EXPERIMENTAL GLOMERULONEPHRITIS IN A MONKEY *

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This experiment deals with a monkey which was given repeated intravenous injections of streptococci over a period of four years. It was thought that repeated infections over a long period of time might simulate the conditions under which chronic glomerulonephritis develops in man.

A large male rhesus monkey was selected. Before the experiment was begun the urine was examined repeatedly and found free of albumin, erythrocytes and casts.

The organism used was a stock culture of *Streptococcus viridans* which was originally obtained from the blood of a patient with acute rheumatic fever. The bacteria injected were taken from agar slants incubated twenty-four hours at 37°C. Suspensions of one or more agar slants were made in 10 cc. of normal salt solution. The size of the injection is indicated in the table, + indicating one agar slant, ++ two or three slants, and +++ five slants. The dosage varied somewhat with the amount of growth on the agar.

The urine was collected in a metabolism cage. The animal was not catheterized. The amount of albumin is indicated roughly in the table, + indicating a trace, ++++ when the urine was semisolid on boiling, and ++ and +++ intermediate amounts.

The amount of gross blood is indicated roughly in the table, +++ representing a definitely red color, and + a barely visible redness. Small amounts of blood were frequently checked by microscopic examination.

The injections were discontinued occasionally because of the physical condition of the monkey, since we were anxious to keep the animal alive as long as possible. During the latter part of the experiment particularly, the injections were usually followed by severe reactions during which the animal often seemed near death for several hours. When albuminuria decreased or disappeared, heavier and more frequent injections were given. During the last two years of the experiment only occasional small injections were sufficient to keep up a persistent albuminuria.

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Gross blood was present in the urine on 50 out of 119 examinations. It was found much oftener during the latter half of the experiment. The amount of blood was greatest immediately following an injection, after which time it usually decreased gradually.

No edema was present at any time. The blood pressure was not recorded. During the last year of the experiment the animal gradually lost weight and finally became emaciated.

The details of the experiment are given in the following table:

The postmorten examination was made a few hours after death. Definite emaciation was noted. There was no subcutaneous edema, and no fluid was found in the serous cavities. The heart was small, indicating that hypertension had not been present. The lungs were entirely normal. No tuberculosis was present in any part of the body. No disease was found in any organ except the kidneys.

The kidneys were slightly enlarged, weighing together 44 gm. The external surfaces were smooth. On section the cortices were of pale color, not yellowish. Microscopic sections stained with scarlet red showed only occasional fat droplets in the tubules.

Under low magnification a moderate tubular atrophy is found throughout the kidneys. This is indicated by the increased connective tissue between the tubules. The atrophy is diffuse but is more pronounced in some areas than in others. Fig. 1 shows an area with rather conspicuous tubular atrophy.

None of the glomeruli are hyaline, but they all show definite narrowing and occlusion of the glomerular capillaries (Fig. 2). This appearance is present in every glomerulus and therefore cannot be interpreted as a focal lesion. The glomeruli are not enlarged. Very few erythrocytes are seen because of the narrowing and closure of the capillaries. Many of the glomerular lobules have a hyaline appearance.

It is easily seen with the iron-hematoxylin stain (Fig. 2) that there is a widespread obstruction in the glomerular circulation which is sufficient to explain the tubular atrophy. But this stain does not show the details of the glomerular lesion.

