Fifteen years ago she was confined to bed for one year with generalized edema. No further information about this attack could be obtained. From that time on her health was fair except for occasional attacks of edema of the ankles and some "stomach trouble." About Aug. 1, 1926, the edema became worse, and she noticed swelling of the abdomen, dyspnea, orthopnea and scanty urine. Her tongue was sore, and she noticed numbness of the hands occasionally. On admission her temperature was 97.7° F; pulse 100; respirations 30; blood pressure 134/82. Dyspnea, edema and weakness were pronounced. The skin and mucosae were pale. Soft systolic murmur at the apex. Ascites. Knee jerks absent. Babinski negative. Hemoglobin 40 per cent. Erythrocytes 1,310,000. The smear showed anisocytosis, poikilocytosis, macrocytes, nucleated reds and polychromatophilia. Leucocytes 2500. Neutrophils 59 per cent, lymphocytes 21 per cent, monocytes 20 per cent. Urine: albumin +++, hyaline and granular casts and a few erythrocytes. Blood urea nitrogen 25.2 mg., creatinin 1.36 mg. Death Sept. 12, 1926.

Postmortem: Marked general anasarca; ascites (7000 cc.); bilateral hydrothorax (150 cc. each). Heart 330 gm. Spleen 37 gm. Red bone marrow in the shafts of the femurs. Kidneys together weigh 260 gm., external surfaces smooth, cortices of normal thickness.

Microscopic Examination: Sclerosis of the larger branches of the renal arteries, but no involvement of small arteries or arterioles. No tubular atrophy. Slight dilatation of the convoluted tubules. The cells of the convoluted tubules contain a small amount of fat and a large amount of blood pigment. All the glomeruli have a hyaline appearance (Fig. 10). The lumina of the capillaries are largely obliterated. The anilin blue stain (Fig. 11) shows that the extreme narrowing of the capillaries is due to a massive thickening of the base-

TABLE

Summary of Clinical Data in

	Case number	Sex	Age in yrs.	Duration	Edema	Albuminuria	Cholesterol mg. per 100 cc.	Serum albumin	Serum globulin	Total protein	Blood pressure	Blood urea mg. per 100 cc.	Urea nitrogen mg. per 100 cc.	N.P. nitrogen mg. per 100 cc.	Phenolsulphonephthalein
Pure lipoid nephrosis	I	M	28	4 wk.	+++	++++	372 383 240	0.12	3.88	4	120–80 140–		13.5 16.7 48.5		14.6 27
	II	F	4	5½ mo.	0 to +++	++++	360 284	2.63 1.90	1.78 1.71	4.41 3.61	108–64 118–80		24.0 20.0 18.0 15.0 30.4	50 62 37 49	
	III	F	6	6 mo.	+ to +++	++							27.0 19.0		10 15
	IV	M	17	7 wk.	+++	++++					120–70	106 144			
Mixed type	V	F	18	7 mo.	+ to +++	+ to ++++					160–100		14.9 19.0		70
	VI	F	34	7 mo.	+++ to +	+++					182–130 208–140		24.2 31.2 47.0		
	VII	M	54	1 yr.	+ to +++	++					155–80 175–95 190–95		13.0 23.7		72 52 35 20
Uncertain types	VIII	F	43	1 yr.	+	+					110–70				
	IX	F	62	15 yr. (6 wk.)	0 to +++	+++					134–82		25.2		
	X	F	52	2 yr.	++										

III

Ten Cases Studied at Postmortem

Oliguria	Wasser-mann	Basal metabolic rate	Peritonitis	Weight of kidneys in gm.	Possible etiological factors	Fat in tubules	Glomerular lesion
+	−	+27	+	510	Common cold	+++	Capillaries partly obstructed by enlarged fatty endothelial cells. (Figs. 1 and 2)
+			−	200	Common cold, nasal discharge, otitis media, sinusitis.	+++	Swollen endothelium, thickened basement membrane. (Fig. 3)
			+	275	Common cold (?)	+++	Swollen endothelium.
			+	843		+	Uneven thickening of basement membrane, slight endothelial swelling.
+	+		+	335	Antisyphilitic treatment.	+++	Thickened basement membrane, enlarged epithelial cells. (Fig. 4)
			−	300		++	Swollen endothelial cells, thickened basement membrane, rarely glomerulonephritis. (Figs. 5 and 6)
	−		−		Exposure to cold and dampness.	++	Thickened basement membrane, enlarged epithelial cells, focal glomerulonephritis. (Fig. 7)
			−	304(?)		+	Marked thickening of basement membrane, increase of endothelium. (Figs. 8 and 9)
			−	260		+	Extreme thickening of basement membrane, increase of endothelium. (Figs. 10 and 11)
			+	350		++++	Very large fatty and hyaline epithelial cells, glomerulonephritis. (Fig. 12)

ment membrane. The nuclei all seem to belong to endothelial cells. There is a close resemblance to Case VII (Fig. 8), but the thickening of the membrane is more pronounced and the endothelial cells are less conspicuous.

It is not clear whether death was due to anemia or to renal insufficiency.

CASE X. *Clinical History:* A–27–305. Female 52 yrs. old. History of edema of the legs and ankles for the past two years. She first noticed distention of the abdomen on March 15, 1927. At the same time she had cramp-like abdominal pains and vomited throughout the day. On March 16, she continued to have acute abdominal pain but did not vomit. Admitted March 18. Rapid labored respiration. Crackling râles at the bases of the lungs. Abdomen distended and tender but not rigid. Edema of legs and feet. Temperature 101.8° F. Leucocytes 21,000 — 79 per cent polymorphonuclears. Hemoglobin 80 per cent. Erythrocytes 4,260,000. Death March 18.

Postmortem: Diffuse purulent peritonitis. Heart 315 gm. Edema of lungs. Kidneys together weigh about 350 gm., surfaces smooth, cortices yellowish.

Microscopic Examination: Large numbers of fat droplets in the convoluted tubules, glomeruli and interstitial connective tissue cells. The glomerular fat is very prominent and is situated chiefly in the epithelial cells within the glomerulus and on its surface. About 10 per cent of the glomeruli are hyaline, and these are associated with completely atrophied tubules. The other tubules show no atrophy or dilatation. There is no arterial or arteriolar disease. The glomeruli are large and have an unusual appearance (Fig. 12). The lumina of the capillaries are either greatly narrowed or completely occluded. Large hyaline granules are seen which are chiefly situated within the epithelial cells. The anilin blue stain shows very large epithelial cells filled with hyaline masses. The occluded capillaries are filled with endothelial cells and a network of hyaline fibers such as are found in typical glomerulonephritis. The enlargement of the glomeruli and the narrowing of the capillary lumina are due to two processes: (*a*) marked enlargement of the epithelial cells with fatty and hyaline degeneration, and (*b*) enlargement of endothelial cells and formation of hyaline fibers within the lumina of the capillaries. The disease may be interpreted as a modified form of typical glomerulonephritis.

