HYPERSENSITIVITY IN THE PATHOGENESIS OF THE HISTOPATHOLOGIC CHANGES ASSOCIATED WITH SULFONAMIDE CHEMOTHERAPY*

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An earlier report on the effects of the sulfonamide drugs in tissues was published in collaboration with C. V. Weller in 1942.[1] At that time few reports of this character had been released, but subsequently there has been an increasing number in the literature. As each new sulfonamide derivative was introduced, the hope that it would prove to be less toxic than preceding ones was revived; however, after it had been used for a time, investigation proved that comparable tissue changes took place in one or several organs of the body.

The material utilized in this report includes 76 fatal cases investigated at the Army Institute of Pathology from 1937, when neoprontosil was first used therapeutically in Army hospitals, until 1943, when a variety of sulfonamides were being employed.

Skin taken for biopsy from 2 other cases was included in the material, making a total of 78 cases. This series is approximately one-sixth of more than 500 cases in which one or another type of lesion had resulted from the administration of sulfonamides, but complicating disease factors caused the other cases to be eliminated. All cases were excluded in which sulfonamide drugs had been given in the treatment of any of the following conditions: septicemia, confirmed by blood culture; rheumatic fever; cardiovascular disease, including coronary thrombosis; poliomyelitis; scrub typhus or other proved viral or rickettsial infection; trichinosis; diphtheria; scarlet fever; typhoid fever; or miliary tuberculosis. However, in the presence of many of these complicating diseases, cellular infiltrates were observed which were identical with those regarded as the characteristic sulfonamide effect.

The sulfonamide drugs which had been administered to the patients in this series included neoprontosil, sulfanilamide, sulfathiazole, sulfapyridine, sulfaguanidine, sulfadiazine, and the sodium salts of sulfathiazole, sulfapyridine, and sulfadiazine. Various combinations of these drugs were given to 24 patients. In four instances "sulfonamide therapy" was reported without reference to the specific drug employed (Table I).

The total dosage of sulfonamide drugs received by the patients during the terminal illness varied from 8 to 340 gm., over periods ranging

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from several days to 6 weeks. No case was included in the series in which death occurred later than 1 month after cessation of sulfonamide therapy. In all but 2 cases chemotherapy had been instituted at least 72 hours before death, but in these the drug had been given intravenously in moderately high dosage.

Clinical Data. Sulfonamide drugs were administered to 30 patients who were admitted to the hospital with a diagnosis of nasopharyngitis. Lobar pneumonia due to type I pneumococcus developed in 3 of these cases, due to type III pneumococcus in one, and in the remaining 26 there was terminal bronchopneumonia. Eleven of the 76 patients were being treated for gonorrhea and the remaining 35 for a variety of clinical conditions including fracture, perforated appendix, duodenal ulcer, and otitis media.

TABLE I

*Sulfonamide Drugs Administered to Patients Included in the Reported Series**

Drug	No. of cases
Neoprontosil	1
Sulfanilamide	6
Sulfathiazole	22
Na sulfathiazole	3
Sulfapyridine	1
Na sulfapyridine	1
Sulfadiazine	11
Na sulfadiazine	4
Sulfaguanidine	1
Combinations	24
"Sulfonamide therapy"	4

* Two biopsy cases included.

Induced Sensitivity. In approximately one-half of the cases reported in this series there was clinical evidence of some reaction denoting sensitivity to the sulfonamide drugs. Table II lists these clinical complications which suggested sensitivity.

In 14 cases, more than one course of treatment with sulfonamides had been resorted to during the terminal illness of the patient. The first therapeutic course did not produce severe complications in all cases; apparently, in some the degree of sensitivity increased with repeated courses of the drugs. Rash, fever, chills, nausea, vomiting, cyanosis, or leukopenia were the usual signs of unfavorable reaction with the first course of sulfonamide therapy; hypoplastic anemia, icterus, anuria, dermatitis, or combinations of such grave complications, with a subsequent course of treatment. The exact length of treatment was not stated in the brief clinical summaries submitted with the protocols in most instances, so that the relationship of duration of therapy to clinical complication could not be calculated. Patients with hypoplastic or hemolytic anemia, dermatitis or anuria died following varying periods of therapy, but no definite relationship between induced sensitivity and duration of therapy, dosage, or a specific sulfonamide drug was apparent in cases completely reported. Multiple courses of sulfonamide therapy separated by intervals varying from hours to weeks appeared to result in acquired sensitivity.

Histopathology

Histopathologic lesions were found most frequently in the heart, liver, and kidney. Sections of intestine, gallbladder, urinary bladder, prostate, testis, lymph node, bone marrow, skin, skeletal muscle, and meninges were only occasionally represented in the material examined so that the corrected incidence of pathologic changes in these organs probably would be somewhat higher. The normal cellularity of organs such as the spleen, lymph nodes, and bone marrow contributed to the difficulty of establishing an increase in cell content, but the acidophilic cellular reactions to the sulfonamide drugs were obvious in these organs.

Table II

Clinical Complications in the Reported Cases Associated with the Administration of Sulfonamide Drugs

Clinical complications	No. of cases
Dermatitis	19
Anuria	9
Icterus	8
Aplastic anemia	7
Fever and/or chill	6
Eosinophilia in peripheral blood	2
Hemolytic anemia	2
Leukopenia	2

Heart

The heart lesions indicative of sulfonamide intoxication were those described by French and Weller [1] in experimental and clinical material and confirmed by Frist [2] and Flynn.[3] The characteristic cell found in the lesions in the heart and in all other organs examined was the acidophilic histiocyte. This cell, with variable numbers of other mononuclear and polymorphonuclear cells, both acidophilic and neutrophilic, was present in paravascular foci, or diffusely distributed between the cardiac muscle fibers, in the subepicardial areolar tissues, and beneath the endocardium. Necrosis was neither constant nor prominent in the tissues in which these cellular infiltrates were found, but did occur in the more severe cases (Figs. 1 and 2).