Sections stained by McGregor's method (Heidenhain's modification of Mallory's anilin blue) show the nature of the capillary obstruction. In Fig. 3 it is seen that the chief cause of capillary obstruction is a marked increase in the number and size of the capillary

TABLE I

Experimental Data on Monkey Injected with Streptococcus Viridans

Injections		Urine examination			Injections		Urine examination		
Date	Size	Date	Albumin	Gross blood	Date	Size	Date	Albumin	Gross blood
12/21/25	+	12/23/25	−	−	6/3/27	+	6/6/27	+	−
12/28/25	+	..	..	..	6/11/27	++	6/13/27	+++	−
12/31/25	++	1/2/26	+++	−	6/17/27	++	6/18/27	+++	+
1/4/26	++	1/6/26	−	−	..	..	6/26/27	++	−
1/8/26	++	..	..	..	6/27/27	+	6/28/27	++++	−
1/12/26	+	1/13/26	−	−	..	..	6/30/27	++++	+++
1/15/26	++	1/16/26	−	−	..	..	7/1/27	+++	+++
1/18/26	++	1/26/26	−	−	..	..	7/5/27	++	−
1/28/26	++	1/30/26	−	−	..	..	8/30/27	−	−
2/1/26	+++	2/3/26	−	−	9/9/27	++	9/10/27	++++	−
2/5/26	+++	2/5/26	−	−	..	..	9/12/27	+	−
2/11/26	+++	2/13/26	+	−	9/15/27	++	9/16/27	−	−
2/15/26	+++	2/16/26	−	−	..	..	9/19/27	+++	−
3/15/26	+++	3/16/26	++	−	9/22/27	++	9/22/27	+++	−
3/23/26	+++	3/25/26	++	+	..	..	9/23/27	++++	+++
4/9/26	+++	4/12/26	++++	+++	..	..	9/24/27	++++	+++
..	..	4/15/26	++	−	..	..	9/26/27	+++	+++
4/16/26	+++	4/17/26	++	−	9/28/27	++	9/30/27	++++	+++
4/21/26	+++	4/24/26	++	+	..	..	10/1/27	++++	+++
5/4/26	+++	5/5/26	+++	+++	..	..	10/3/27	++++	+++
..	..	5/11/26	+++	++	..	..	10/5/27	++++	++
5/12/26	+++	5/18/26	++	++	..	..	10/8/27	+++	−
5/22/26	+++	5/24/26	++	++	10/10/27	++	10/11/27	++++	+++
..	..	5/29/26	++	+	..	..	10/12/27	++++	+++
6/5/26	+++	6/7/26	+++	+++	..	..	10/13/27	++++	+++
6/12/26	+++	6/14/26	++	+	..	..	10/15/27	++++	+++
6/17/26	+++	6/21/26	+	−	..	..	10/18/27	++++	+++
6/22/26	+++	6/23/26	++	+	..	..	10/21/27	+++	−
6/24/26	+++	6/26/26	+	−	..	..	10/25/27	++	−
6/29/26	+++	6/30/26	+	−	..	..	10/28/27	++	−
7/2/26	+++	7/3/26	++	−	10/30/27	+	11/1/27	+++	−
7/9/26	+++	7/10/26	+	−	..	..	11/2/27	++++	+++
9/20/26	+++	9/21/26	−	−	..	..	11/4/27	++++	+
..	..	9/24/26	−	−	11/14/27	+	11/14/27	++	−
10/1/26	+++	10/2/26	−	−	..	..	11/15/27	++++	+++
10/8/26	+++	10/9/26	−	−	..	..	11/18/27	++++	+++
10/22/26	+++	10/23/26	+++	+++	..	..	11/23/27	+++	+++
10/28/26	+++	10/30/26	+++	++	12/3/27	++	12/5/27	++++	+++
..	..	11/5/26	+	−	..	..	12/7/27	+++	+++
11/10/26	+++	11/11/26	++	+	..	..	1/3/28	++	−
..	..	11/13/26	++	++	1/9/28	+	1/10/28	++++	++
11/19/26	+++	11/20/26	++	+	..	..	1/12/28	++++	+++
..	..	11/26/26	−	−	1/23/28	++	1/25/28	++++	+++
12/3/26	+++	..	..	..	2/17/28	+	2/20/28	++++	+++
12/14/26	+++	12/20/26	−	−	..	..	3/19/28	+++	−
12/29/26	+++	12/30/26	++	−	..	..	5/9/28	+	−
1/6/27	+++	1/6/27	+	−	5/12/28	+	5/14/28	+++	++
1/18/27	+++	1/20/27	−	−	..	..	6/27/28	++	−
2/12/27	+++	2/12/27	−	−	7/12/28	++	7/14/28	++++	+++
2/18/27	+++	2/21/27	+++	−	9/26/28	+	9/26/28	++	−
..	..	2/24/27	+++	−	..	..	10/1/28	++++	+++
..	..	2/28/27	+++	−	..	..	11/24/28	++	−
..	..	3/3/27	++	−	11/26/28	++	11/28/28	++++	+++
3/3/27	+++	3/5/27	++	−	1/30/29	++	2/1/29	++++	+++
..	..	3/11/27	+	−	7/3/29	+	7/5/29	+++	++
3/26/27	+++	4/24/27	+	−	..	..	7/9/29	Blood urea	
4/25/27	+++	4/27/27	−	−		..		nitrogen 48.53	
..	..	4/30/27	+++	−	..	..	1/2/30	−	−
..	..	5/3/27	−	−	1/6/30	++	1/9/30	+	−
5/6/27	++	5/9/27	−	−	1/27/30	++	1/30/30	++	−
5/17/27	++	5/19/27	−	−	..	..	5/8/30	++++	++
5/23/27	++	5/25/27	+++	++			Died 7/26/30		