A summary of the clinical and anatomical data in the ten cases just described is given in Table III.

Discussion of the Various Phenomena of Lipoid Nephrosis

1. *Albuminuria* is a constant finding. Edemas without protein in the urine are not nephroses. In the early stages, in the remissions and in the stage of recovery there may be only a trace, but usually the amount of protein is very large. Amounts as high as 6 per cent have been reported. Epstein estimated that as much as 50 gm. of protein may be excreted daily, and since the total protein in the blood is only about 210 gm., he considers the loss of blood protein one of the most important phenomena of the disease.

Epstein believes that the loss of blood protein in the urine is the cause of the edema in that it results in a decrease of the osmotic pressure of the blood, but there are so many instances of low plasma protein without edema, and *vice versa*, that a causal relationship between albuminuria and edema is uncertain.

2. *Oliguria* is usually noted when the disease is at its peak, but normal or increased output occurs when the edema is lessening. A twenty-four hour excretion of 200 to 800 cc. of urine is frequently seen. A period of anuria was observed in only one case (Kaufmann and Mason).

3. *Lipoiduria* is considered by Munk as pathognomonic of lipoid nephrosis. In his first publication he seems to have considered albuminuria, edema and lipoiduria as sufficient to establish the diagnosis. Doubly refractive bodies are readily demonstrated by attaching a polariscope to an ordinary microscope.

Reference to the tables will show that lipoids were found in the urine in 16 of 19 cases in which they were looked for. Lipoiduria is therefore a rather constant finding in lipoid nephrosis. But Genck has shown that not all doubly refractive bodies in the urine are of fatty nature. Spherocrystals of various kinds are doubly refractive. Lipoiduria has been found in glomerulonephritis (Laweynowicz, 2 of 12 acute cases; Genck, 1 of 6 acute cases; Finger and Kollert, 32 of 76 acute or subacute cases, and 5 of 21 chronic cases; Kollert and Finger, 101 of 289 war nephritics [glomerulonephritis]). It has also been found in diabetes, amyloid disease and pyelonephritis. Tietz found lipoiduria in renal diseases of various types. It is obvious therefore that lipoiduria is not peculiar to lipoid nephrosis.

4. *Lipemia:* An increase of the blood lipoids is found constantly in lipoid nephrosis and usually in glomerulonephritis with edema. The milky serum of nephritics was known to Richard Bright. Erben, in 1904, called attention to the high fat and lecithin content of the blood in nephritics. Chauffard, Laroche and Grigaut in 1911 found hypercholesterolemia in cases of renal edema with albuminuria and noted also that there was no increase of cholesterol in nephritics with nitrogen retention. Epstein has published a series of papers dealing with lipoid nephrosis and glomerulonephritis with a nephrotic tendency. He found hypercholesterolemia a characteristic feature.

Values from 300 to 600 mg. per 100 cc. of blood are commonly reported. Rarely much higher values are recorded (1000 mg. Hahn and Wolff; 1350 mg. Epstein and Lande). Often the serum is of milky appearance, but a high lipoid content may be found when the serum does not have this cloudy appearance (Hahn and Wolff).

The increase of blood lipoid is largely represented by cholesterol, but there is also a marked increase of lecithin and fatty acids (Knaur, Daniels).

Strauss and Schubardt found cholesterol values of over 200 mg. in 6 of 17 cases of acute glomerulonephritis, and in 11 of 44 chronic cases.

Lipemia and renal edema are closely associated. Bennett doubts the occurrence of renal edema without hypercholesterolemia. Maxwell in an extensive study of nephritis found hypercholesterolemia in both acute and chronic forms whenever edema was present. He found only one exception to the rule that renal edema never occurs without hypercholesterolemia.

When uremia develops in chronic glomerulonephritis, the cholesterol sinks to a normal level (Chauffard, Stepp, Maxwell).

Amyloid disease of the kidneys usually shows lipemia. The blood lipoids are usually slightly increased during pregnancy, and in eclampsia there is often a definite increase above the normal level of pregnancy (Hinselmann). An increase has also been noted in sublimate poisoning (Wichert and Russjajewa-Oparina).

Lipemia is not restricted to renal disease. A moderate increase of blood lipoids is often found in diabetes, and sometimes a very marked lipemia is observed. In 25 diabetics Bing and Heckscher found normal lipoid values in 11, moderate increases in 13, and a severe lipemia in one. Strauss and Schubardt found lipoid values in diabetics regularly about 250 mg.

There is often some increase of lipoids in obstructive jaundice (Stepp, Strauss and Schubardt).

Increase of the blood lipoids is a characteristic feature of lipoid nephrosis, but this finding alone does not differentiate this disease from glomerulonephritis with edema, from amyloid nephrosis, or even from certain extrarenal diseases.

Edema may occur without lipemia and *vice versa*, but the close association of edema and lipemia in renal disease suggests a common etiology. Little is known of the underlying causes of lipemia. The fats are believed to come from the ingested food since a pronounced lipemia may be produced in rabbits by intensive cholesterol feeding (Thölldte). It has been suggested that the lipemia in renal disease is due to an inability to utilize fat as it presumably is in diabetes, but Hiller, Linder, Lundsgaard and Van Slyke find that nephritics with constant lipemia burn fat as efficiently as normals.

5. *Edema:* The diagnosis of lipoid nephrosis should not be made if edema has not been present at any time. Apparently only two authors have made this diagnosis in the complete absence of edema, *viz.*, Stepp and Epstein. Epstein's case is obviously chronic glomerulonephritis, and the data in Stepp's case are insufficient for accurate diagnosis. However, in typical cases edema may be absent in the early stages and in the remissions, and it may disappear spontaneously or as a result of treatment.

Edema is commonly severe at the peak of the attack and is often the chief cause of the patient's discomfort. Therapeutic procedures should therefore be directed toward the relief of this symptom when it is pronounced. In general the most successful therapy appears to be a diet with restricted salt and fluid content, and the liberal use of mild diuretics. Epstein strongly recommends a high protein diet on the theory that it will replace the blood proteins lost in the urine. He believes that the edema is due to the loss of plasma proteins in the urine which lowers the osmotic pressure of the blood and results in an excessive accumulation of fluid in the tissue spaces. Edema fluids in nephrosis are poor in protein.

6. *Retention of Sodium Chloride:* There is a retention of sodium chloride in nephrotic edema. It is apparently held in the tissues since it is not increased in the blood. There is no satisfactory evidence that the ability of the kidney to excrete water or salts is seriously impaired. It is possible that edema is due to an injury of the

tissue cells throughout the body which causes them to retain water and crystalloids in the tissue spaces.