Distinctive vascular involvement (Figs. 3 and 4), such as that described by Rich [4] and confirmed in a personal review of this material by him, was noted in many of the hearts examined. In 16 cases vascular lesions were seen in organs other than the heart. The lesions consisted of endothelial edema and proliferation, fibrinoid necrosis of the vessel wall, and endarteritis and periarteritis with acidophilic histiocytes and eosinophils predominating in the inflammatory cellular reaction. The infiltrate in older lesions contained fewer eosinophils and relatively more histiocytes.

In addition to the inflammatory cellular reaction, epicardial, myocardial, or subendocardial hemorrhages, petechial or diffuse in character, were seen in the sections. Characteristic cellular infiltrates were

present throughout the walls of capillaries and venules adjacent to or in the hemorrhagic areas. In a few instances early fibroblastic proliferation was associated with inflammatory infiltrates; however, experimental reproduction of this change will be required before its significance in relation to the sulfonamide drugs can be evaluated.

Extensive focal calcification of the myocardium was observed in one case and calcification of isolated muscle fibrils in another; in neither was there evidence of vascular occlusion or other cardiac disease. A minimal acidophilic cellular infiltration in the adjacent myocardium was attributed to the sulfonamide drugs (Fig. 5). The significance of calcification of the myocardium was not apparent and its interpretation must await further experimentation. Calcification of the myocardium in rats fed sulfonamides, as reported by Endicott, Kornberg, and Daft,[5] may be a comparable lesion.

Liver

Lesions in the liver believed to result from the administration of sulfonamide drugs included infiltrations containing acidophilic histiocytes and neutrophils with varying degrees of focal necrosis or micro-abscess formation (Fig. 6). The presence of dense cellular infiltrations containing characteristic acidophilic cells, in the absence of other known cause for such collections of inflammatory cells (*i.e.*, cholelithiasis, choledocholithiasis, or other detectable biliary tract disease) was interpreted as evidence of reaction to sulfonamide drugs during the terminal illness.

In the liver as in the heart there was a minor degree of cellular infiltration in the wall of an occasional central vein. Hemorrhage was not noted in the liver.

Kidney

Renal lesions of many kinds were encountered in approximately one-half of the cases reviewed. Those believed to have been caused by the action of sulfonamides included *interstitial nephritis,* in which characteristic acidophilic mononuclear and polymorphonuclear cells were conspicuous components (Fig. 7); crystal formation (Fig. 8), often associated with calcium deposition, or with accumulations of bluish staining material both intratubularly and extratubularly; and vascular fibrinoid necrosis, thrombosis, subpelvic hemorrhages, and cellular infiltrates. Both focal necrosis and cellular infiltrates were seen in sections showing interstitial nephritis.

Tubular lesions were for the most part limited to the distal portions of the nephron, including the ascending limb of Henle's loop and the distal convoluted and collecting tubules, in which necrosis of the tubu-

lar epithelium and regeneration of the lining cells were seen. The lumina were plugged and the tubules distended with hemoglobin casts, crystals, crystals combined with calcium salts, erythrocytes, leukocytes, and amorphous protein precipitates. Some tubules showed necrosis of the lining with rupture of the walls and escape of crystals into the adjacent interstitial tissues. Glomerular and proximal tubular lesions were less frequent but glomerular vascular lesions were striking when present.

Subpelvic hemorrhages were conspicuous if ureteral and pelvic catheterization had been employed before death in an attempt to remove sulfonamide crystals. Hemorrhages and characteristic cellular infiltrates beneath the pelvic epithelium were also seen when there had been no surgical intervention. As in the heart, these hemorrhages and infiltrates were believed to be attributable to the sulfonamide drugs.

Skin

Sections of skin were included in only 2 of the fatal cases and were submitted for biopsy in 2 others. Inasmuch as a rash was reported in 18 cases, the skin changes must be regarded as significant. In the 4 specimens examined the characteristic acidophilic cells were present. The lesions, both clinically and histopathologically, were like those seen in erythema multiforme with vesiculation (Fig. 9) and in erythema nodosum (Fig. 10). The cellular infiltrates were mainly paravascular with some diffusion of cells in the more severe cases. Vascular involvement was not a salient feature.

Testis

Acidophilic histiocytes were striking in the sections of testis included in 4 cases in the series (Fig. 11). Because testicular tissue was submitted in so few cases, the true incidence of lesions in the testes could only be estimated. Although the acidophilic histiocytes were distributed in the supporting tissues of the testis, there was no possibility of confusion with Leydig cells. No necrosis or hemorrhage was present in the sections of testis examined.

Spleen, Lymph Nodes, and Bone Marrow

Specimens of spleen were received in 64 of the 76 cases studied. In 7, miliary foci of necrosis, similar to those reported by Lederer and Rosenblatt,[6] and Merkel and Crawford,[7] were encountered in the red pulp. These foci of necrosis were associated with acidophilic histiocytes and neutrophilic leukocytes (Fig. 12).

Lymph node lesions were present in 3 cases. As in the spleen and

bone marrow, microscopic foci of necrosis were seen in association with acidophilic histiocytes, granular leukocytes, and hyperplastic reticulum cells (Fig. 13).

Bone marrow changes were present in 5 cases in the form of miliary areas of focal necrosis and infiltrations of acidophilic histiocytes and polymorphonuclear cells.

Lung

Pulmonary lesions were the most difficult to interpret because of the bacterial inflammatory reaction usually present. However, in 4 instances definite intra-alveolar and interalveolar, peribronchiolar, peribronchial, and perivascular infiltrations of acidophilic histiocytes and polymorphonuclear cells were present. Vascular fibrinoid necrosis, capillary thrombosis, fibrinoid plaques in the alveoli, and interstitial cellular foci were noted in the lungs in addition to hemorrhage.