endothelial cells. A few free mononuclear cells are seen which are possibly of hematogenous origin, but nearly all the cells appear to be attached to the basement membrane and are therefore interpreted as endothelial in origin. Only an occasional erythrocyte is seen. The capillary basement membrane is thickened and often appears as a double layer. There is no change in the glomerular epithelium except some evidences of degeneration.

Nearly all the glomerular tufts show a structure similar to that shown in Fig. 3, but those tufts that have a hyaline appearance in the hematoxylin-eosin preparation have a somewhat different structure (Fig. 4). These show a similar increase of endothelial cells, but a very marked increase in the number of layers of the capillary basement membrane. The hyaline appearance of the tuft is clearly due to multiplication of the layers of the basement membrane. Tufts of this structure are no longer permeable to blood.

The renal lesion is therefore characterized by a diffuse proliferation of capillary endothelium and an increase in the thickness and number of layers of the capillary basement membrane. It differs from typical clinical glomerulonephritis in the absence of intracapillary hyaline fibers.[1] There is, however, a notable resemblance in glomerular structure to some human cases of "lipoid nephrosis of mixed type" or "nephritis with nephrotic tendency;"[2] but the similarity goes no further since there is practically no lipoid in the tubular epithelium and there was no edema.

It is highly probable that death was due to uremia. The blood urea nitrogen was 48.5 mgm. per 100 cc. seventeen months before death, but unfortunately it was not determined again. The glomerular obstruction and the tubular atrophy support this interpretation, and no other cause of death was found at postmortem.

In our judgment we have produced a form of chronic diffuse glomerulonephritis which resembles the "parenchymatous" type of the human disease, but does not correspond to any human lesion in all respects. The marked increase of capillary endothelial cells seems to justify the diagnosis of glomerulonephritis.

The lesion was produced by the repeated introduction of streptococci into the blood stream. Whether the bacterial bodies or their soluble toxins are responsible for the injury was not determined. The kidneys were at first resistant to injury, but later became highly

susceptible. This increased susceptibility of the glomeruli is probably merely a response of injured tissue to repeated irritation. It is not necessary to assume that allergic hypersensitiveness existed.

Summary

1. A form of chronic diffuse glomerulonephritis was produced in a monkey by repeated intravenous injections of streptococci over a period of four years.

2. The lesion is characterized histologically by marked increase in capillary endothelium and increase in the thickness and number of layers of the capillary basement membrane.