7. *Decrease of Plasma Proteins:* Richard Bright knew that the plasma proteins were decreased in nephritis. Erben, in 1904, records a decrease of albumin and globulin and an increase of fibrin in "chronic parenchymatous and subchronic nephritis." In 1905 he observed a shift of the albumin:globulin ratio in favor of globulin so that globulin sometimes exceeded albumin.

Epstein has made extensive studies on the plasma proteins and found them characteristically decreased with reversal of the albumin:globulin ratio in pure lipoid nephrosis as well as the mixed type. In the 10 cases listed in Tables I and II, in which the proteins were studied, they were found decreased in 8. The total protein was greatly decreased in the 2 cases of my series that were studied (Table III), but the albumin:globulin ratio was not reversed in one of them.

The protein lost is almost entirely albumin. Epstein gives an example of a nephrosis in which albumin was 0.466 mg., and globulin 3.462 mg. In one of my cases (Table III) the total protein was 4 mg. of which albumin was 3 per cent and globulin 97 per cent. The normal albumin:globulin ratio is 1.4 to 1.8. Linder, Lundsgaard and Van Slyke found reduction of the plasma proteins with a low albumin:globulin ratio in chronic nephrosis and chronic nephritis with edema but not in nephrosclerosis (hypertension kidney). Fahr and Swanson found a definite reduction of the total plasma protein largely due to loss of serum albumin in 7 of 10 cases of acute and subacute glomerulonephritis. In 5 of 9 cases of chronic glomerulonephritis the total protein was below 6 mg. Decrease of plasma protein evidently does not differentiate lipoid nephrosis from glomerulonephritis.

Epstein believes that edema is due to loss of albumin in the urine and consequent decreased osmotic pressure of the plasma. Low plasma protein and edema are both characteristic of lipoid nephrosis, but they are often not present simultaneously. A low protein level may persist long after edema has disappeared, and intense edema may develop before the blood proteins show any change. It seems more probable that both conditions are due to some underlying cause than that edema is caused by the low protein level.

A decrease of plasma proteins with reversal of the albumin:globulin

ratio has been found in lobar pneumonia in the complete absence of edema and with only a trace of protein in the urine (Geill, Kumpf). Evidently a decrease of protein may occur without a loss in the urine. It has not been proved that the regeneration of plasma proteins is hastened by a high protein diet.

8. *Hematuria:* Macroscopic blood is never found in lipoid nephrosis, but some observers have noticed a few erythrocytes in microscopic preparations. Glomerulonephritis commonly does not show hematuria except in the acute stages and during exacerbations.

9. *Chloride Retention:* When edema is prominent there is usually a decreased elimination of chlorides in the urine. Since there is no increase in the blood it is inferred that the chlorides are retained in the tissues. There is a similar chloride retention in glomerulonephritis with marked edema.

10. *Basal Metabolism:* The basal metabolic rate was low in 13 of the 15 cases in which it was studied (Tables I and II), but this is probably of little significance since the authors do not make corrections for the weight of the edema fluids. G. Fahr * has shown that the basal metabolic rate is usually normal if calculations are based upon the normal weight of the individual.

Epstein believes that certain nephroses are related to myxedema and that they respond favorably to thyroid medication.

11. *Renal Function:* On this point a distinction between lipoid nephrosis and chronic glomerulonephritis is usually made. Whenever a definite nitrogen retention is demonstrable it is assumed that the case is not pure nephrosis but a mixed type (nephritis with nephrotic *Einschlag*). But the various authors do not agree as to the nitrogen level that is admissible to the nephrotic group. It is to be remembered that ordinary mild cases of chronic glomerulonephritis often show no nitrogen retention, and it is uncommon to find urea nitrogen much above the normal except in advanced stages of the disease.

Bannick and Keith in using a level of 40 mg. of blood urea to separate nephrosis from nephritis may have included some cases of glomerulonephritis with the nephroses. In three instances (Table I), in which the postmortem report was pure lipoid nephrosis, there was a definite nitrogen retention. In one of my cases (Case I, Table III)

* Personal communication.

which corresponds to pure lipoid nephrosis in every other respect, the last blood urea nitrogen was 48.5 mg.

It is clear that some cases that are anatomically pure lipoid nephrosis have a moderate nitrogen retention and that many mild cases of chronic glomerulonephritis do not. No instance of pure lipoid nephrosis with uremia has been reported. It may be concluded that renal edema with uremia is not pure lipoid nephrosis, and that with moderately increased or normal blood nitrogen it may or may not belong in this group.

Phenolsulphonephthalein: In the cases reported (Tables I and II) the phthalein excretion is moderately diminished in most instances. The lowest observation was 15 per cent. When phthalein is injected intramuscularly, edema interferes with its absorption and tends to give too low a reading. This may have been the cause of the low reading in Case III (Table III), but in Case I (Table III) the phthalein was injected intravenously. The results with phthalein indicate a moderate impairment of renal function. Chronic glomerulonephritis also shows only a moderate decrease of phthalein elimination before the final stage begins.

12. *Blood Pressure:* It is commonly assumed that when the systolic blood pressure is above 140 mm. Hg. in a case which otherwise has the characteristics of lipoid nephrosis, it is a mixed type, *i. e.*, nephritis with nephrotic *Einschlag*. Volhard states that hypertension is the only symptom by which nephritis with nephrotic *Einschlag* may be distinguished clinically from pure nephrosis. Several authors have reported clinical cases with high blood pressure as lipoid nephrosis, but these have been omitted from Table II. Apparently no extensive studies have been made to determine whether there is an anatomical basis for the exclusion of a case from the "pure lipoid nephrosis" group because of hypertension.

One often sees acute and mild chronic glomerulonephritis with a systolic blood pressure below 140 mm. Hg. There is no justification for classifying all of these as lipoid nephrosis.

13. *Causes of Death in Lipoid Nephrosis:* In the postmortem reports (Table I) it will be noted that eleven of the twenty-four patients died of peritonitis. In the cases in which bacteriological studies were made the invading organisms were found to be pneumococci. Volhard states that all his fatal cases died of pneumococcic peritonitis. Three of my four cases of the pure type and

one of three of the mixed type died of peritonitis (Table III). The tendency to develop peritonitis seems to be characteristic of pure lipoid nephrosis and the mixed type. Of fifty-three examples of typical subacute and chronic glomerulonephritis that I have studied, none died of peritonitis.

Over half of the fatal cases reported died of infections other than peritonitis, such as pneumonia and septicemia. None died of uremia.

14. *Frequency of Lipoid Nephrosis:* Volhard states that he has seen about a dozen cases. Epstein observed 15 cases of "chronic nephrosis" among 193 cases of renal disease, but "chronic nephrosis" includes amyloid kidney, pure lipoid nephrosis and nephrosis with nephrotic *Einschlag*. McElroy diagnosed lipoid nephrosis nineteen times in 600 cases of Bright's disease. Schlayer saw only 6 cases in 300 cases of nephritis and was uncertain of some of these. Bannick and Keith report a surprisingly high incidence — 25 cases of "chronic nephrosis" and 25 cases of "chronic nephrosis of mixed type" in about 90 cases of nephritis. The high incidence noted by these authors is evidently due to their having included as "chronic nephrosis" many cases which others would regard as ordinary chronic glomerulonephritis.