In 2 cases with acidophilic cellular infiltrate, massive pulmonary hemorrhage by diapedesis was present. In one case miliary necrotic foci were present in the lungs as well as in the liver, spleen, lymph nodes, and bone marrow. As already stated, any case in which there was miliary tuberculosis, tularemia, typhoid fever, or other known cause of focal necrosis was excluded from the series.

Other Organs

Foci of eosinophilic histiocytes have been found in practically all organs of the body, including all parts of the gastrointestinal tract, gallbladder (Fig. 14), urinary bladder, skeletal muscle, and meninges. Tissue from these organs was not routinely submitted in the 76 cases reported and, as a result, the lesions were encountered too infrequently to be significant statistically. They are important in that they showed the characteristic cellular infiltrates.

Discussion

Histopathologic changes in the kidneys have received more attention in the literature than those of other organs. As noted by Prien, Crabtree, and Frondel,[8] Climenko and Wright,[9] Antopol, Lehr, Churg, and Sprinz,[10] and Hellwig and Reed,[11] renal tubular damage was usually confined to the distal portion of the nephron, particularly the distal convoluted and collecting tubules. Hemoglobin casts were an outstanding feature in many instances and were indistinguishable, unless associated with crystals of acetylated sulfonamides, from the hemoglobin-laden tubules seen following transfusion incompatibility, hepatitis, blast or crush injury, or death from burns. Interstitial cellular infiltrations,

containing acidophilic histiocytes and neutrophils, and subpelvic hemorrhages were components of the renal lesions noted in cases receiving the sulfonamide drugs.

It is remarkable that so little significance has been attached to the possible clinical effect of the sulfonamide drugs on the heart. Except for the reference of Scheinberg and Ingle [12] to myocardosis in a patient who recovered following treatment with sulfanilamide, no direct reference to the effects of the drugs on the heart was found in the literature surveyed.

Conclusive evidence of a chronic effect of sulfonamide therapy has not been obtained experimentally, but focal calcification and minor degrees of early fibroblastic proliferation have been noted in association with cellular infiltrates. In one case of periarteritis nodosa, secondary cellular infiltration attributable to sulfonamide drugs appeared comparable to that described in Rich's [4] report. Dense cellular infiltrations, hemorrhages, and focal necrosis might be expected to result in at least minor degrees of fibrosis. The focal myocardial calcification noted in 2 cases in the series may be regarded as a more permanent effect of the drug than the cellular infiltration and may be an example in human material of the lesions noted in rats fed sulfonamide by Endicott, Kornberg, and Daft.[5]

Hepatic infiltration and necrosis, with or without icterus, were frequent findings. When combined with lesions of the heart, kidneys, skin, and blood-forming organs, the fatal termination can be attributed to the severity of the total reaction.

The extensive pulmonary hemorrhages in 2 cases were comparable to hemorrhagic lesions encountered in the heart and kidney. The possibility of a relationship between hemorrhage by diapedesis and sensitivity to sulfonamide drugs must await further experimental confirmation. However, Pinkerton [13] and Gessler [14] have reported similar cases related to sulfonamide therapy.

Skin sections were taken in 4 instances of frank dermatitis. These 3 cases of erythema multiforme with vesiculation and one of erythema nodosum were striking. Loveman and Simon [15] reported a similar example of erythema nodosum in which the lesion was reproduced by repeated administration of the sulfonamide drug. It was significant that in 3 of the 18 cases that showed a skin rash dermatitis of severe proportions developed.

Skin reactions were the most striking clinical evidence of sensitivity to the sulfonamide drugs. From this series of cases the conclusion appears to be justified that any skin reaction other than simple erythema should be a contraindication to the continued use of any member of this

group of drugs. The utmost care must be exercised and adequate clinical study maintained if a patient who has had any type of skin reaction is subjected to further use of sulfonamides. Repeated courses of sulfonamide treatment given to a patient once shown to be sensitive appeared to magnify the severity of the complications, as 14 patients who exhibited sensitivity had had two or more courses of the drug. A change in form of the drug appeared to reduce the hazard if sulfonamide therapy was reinstituted, but even then the reaction might be severe or fatal.

The prophylactic use of sulfonamide drugs against meningitis, gonorrhea, and other infectious diseases may well result in sensitizing patients to the drug, as noted by Lyons and Balberor,[16] Nelson,[17] Kalz and Steeves,[18] and Stiles.[19] While this possibility should not be considered a contraindication to the prophylactic use of sulfonamides, it must be recognized if fatal reactions are to be avoided. The protection afforded the majority is the paramount consideration, and should not be disregarded because death occasionally occurs in a sensitized individual. On the other hand, the dangers of the indiscriminate use of sulfonamide drugs for prophylaxis or in the therapy of minor infections cannot be overemphasized.

Conclusions

1. Striking histopathologic changes were seen in the material from 76 autopsies and in 2 additional specimens of skin taken for biopsy from patients who apparently had been sensitized to sulfonamides, as reviewed at the Army Institute of Pathology.

2. Characteristic acidophilic histiocytes were present in focal and diffuse infiltrations in the heart, liver, kidney, lung, spleen, lymph nodes, bone marrow, skin, testis, intestine, gallbladder, prostate, urinary bladder, skeletal muscle, thyroid, aorta, and meninges.

3. Significant vascular lesions were characterized by fibrinoid necrosis, endothelial edema, and proliferation.

4. Interstitial pneumonitis and hemorrhage by diapedesis in the pulmonary alveoli were attributed to sulfonamide sensitivity.

5. Focal subendocardial, subepicardial, and subpelvic renal hemorrhages were associated with typical acidophilic histiocytic infiltrates.

6. Sulfonamide crystals combined with calcium deposition were demonstrated in and adjacent to the distal convoluted and collecting renal tubules.

7. Evidence of individual susceptibility to initial and repeated courses of the sulfonamide group of drugs has accumulated in the literature and is substantiated by this series of cases.