3. Histologically the glomerular lesion resembles human "lipoid nephrosis of mixed type," except that no fat is present.

REFERENCES

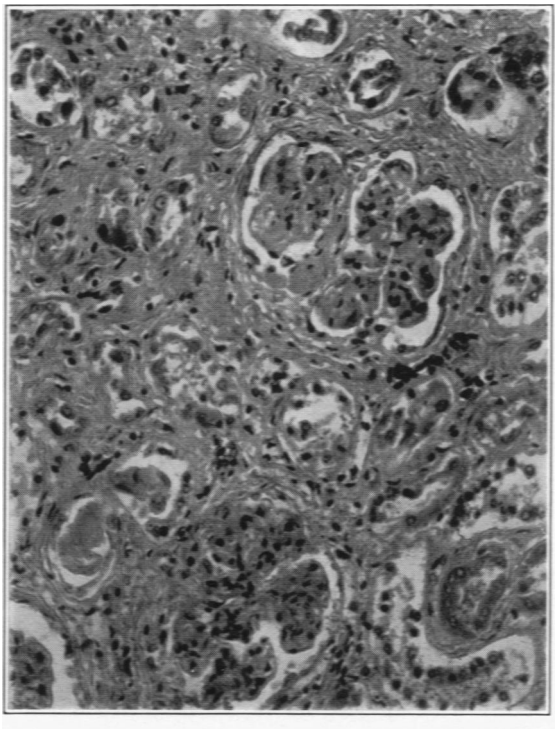
1. McGregor, L. The finer histology of the normal glomerulus. *Am. J. Path.*, 1929, **5**, 545.
2. Bell, E. T. Lipoid nephrosis. *Am. J. Path.*, 1929, **5**, 587.

DESCRIPTION OF PLATES

PLATE 10

FIG. 1. Area from the cortex showing moderate tubular atrophy. The glomerular lobules are fused to the capsular layer in some places and their capillaries are partially or completely closed. Iron-hematoxylin stain.

FIG. 2. Two lobules from a glomerulus shown in Fig. 1, under higher magnification. Note occlusion of the capillaries. Iron-hematoxylin stain.



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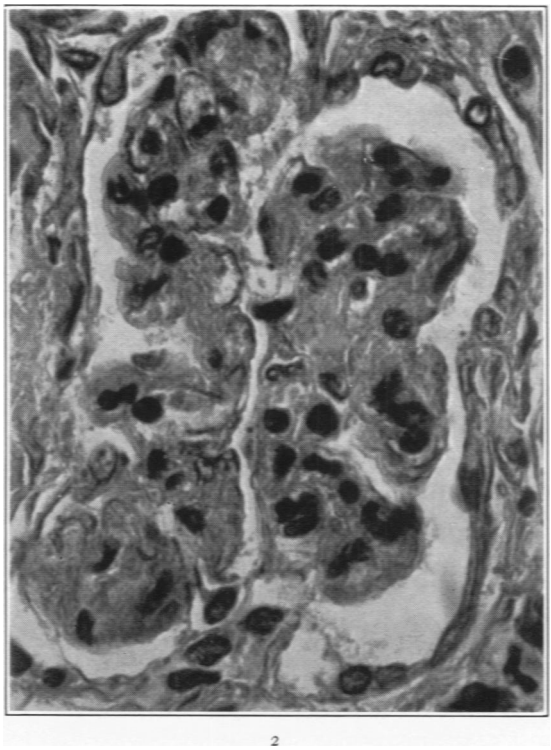