I have made postmortem studies on 53 cases of subacute and chronic glomerulonephritis, 3 that may be called glomerulonephritis with nephrotic *Einschlag*, 4 of pure lipoid nephrosis and 3 of uncertain classification.

15. *Duration and Prognosis:* The duration of the 24 fatal cases (Table I) was as follows: 1 mo., 3; 1–3 mo., 5; 3–6 mo., 3; 6 mo.–1 yr., 6; 1–3 yr., 7. Six cases are recorded (Table II) as having recovered completely, but the great majority still had albuminuria at the time of the report. Munk thinks that most cases of lipoid nephrosis end in healing but albuminuria may last for years or decades. He mentioned one patient who had albuminuria for ten years but was entirely well fifteen years after the onset of her illness. Steinitz thinks that the prognosis is good as to life but poor as to recovery from albuminuria. Volhard mentioned 6 fatal cases among more than a dozen that he had seen.

The duration of my 4 cases of pure lipoid nephrosis was four weeks, seven weeks, five and a half months, and six months, respectively. The 3 cases of mixed type lasted seven months, seven months, one

year respectively (Table III). Dr. G. Fahr has furnished me the record of a patient he has had under observation for four years. He was confined to the hospital about one year, with all the typical features of pure lipoid nephrosis. He left the hospital practically recovered and was entirely free of all signs of the disease three years later.

Examples may be found in the older literature of "chronic parenchymatous nephritis" that recovered. Some of these are no doubt instances of what is now called lipoid nephrosis.

16. *Pathological Anatomy:*

(*a*) *Pure Lipoid Nephrosis:* The kidneys are always enlarged and pale. In one of my cases the combined weight of the two kidneys was 843 gm. The external surfaces are smooth. The color of the cortex varies from pale to yellow. There are always some lipoid droplets in the convoluted tubules and they are often in the glomerular epithelium also, but the amount of fat is not always excessive. There may be only a small amount of fat insufficient to give the cortex a yellow color. The convoluted tubules and capsular spaces are usually dilated. An outstanding feature is the absence of tubular atrophy. Often many of the convoluted tubules are filled with coarse hyaline granules, and these granules may also be found in the epithelial cells of the glomerular tuft both on the surface and between the loops.

The glomeruli are described as normal by nearly all the authors who have reported cases of pure lipoid nephrosis. In fact, normal glomeruli are generally considered necessary to establish the diagnosis of the pure type. However, some observers have realized that they are not entirely normal. Stolz finds them almost normal but containing polymorphonuclear leucocytes. Major and Helwig noted that some glomeruli showed swollen endothelial cells and others contained lipoid droplets. Munk finds no changes at first except some increase of leucocytes. He states, however, that later a definite glomerulitis may develop that leads to a contracted kidney. Volhard finds that the glomerular capillaries are not occluded, but the cells may contain hyaline, granular or lipoid droplets. Fahr noted minor lesions in individual glomeruli in some of his cases. He mentions very slight proliferation, hyaline clumps, collapsed capillaries and fusion between the glomerulus and its capsule.

In sections stained with hematoxylin and eosin the glomeruli appear to be normal except for an increased number of leucocytes in

some of the capillaries, but in sections stained by the anilin blue method definite abnormalities can be made out. In Case I the capillaries were filled with swollen endothelial cells heavily laden with lipoid droplets (Fig. 2). This corresponds with clinical glomerulonephritis except for the absence of hyaline fibers in the capillaries. Case II showed some increase of endothelium and a patchy thickening of the basement membrane (Fig. 3). No special stain could be made on Case III. Case IV showed a fairly diffuse thickening of the basement membrane with narrowing of the capillaries and some increase of endothelium.

The lesions are not exactly the same in any two instances, but they all show enlargement and increase in number of the endothelial cells in some degree as well as thickening of the basement membrane.

In clinical glomerulonephritis the characteristic lesion is a plugging of the capillaries with swollen endothelial cells among which are many hyaline fibers (McGregor). There is therefore a fundamental resemblance to glomerulonephritis, but the endothelial swelling is not so pronounced, there are no hyaline fibers and the capillary lumina are only partially obstructed.

(*b*) *Nephritis with Nephrotic "Einschlag," (Nephritis with Nephrotic Tendency — Mixed Type)*: Clinically this type is defined as a disease with all the features of pure lipoid nephrosis except for the presence of hypertension or definite renal insufficiency. I have not found any descriptions of the pathological changes in the kidneys. Cases V, VI, and VII belong to this group. They differ from pure lipoid nephrosis clinically only in the presence of hypertension. Macroscopically the kidneys cannot be distinguished from those of pure lipoid nephrosis.

On microscopic examination lipoid droplets are found in the tubules. The glomeruli show transitions to typical glomerulonephritis in that entire glomeruli (1 case) or parts of glomeruli (1 case) may show the characteristic lesion of glomerulonephritis. Increase in the size and number of the endothelial cells was conspicuous in 2 cases, and thickening of the basement membrane was noted in all 3. Enlargement of the glomerular epithelial cells was the most conspicuous change in one case. The mixed type, nephritis with nephrotic *Einschlag*, therefore resembles both pure lipoid nephrosis and typical glomerulonephritis in that endothelial increase is one of its histological features. The histological structure is not fundamentally

different from that of pure lipoid nephrosis, but there is more obstruction in the capillary bed.

On histological grounds one cannot make a sharp distinction between glomerulonephritis and either the mixed or pure type of lipoid nephrosis. There is a fundamental resemblance in that all three types show endothelial swelling and increase. The differences seem to be in degree rather than in kind.

(*c*) *Renal Lesions of Uncertain Type:* I have studied 3 cases in which the clinical data are inadequate to establish a clinical diagnosis. The kidneys are large and fatty, and there is no tubular atrophy. In the older terminology they would be called chronic parenchymatous nephritis. The glomerular lesions are very prominent. In Case VIII (Figs. 8 and 9) the glomeruli are large, and there is an increase of endothelial nuclei and a marked thickening of the basement membrane with narrowing of the capillaries. In Case IX (Figs. 10 and 11) the thickening of the basement membrane is so extreme that the capillaries are almost obliterated. The clinical picture in this case was that of lipoid nephrosis, *viz.*, severe albuminuria, edema, normal blood pressure and no nitrogen retention, associated with pernicious anemia. However, there was no determination of blood lipoids, and the kidneys had only a small amount of fat.

In Case X (Fig. 12) the epithelial cells are greatly enlarged and they show an extreme hyaline and fatty degeneration. The capillaries contain large endothelial cells and hyaline fibers as in clinical glomerulonephritis. This case is closely related histologically to glomerulonephritis. The enormous accumulation of fat in the kidneys, the edema and the peritonitis are almost sufficient to put it in the clinical group of lipoid nephrosis.