8. Sensitization of large groups of patients with prophylactic doses of sulfonamide drugs may result in an increase in the number of histopathologic lesions encountered at autopsy. Many of these lesions were significant causes of death.

9. Increased caution must be observed in the prophylactic and therapeutic use of the sulfonamide drugs for minor infections.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 131

(A.I.P. = Army Institute of Pathology)

FIG. 1. Paravascular and interstitial infiltration of acidophilic histiocytes in the myocardium. Although monocytes predominate, a few polymorphonuclear cells are present also. × 240. A.I.P. neg. 79036.

FIG. 2. A small area in the upper right quarter of the preceding illustration is shown at a higher magnification. The many mononuclear histiocytes which occupy the greater part of the field were chiefly acidophilic. A few cells of the granulocyte series are included in the infiltration. The muscle fibers are not necrotic. × 1000. A.I.P. neg. 79039.

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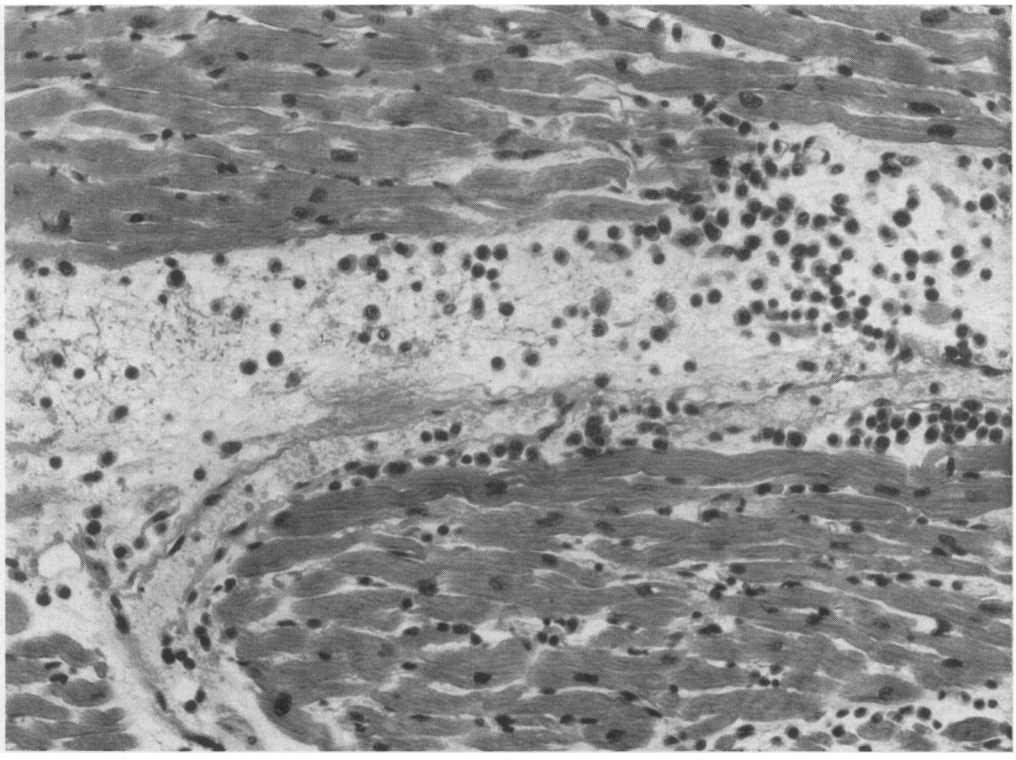

