necessary to have some sort of quantitative measure of the febrile reaction. This is most simply obtained by determining with a planimeter areas under the febrile portion of the temperature-curve. Such areas from the experimental series illustrated in Fig. 1 and from a second similar series are listed in Table I. Throughout this work a guinea pig is considered to be febrile whenever its temperature exceeds 39.7°C. The data from the third series of experiments are less complete because of seriously interfering intercurrent infection in the available guinea pigs; none of the results of this third series, however, conflicts in any respect with those outlined above. It is obvious from the foregoing that serum administered as much as 5 days following infection has a positive therapeutic effect in guinea pigs diseased with epidemic typhus.

13680 P

Lesions Produced with Sulfadiazine.*

BERNARD MAISEL, BARTON MCSWAIN AND FRANK GLENN.
(Introduced by W. Dock.)

From the Departments of Pathology and Surgery, New York Hospital, and the Cornell University Medical College.

This study was undertaken to note the effects of sulfadiazine on the tissues of the dog.

Changes apparently due to the sulfonamides have been reported in man and in experimental animals by several investigators.[1-7] Some of the changes observed by us have not been hitherto described.

Eight dogs, weighing from 8.2 to 16.4 kg, were used. In a 20% aqueous solution, one-tenth g of sodium sulfadiazine per kg of animal weight was injected subcutaneously twice daily. Tissues were examined from 6 to 21 days after the initial dose of this drug.

* The sodium sulfadiazine used in this experiment was supplied by Lederle Laboratories, Inc.

1 French, A. J., and Weller, C. V., *Am. J. Path.*, 1942, **1**, 109.

2 Antopol, W., and Robinson, H., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 428; *Ibid., Arch. Path.*, 1940, **29**, 67.

3 Antopol, W., Lehr, D., Churg, J., and Sprinz, H., *Arch. Path.*, 1941, **31**, 592.

4 Stryker, W. A., *J. A. M. A.*, 1940, **114**, 953.

5 Davis, H. A., and Higgins, G. M., *Am. J. M. Sc.*, 1939, **198**, 804.

6 Toomey, J. A., Reichle, H. S., and Takacs, W. S., *J. Pediat.*, 1940, **16**, 179.

7 Machella, T. E., and Higgins, G. M., *Am. J. M. Sc.*, 1939, **198**, 804.

During the first 6 days blood levels were from 10 to 25 mg %; higher levels (up to 100 mg %) were found after the second week. All animals developed high values for blood urea nitrogen, became listless, and 6 died within 21 days. The 2 which remained were killed.

A moderate bronchopneumonia was found in 2 animals. There were no other gross changes except for the presence of crystalline deposits in the pelves and calyces of all animals.

The most striking changes in all experimental animals were found in the kidneys. This drug apparently affects several renal structures at approximately the same time. The lesions indicated below were present after 6 days, and with increased time the characteristics became more obvious.

A moderate number of glomeruli were damaged. The first evidence of damage was the presence of protein and blood elements in Bowman's space and the urine. Later, inflammatory changes were encountered resulting in the destruction of the glomeruli. The leukocytic reaction consisted of monocytes, plasma cells, lymphocytes and a few polymorphonuclear neutrophils and eosinophils. This reaction was accompanied by the development of fibroblasts, collagen deposition and multinucleated giant cells producing a granuloma.

The tubular system was simultaneously affected. Metachromatic, often quite basophilic, protein-sulfadiazine crystalline casts were found as high as the descending loop of Henle. Many of the tubules, particularly the proximal and distal convoluted tubules, showed swelling and early necrosis of the lining cells, with a mononuclear leukocytic reaction in the regional stroma. In many areas materials in tubular casts had broken through the necrotic part of the tubular wall so as to permeate the interstitial tissues. About this material a leukocytic reaction similar to that described in the glomerular lesion developed. After approximately 3 weeks multinucleated giant cells, epithelioid cells, fibroblasts and collagen appeared, forming a granuloma.

Casts of proteins and crystals often completely filled and obstructed many collecting tubules in medullary pyramids. Some lining cells showed evidence of early necrosis, and regenerative response as disclosed by mitotic figures was a conspicuous feature.

In the submucosa of the pelvis and calyces there was an inflammatory reaction consisting of the same cells that occurred in the inflammatory lesions in the cortex and medulla.

An inflammatory reaction occurred in and about the walls of several veins of the kidney. The leukocytes were largely mononuclear

in type, with occasional polymorphonuclear eosinophils and neutrophils. Where the inflammatory reaction was found in the vessel wall a mural thrombus was often attached. Many small veins were completely thrombosed, and hemorrhage had occurred into the interstitial tissues of the kidney.

About several of the arteries of the kidney and occasionally of the heart and liver there was a perivascular leukocytic reaction of monocytes, lymphocytes, plasma cells and occasionally a few polymorphonuclear eosinophils and neutrophils.

The sternal bone marrow of 4 animals showed a moderate hyperplasia of all elements. The other 4 animals showed either no change or a slight hypoplasia. One animal had small areas of necrosis in the bone marrow. Two animals showed small areas of hemorrhage in the sternal marrow. In the marrow of all animals there were many mononuclear phagocytic cells filled with hemosiderin.

In the spleen there was a large amount of intracellular and extracellular hemosiderin. All animals showed a prominent "toxic" change of the germinal centers.

In 7 animals the Kupffer cells of the liver were filled with hemosiderin.

Discussion. These findings indicate that sodium sulfadiazine produces several types of lesions in dogs. Those occurring about tubules, calyces and renal pelves are probably due to the chemical irritation in these parts. Damage to the glomeruli and tubules often terminates in the destruction of these structures with occasional production of a granulomatous lesion characterized by mononuclear leukocytes, multinucleated giant cells, fibroblasts and collagen deposition. The hemosiderosis in the bone marrow, spleen and liver is probably secondary to the destruction of erythrocytes. The hyperplasia of the bone marrow in 4 dogs is a response to the destruction of erythrocytes. The hemorrhage, repression of activity and necrosis of bone marrow in some animals is unexplained, as are the vascular lesions, including those of the glomeruli.