These 3 cases raise the question whether all cases with albuminuria, edema, normal blood pressure and large fatty kidneys should be regarded as lipoid nephrosis regardless of the type of glomerular lesion present.

17. *Etiology:* Munk laid great emphasis upon lues as a causative factor but did not think that all cases were due to lues. Lues is considered an important etiological factor by Volhard, Fahr, Felber, and Karger and Ullmann. However, it is shown in Tables I, II and III that among twenty-one patients examined for lues only three were found to be positive. Syphilis cannot therefore be considered of any particular importance in the etiology of lipoid nephrosis.

Several authors hold the view that lipoid nephrosis is a general metabolic disturbance in which the kidney is affected but that it is not a primary renal disease. Kollert believes that an infection or an intoxication causes a prolonged injury of numerous body cells which expresses itself as a metabolic disturbance. The renal injury is a part of the picture. He offers the same explanation for nephritis with nephrotic *Einschlag*. Knaur does not consider lipoid nephrosis a renal disease. He believes that the primary disturbance is hypotension with resulting poor filtration of water. Schlayer attributes the disease to universal capillary injury. Epstein and Löwenthal regard it as a constitutional disease with secondary renal changes, but not restricted to the kidney. The features which suggest a constitutional disease are the general disturbances such as edema, hypercholesterolemia, alterations in the plasma proteins, etc.

Volhard and Fahr seem to consider lipoid nephrosis as essentially a disease of the renal tubules.

Löhlein, in 1918, expressed the opinion that nephrosis and nephritis with nephrotic *Einschlag* begin as glomerulonephritis and may end with uremia and retinitis. Elwyn has observed several cases of lipoid nephrosis which began as acute diffuse glomerulonephritis.

Clausen stresses the importance of sinus infections. Two of my cases and possibly a third began with a common cold, and another followed exposure to cold and dampness (Table III). This is not unlike the history of acute glomerulonephritis and suggests that infection may be the causative factor.

18. *Is Lipoid Nephrosis Primarily a Renal Disease?* The writers who contend that the disease is a general metabolic disorder with a secondary renal disturbance have not properly appreciated the degree of the renal injury. The glomeruli are regarded as normal, and the only renal lesion is considered to be lipoid infiltration of the tubules. The disturbance of lipoid metabolism and the changes in the blood proteins are regarded as strong arguments in favor of a general disorder.

However, the same disturbances in the blood fats and proteins occur in glomerulonephritis, which is certainly a primary disease of the kidneys. Lipoid nephrosis shows heavy albuminuria and minor disturbances of renal function which must be interpreted as indicating renal damage. There are definite and sometimes pronounced structural changes in the glomeruli, and there are transitions to glo-

merulonephritis both clinically and anatomically. Lipoid nephrosis appears to be a renal lesion in which there is partial but not complete obstruction of the glomerular circulation. Uremia does not develop, but in some unknown way there develops an increased susceptibility to infection, especially to peritonitis.

The Relation of Lipoid Nephrosis to Glomerulonephritis

Clinical Relation: It is obvious from the clinical literature that a diagnosis of lipoid nephrosis is made much more frequently by some physicians than by others. The usual requirements for the diagnosis are albuminuria and edema without definite hypertension or nitrogen retention. When this standard is applied to acute renal disease it undoubtedly includes a great many cases of acute glomerulonephritis, and when applied to chronic renal disease it includes some mild cases of chronic glomerulonephritis. When defined in this way lipoid nephrosis is a fairly common ailment. If, however, we require for the clinical diagnosis severe albuminuria, marked edema, normal or low blood pressure, no nitrogen retention, hypercholesterolemia and low plasma proteins, death from peritonitis or other infections, or a prolonged clinical course marked by repeated exacerbations and remissions, lipoid nephrosis becomes a rare disease and the kidneys at postmortem do not show the characteristic lesions of glomerulonephritis.

Even though we accept the restricted definition of lipoid nephrosis, we encounter many transition cases which cannot be distinguished from glomerulonephritis with certainty. The fact that we recognize a mixed type of nephritis and nephrosis (nephritis with nephrotic *Einschlag*) is an admission that the two diseases blend. The mixed type is particularly difficult to define clinically. How high a blood pressure or how much nitrogen retention is admissible to this group? Both hypercholesterolemia and the decrease of plasma proteins are more pronounced in lipoid nephrosis than in glomerulonephritis, but the difference is only in degree. A patient with lipoid nephrosis never develops uremia, but there may be a decreased elimination of phenolsulphonephthalein or a moderate nitrogen retention. The distinction based on renal function is also in degree only. In fact the two diseases blend in every clinical symptom and test. The clinical evi-

dence indicates strongly that lipoid nephrosis is not a distinct disease but a form of glomerulonephritis that does not tend to develop uremia.

Pathological Relation: The assumption that the glomeruli in lipoid nephrosis are practically normal is largely responsible for the view that the disease is entirely different from glomerulonephritis. When special stains are used which bring out the histological details of glomerular structure it is seen that definite lesions are present in every instance (see Table III for summary), but there is no uniform histological change characteristic of lipoid nephrosis.

Typical clinical glomerulonephritis shows uniformly in the acute stages a plugging of the capillaries with swollen endothelial cells, polymorphonuclear leucocytes and interlacing hyaline fibers (McGregor). In advanced stages the hyaline fibers and the basement membrane enlarge and fuse to give rise to a hyaline glomerulus. The histological features are, therefore: enlargement and increase in number of the endothelial cells, polymorphonuclear leucocytes, hyaline fibers and thickening of the basement membrane. In the 10 nephroses studied (Table III) there was a definite increase in the number and size of the endothelial cells in 8. In 8 of 9 cases in which the basement membrane was seen it was definitely thickened. The thickening was marked in four, and extreme in one instance. Hyaline fibers were found in the capillaries in three instances. Two of the cases showed small glomerular lesions indistinguishable from typical clinical glomerulonephritis, and a third case (Case X) corresponds closely with glomerulonephritis.

It may be said, therefore, that there are many points of resemblance in the glomerular structure of lipoid nephrosis and glomerulonephritis. The chief dissimilarity is that the glomerular capillaries are completely obstructed in glomerulonephritis and only partly obstructed in lipoid nephrosis. But a partial obstruction to the glomerular circulation has a very different effect on the subsequent macroscopic changes in the kidneys and the clinical course from that resulting from a complete obstruction. Complete obstruction produces hyaline glomeruli, atrophied tubules, contracted kidneys and finally uremia. Partial obstruction does not produce any of these four conditions, but the tubules become filled with lipoid, and the clinical course is that of lipoid nephrosis. Some years ago Löhlein called attention to the fact that a damaged glomerulus that

still functions is associated with a fatty tubule. Every case of chronic glomerulonephritis shows such glomeruli with fatty tubules (Fig. 13).