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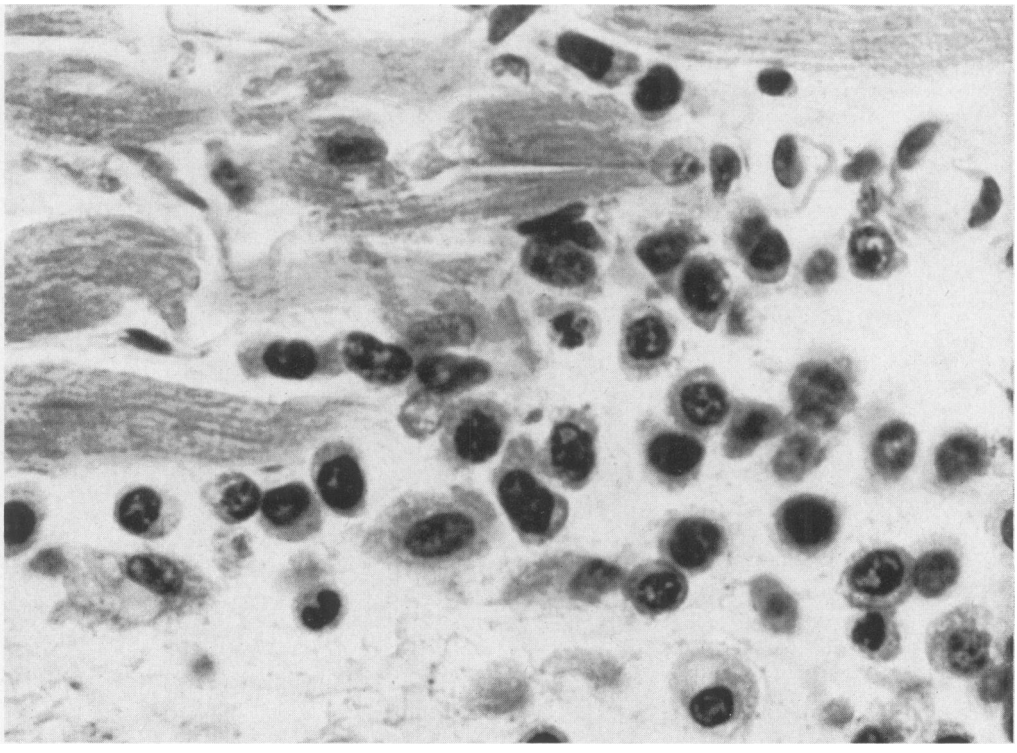
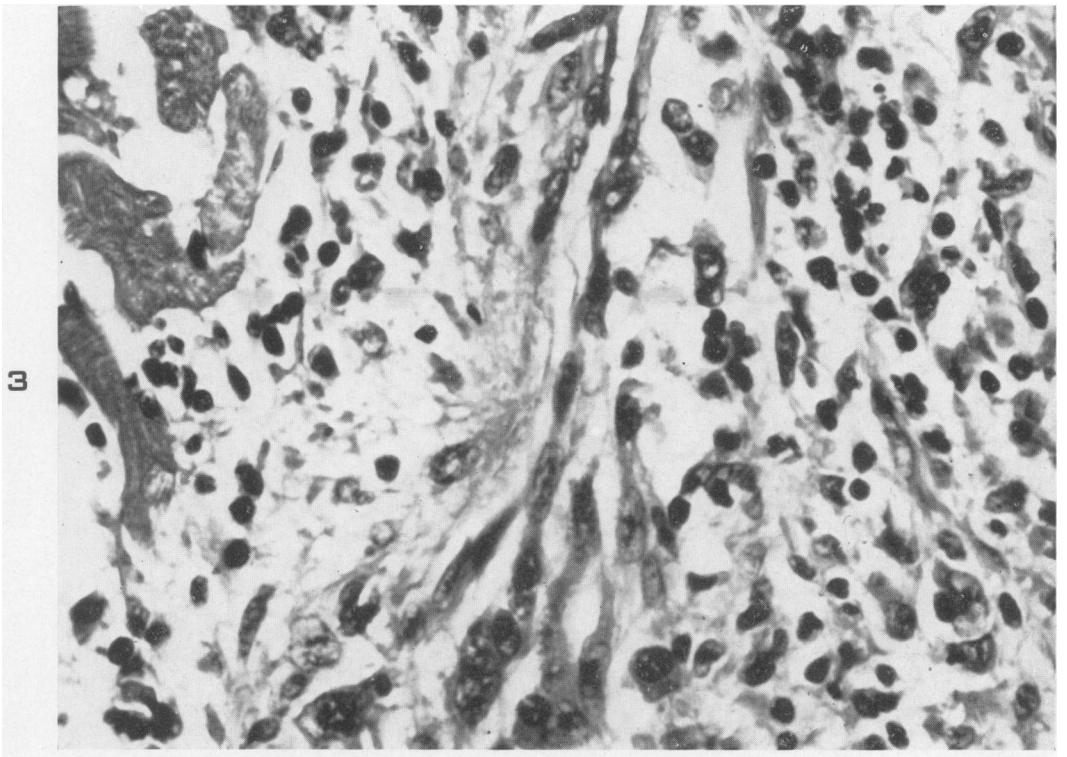


French Histopathologic Changes with Sulfonamides

PLATE 132

FIGS. 3 and 4. Fibrinoid necrosis is present in the walls of capillaries in the myocardium. The paravascular tissues are edematous and infiltrated with acidophilic histiocytes. There is active proliferation of capillary endothelium. × 700. A.I.P. negs. 79129 and 79132.



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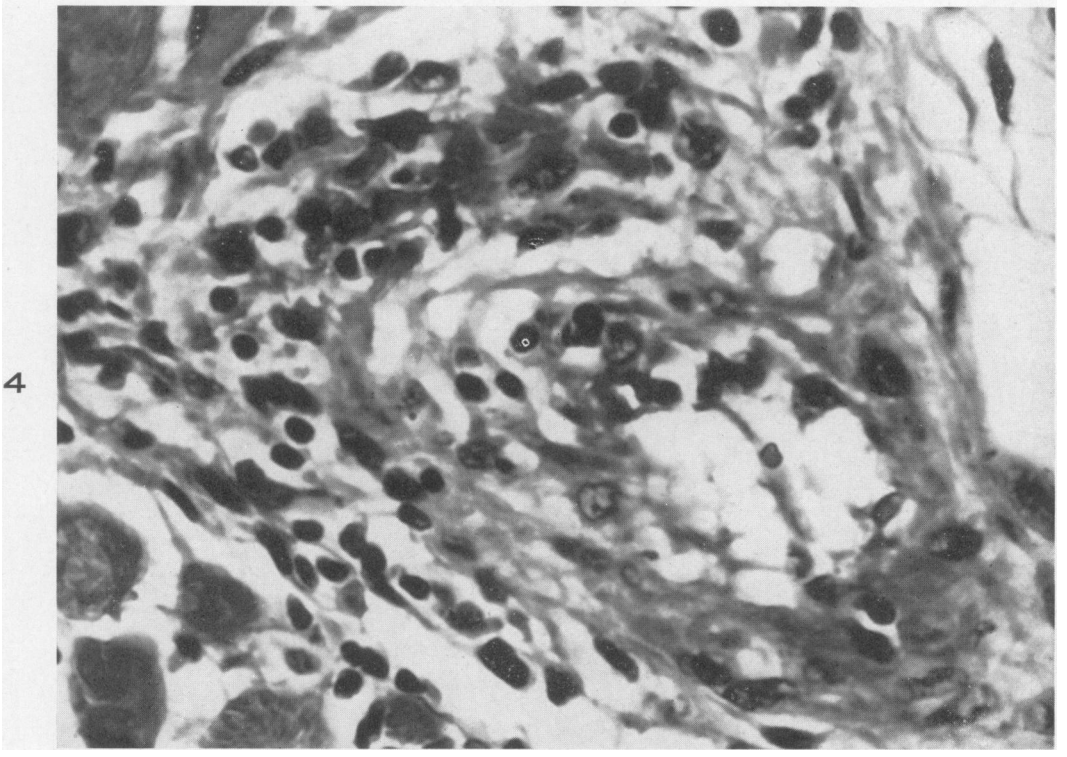