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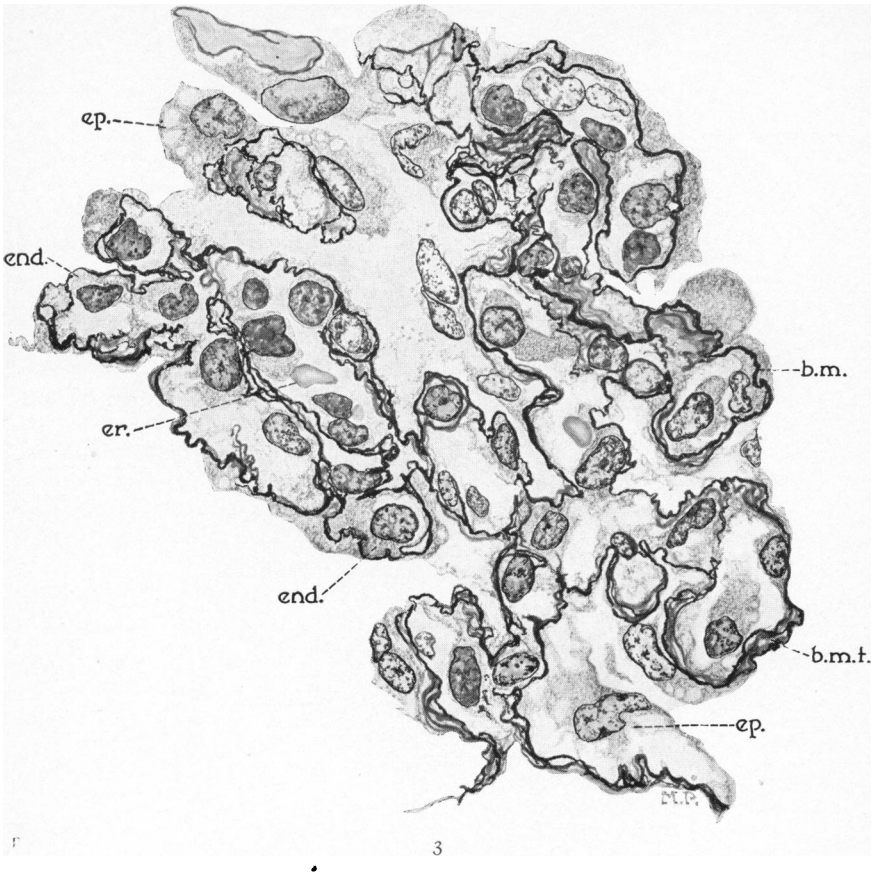
PLATE II

FIG. 3. Area from a glomerulus stained by McGregor's method (Heidenhain's modification of Mallory's anilin blue). Note marked increase of endothelial cells (*end.*). The glomerular epithelial cells (*ep.*) show no changes except evidences of degeneration. The capillary basement membrane (*b.m.*) is thicker than normal and is often represented by two or more layers (*b.m.t.*). (*Er.*) erythrocyte.

FIG. 4. Hyaline lobules from a glomerulus. Stained by McGregor's method. Lettered as in Fig. 3. Note the increase of endothelial cells and the multiplication of layers in the capillary basement membrane.



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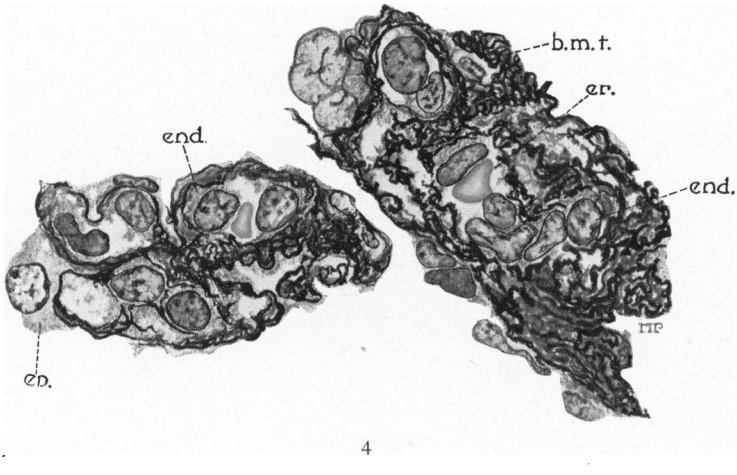

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