Lipoid nephrosis may therefore be regarded as a form of glomerulonephritis in which the glomerular capillaries are damaged but not completely obstructed. Even from this point of view it is still important to recognize typical cases clinically since it is a form of nephritis that does not terminate in uremia. The patient with this form of nephritis either recovers after a prolonged course or dies from an intercurrent infection.

No instance has come under my observation in which a patient with the clinical picture of lipoid nephrosis subsequently developed a contracted kidney.

Summary and Conclusions

1. A survey of recent literature shows a tendency to use "lipoid nephrosis" in a broad way to include all cases of nephritis with edema, albuminuria, normal blood pressure and normal blood nitrogen. This clinical definition includes many cases that are anatomically acute or mild chronic glomerulonephritis.

2. All the clinical phenomena of lipoid nephrosis, *viz.*, albuminuria, edema, normal blood pressure, hypercholesterolemia, decrease of the plasma proteins with reversal of the albumin:globulin ratio and normal blood nitrogen, may occur in a less pronounced form in glomerulonephritis.

3. There are many transition cases between lipoid nephrosis and glomerulonephritis, *viz.*, those that fit the definition of lipoid nephrosis except for the presence of hypertension or moderate nitrogen retention. These are called the mixed type, or nephritis with a nephrotic *Einschlag*. From the clinical standpoint the two diseases cannot be sharply separated.

4. A histological study has been made of 10 cases of large, fatty kidneys, without tubular atrophy, that were clinically nephritis. Four of these are classed as pure lipoid nephrosis, 3 as nephritis with nephrotic *Einschlag* (mixed type) and 3 as of uncertain type because of lack of clinical data.

5. The glomeruli are not normal in any instance, but the lesions are not of uniform type.

6. In pure lipoid nephrosis there is a varying increase in the number and size of the glomerular endothelial cells and an uneven thickening of the basement membrane.

7. In the mixed type (nephritis with nephrotic *Einschlag*) there is a marked thickening of the basement membrane. In one instance the capillaries were compressed by enlarged epithelial cells. In two instances there was a definite increase in the number and size of the glomerular endothelial cells, and a few areas in the glomeruli showed the changes characteristic of typical clinical glomerulonephritis, *i. e.*, capillaries filled with endothelial cells and a network of hyaline fibers.

8. Three large non-contracted kidneys were studied in which the data were insufficient to determine whether they should be classed as lipoid nephrosis. Two of these showed extreme thickening of the basement membrane. The third showed an enormous accumulation of fat in the tubules and glomeruli, large glomerular epithelial cells with hyaline and fatty degeneration, and leucocytes and hyaline fibers within the capillaries as in glomerulonephritis.

9. Lipoid nephrosis is to be regarded as a form of glomerulonephritis in which the glomeruli are damaged but their capillaries are only partially obstructed so that they continue to function and tubular atrophy does not occur.

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DESCRIPTION OF PLATES

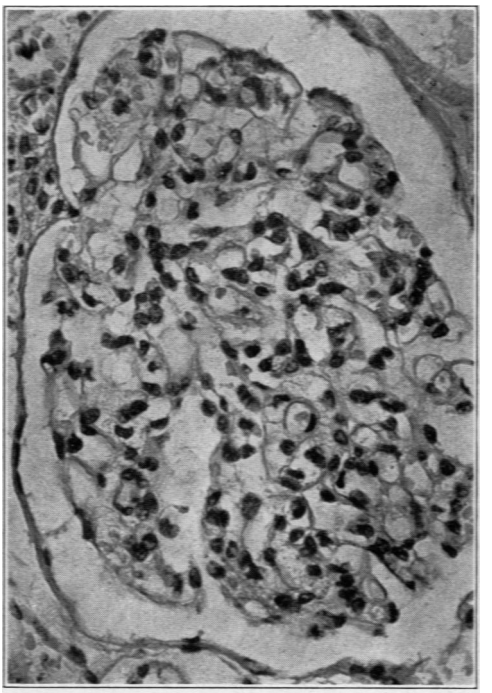
PLATE 107

FIG. 1. Case I. A–28–647. Pure lipoid nephrosis. Hematoxylin-eosin stain. Photomicrograph. The capillaries are largely filled with mononuclear cells with a very pale vacuolated cytoplasm.

FIG. 5. Case VI. A–28–183. Mixed type — Nephritis with nephrotic *Einschlag*. Photomicrograph. Partial occlusion of glomerular capillaries by swollen endothelial cells. Diffuse tubular atrophy.

FIG. 7. Case VII. A–17–145. Photomicrograph. Adhesion of glomerulus to its capsule. The solid portion of the tuft at the site of the adhesion has the structure of typical glomerulonephritis.

FIG. 8. Case VIII. A–27–511. Renal lesion of uncertain type. Photomicrograph. Great increase in number of nuclei. Marked narrowing of the capillaries.



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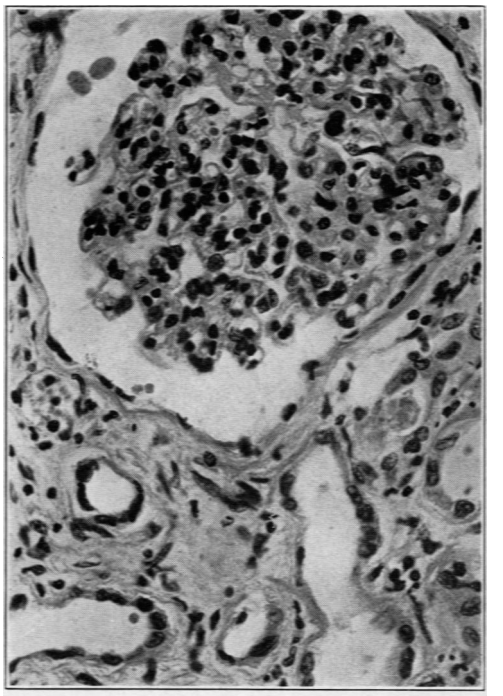

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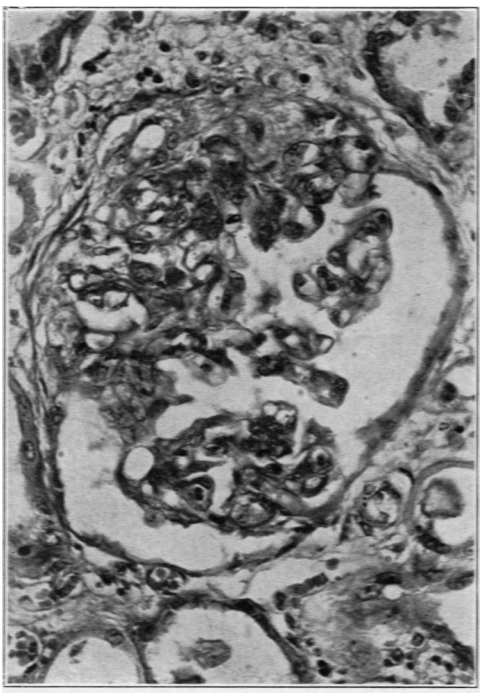