4

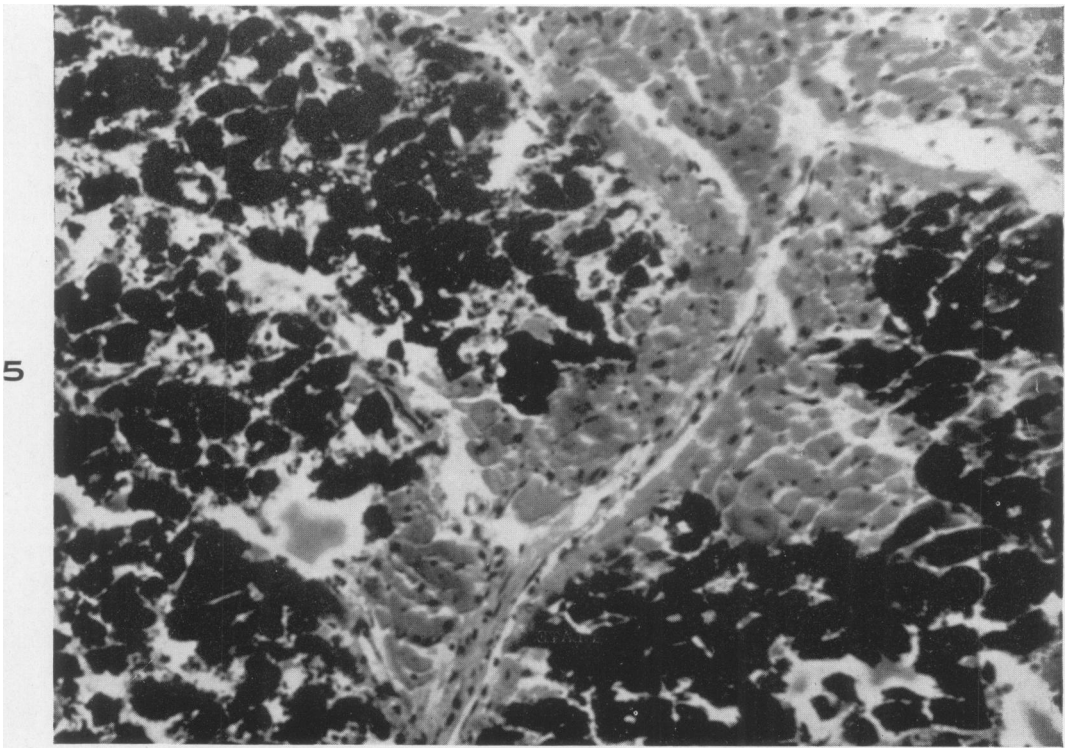
French

Histopathologic Changes with Sulfonamides

PLATE 133

FIG. 5. Marked focal calcific deposits in myocardial fibers unassociated with primary vascular disease. The associated paravascular infiltrations of acidophilic histiocytes suggest a relationship to sulfonamide sensitivity. × 130. A.I.P. neg. 79040.

FIG. 6. Focal necrosis of hepatic parenchyma with acidophilic histiocytes composing part of the exudate. × 280. A.I.P. neg. 79041.



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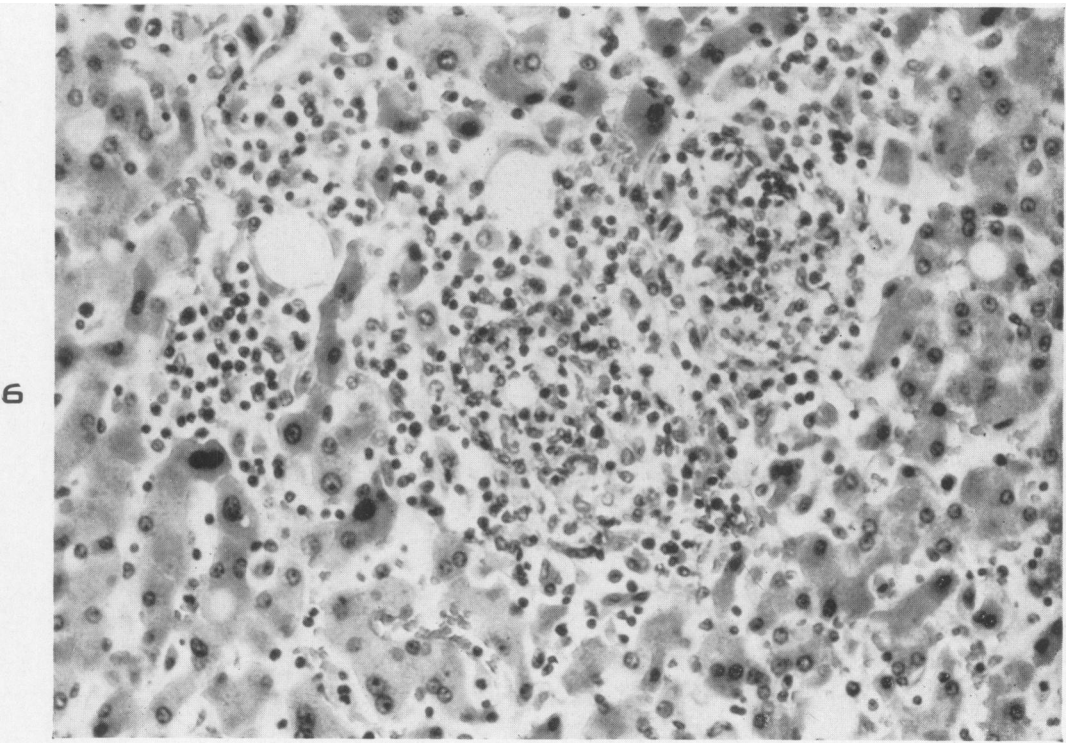

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French Histopathologic Changes with Sulfonamides

PLATE 134

FIG. 7. Severe interstitial infiltration of acidophilic histiocytes and other inflammatory cells in the renal parenchyma. Acute parenchymatous degeneration of the epithelium of the tubules. × 200. A.I.P. neg. 79131.