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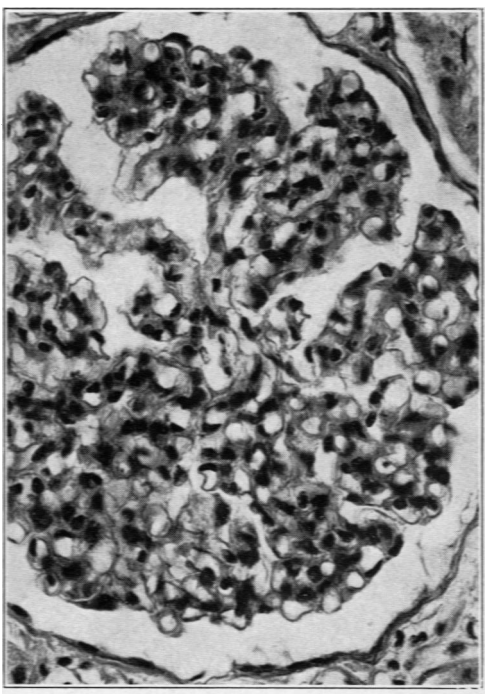

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Bell

Lipoid Nephrosis

PLATE 108

FIG. 2. Case I. A–28–647. Pure lipoid nephrosis. Mallory's anilin blue (Heidenhain, azan-carmine). Drawing of lobule of glomerulus (high magnification). The cells filling the capillaries are shown to be of endothelial origin. The vacuoles in the cytoplasm were occupied by lipoid droplets. The majority of the swollen cells (End. a.) are still firmly attached to the basement membrane, but a few are almost completely detached (End. f.) or entirely free. The basement membrane (B. M.) shows a moderate uneven thickening. The capillary lumina (L.) are markedly obstructed. The epithelial cells (Ep.) are inconspicuous.

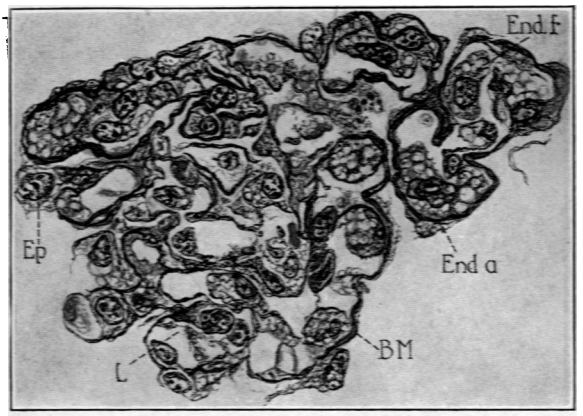
FIG. 3. Case II. A–28–5. Pure lipoid nephrosis. Mallory's anilin blue (Heidenhain azan-carmine). Drawing of part of a glomerulus (high magnification). A number of epithelial cells are seen (Ep.). There are many more endothelial nuclei (End.) than are seen in a normal glomerulus. One large endothelial cell is shown occluding a capillary (End. a.). The basement membrane (B. M.) is moderately thickened throughout, and in several places it shows very marked thickening (B. M. t.). There is partial occlusion of the lumina of some of the capillaries.

FIG. 4. Case V. A–28–193. Mixed type — Nephritis with nephrotic *Einschlag*. Drawing of part of a glomerulus. Stain as in Fig. 3. Prominent glomerular epithelium (Ep.). Increased number of endothelial nuclei. Thick basement membrane (B. M.). Ery., Erythrocytes.

FIG. 6. Case VI. A–28–183. Mixed type — Nephritis with nephrotic *Einschlag*. Drawing of part of a glomerulus. Stain as in Fig. 3. Increased number of endothelial nuclei (End.). Marked thickening of basement membrane (B. M.). Polymorphonuclear leucocyte (P. M. N.). Ery., Erythrocyte; L., lumen of capillary.

FIG. 9. Case VIII. A–27–511. Renal lesion of uncertain type. Drawing of part of a glomerulus. Stain as in Fig. 3. Extreme thickening and duplication of the basement membrane (B. M.). Marked narrowing of lumina of capillaries (L.). Great increase of endothelial nuclei (End.).