FIG. 8. Crystals of acetylated sulfathiazole with slight calcific deposition in renal tubules. Interstitial infiltration of acidophilic histiocytes. × 915. A.I.P. neg. 79045.

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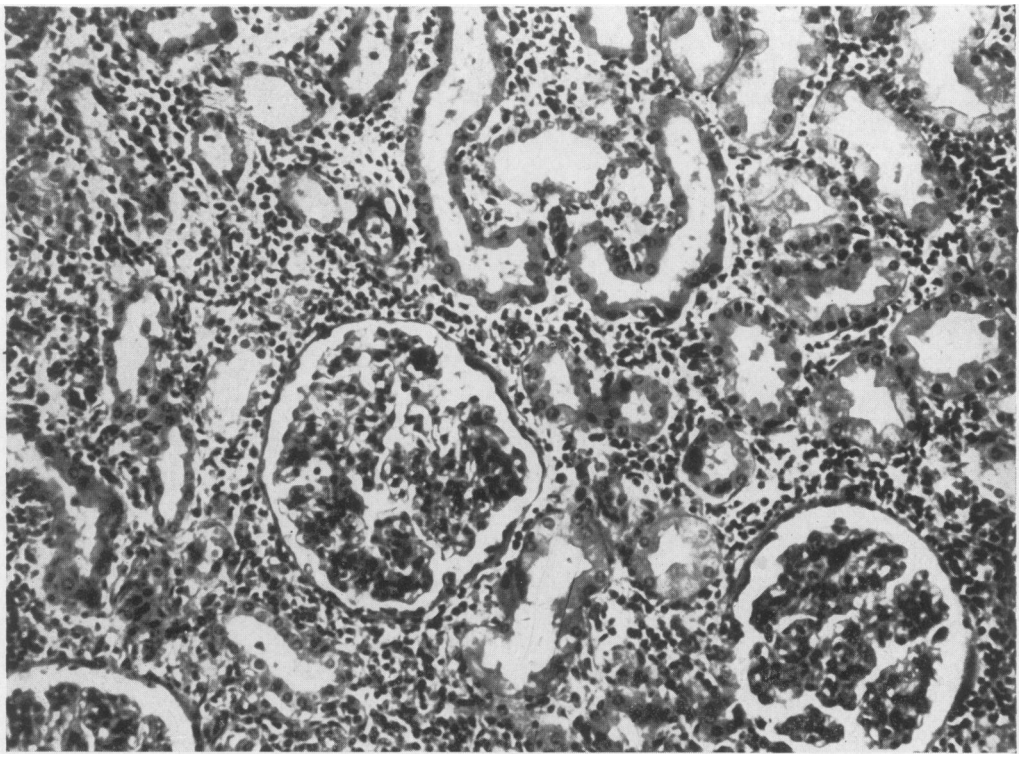

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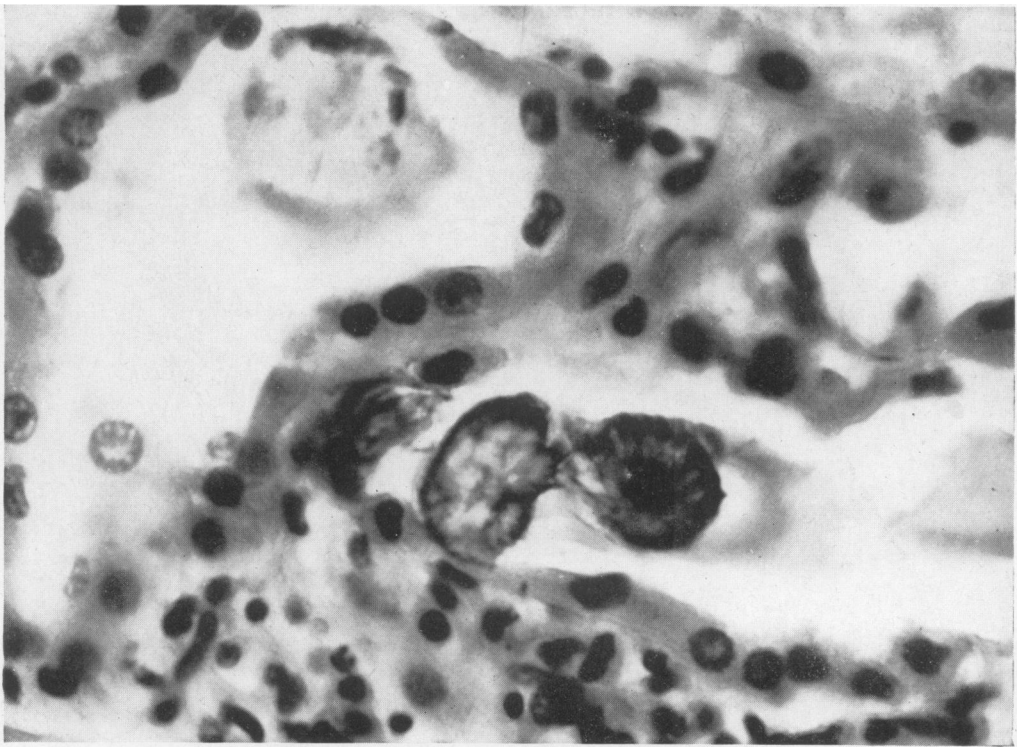
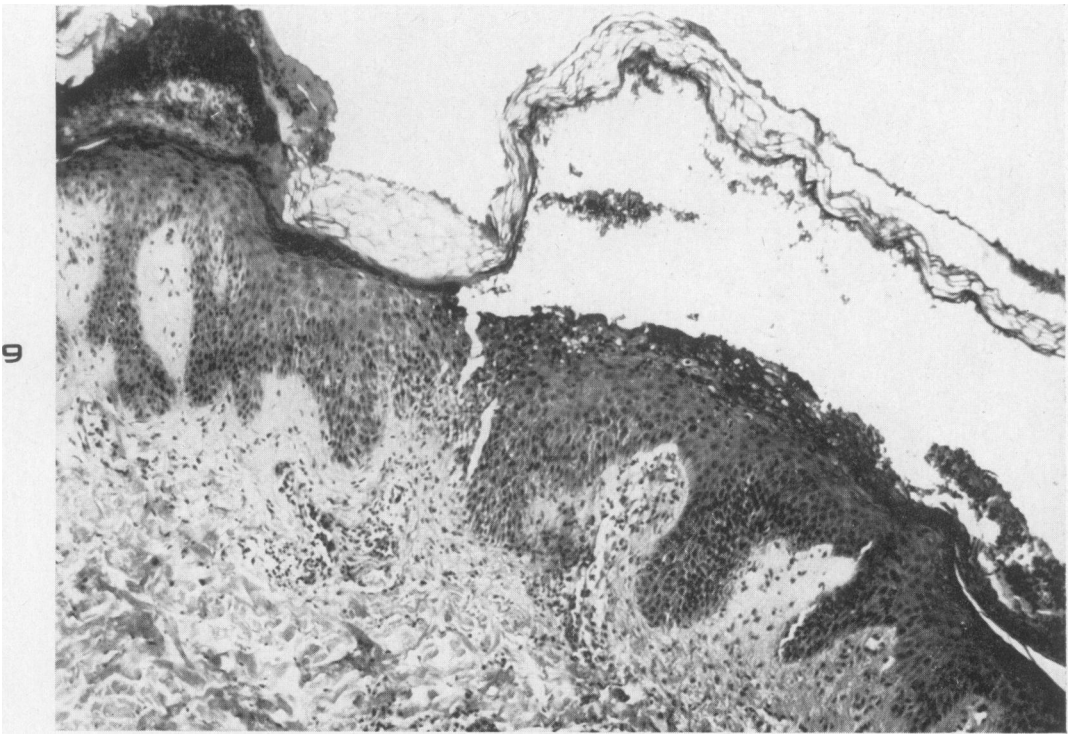