FIG. 11. Case IX. A–26–827. Renal lesion of uncertain type. Drawing of part of a glomerulus. Stain as in Fig. 3. The appearances are similar to Fig. 9, but the thickening of the basement membrane is more extreme, the lumina of the capillaries are smaller, and the endothelial nuclei are less conspicuous.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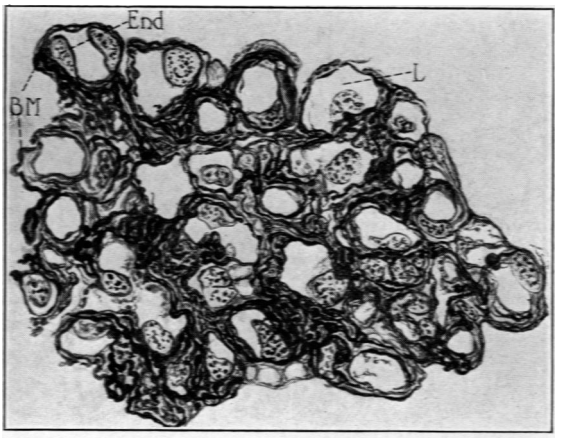
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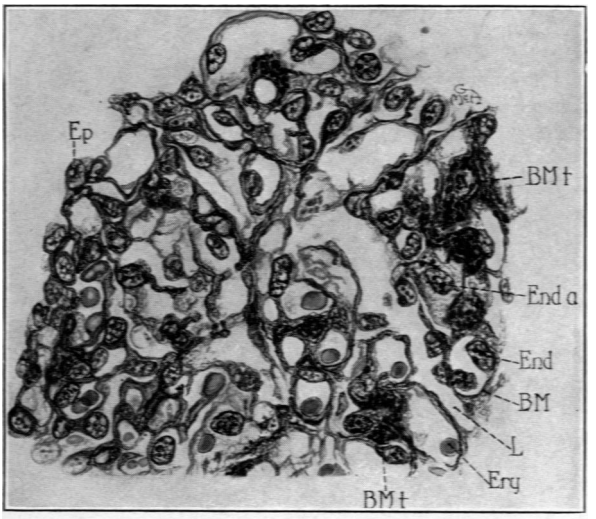
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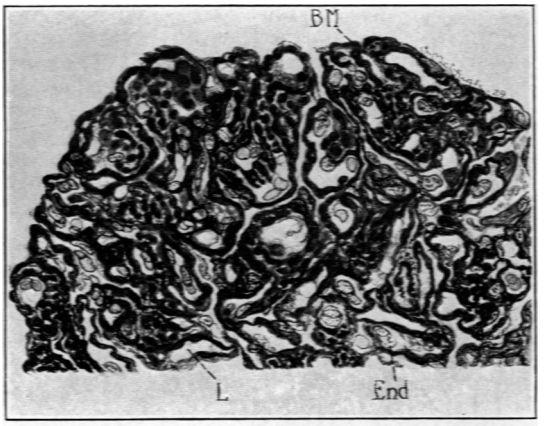
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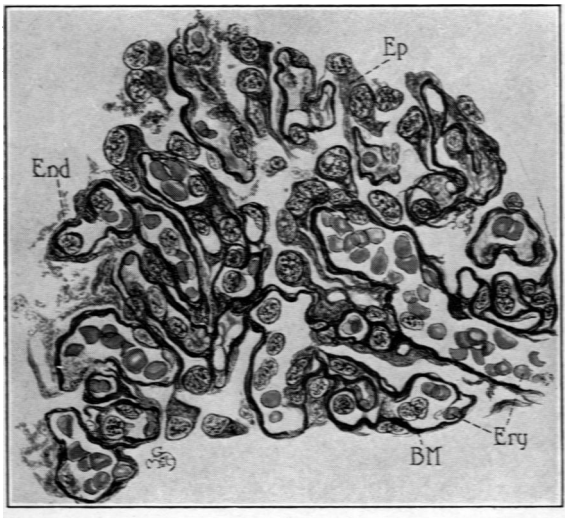
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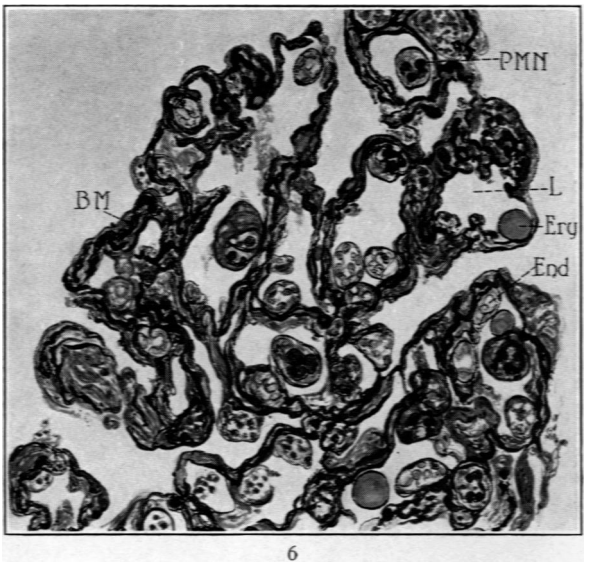
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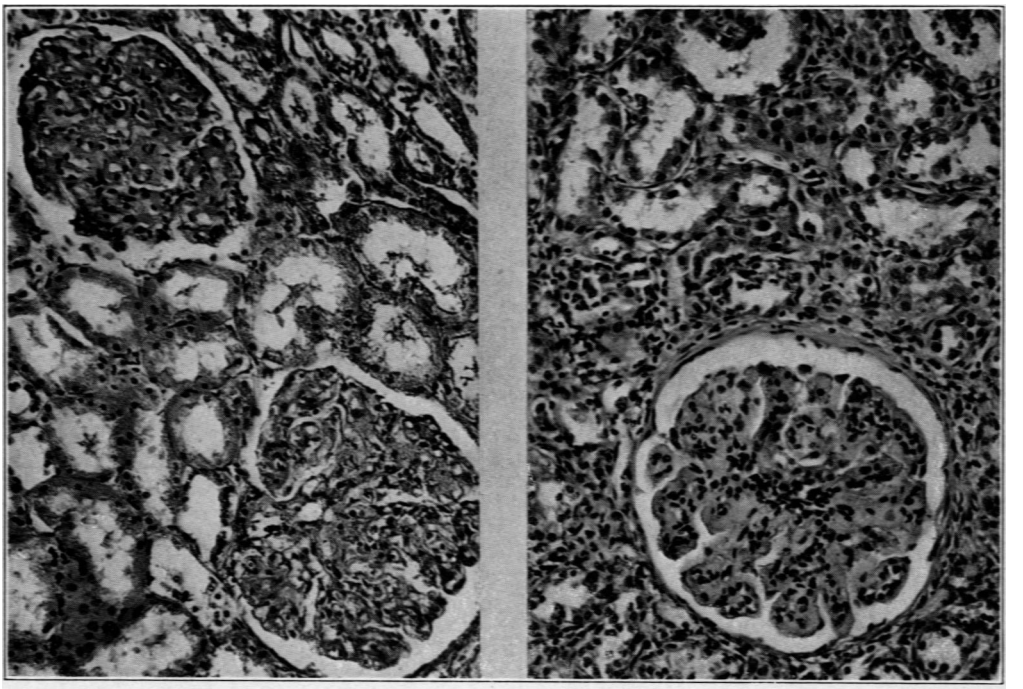
PLATE 109

FIG. 10. Case IX. A–26–827. Renal lesion of uncertain type. Photomicrograph. The glomeruli are of hyaline appearance, but the capillary bed is not completely obstructed. Large convoluted tubules.

FIG. 12. Case X. A–27–305. Renal lesion of uncertain type. Photomicrograph. Enormous enlargement of glomerular epithelial cells. Narrowing and occlusion of capillaries.

FIG. 13. Chronic glomerulonephritis. Photomicrograph. Glomerulus with its associated tubule. The capillaries are markedly narrowed but not completely occluded. The tubule is dilated, and its cells are filled with lipoid droplets.



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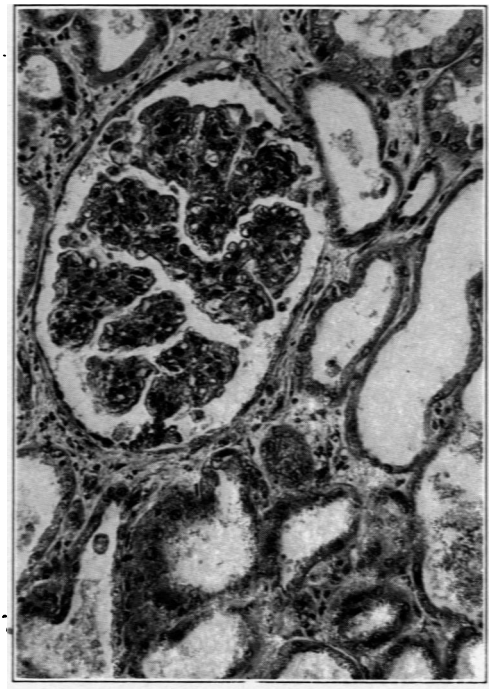

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