French Histopathologic Changes with Sulfonamides

PLATE 135

FIG. 9. Dermatitis with vesiculation in the superficial epidermis, resembling erythema multiforme and accompanied by a slight infiltration of acidophilic histiocytes in the dermis. × 96. A.I.P. neg. 79044.

FIG. 10. Granulomatous focus in the subcutaneous adipose tissue of the type of erythema nodosum. The paravascular character of the infiltration is evident here as elsewhere. × 120. A.I.P. neg. 79038.



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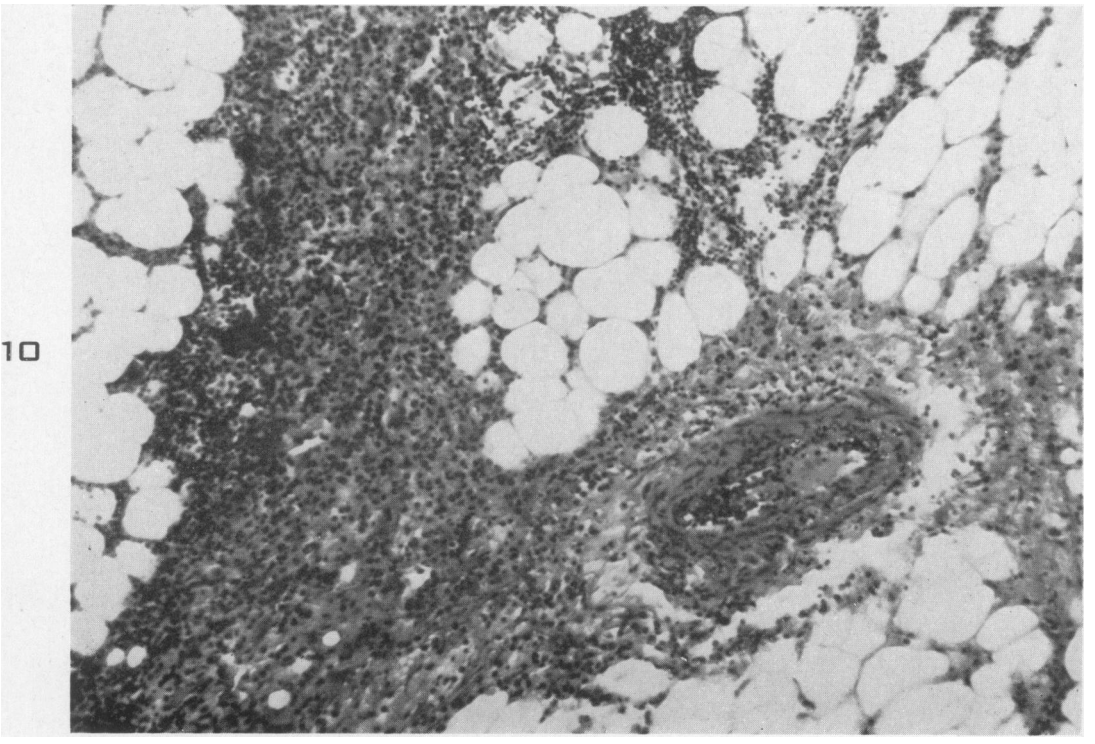

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PLATE 136

FIG. 11. Acidophilic histiocytes infiltrate the interstitial tissues of the testis and are readily distinguishable from the larger interstitial cells of Leydig. The adjacent germinal epithelium shows active maturation. × 1000. A.I.P. neg. 79037.

FIG. 12. Small foci of necrosis are indicated in this area from the spleen by the chromatin dust which is present. Lymphocytes are decreased in the areas showing necrosis, and acidophilic histiocytes are abundant. × 350. A.I.P. neg. 79046.

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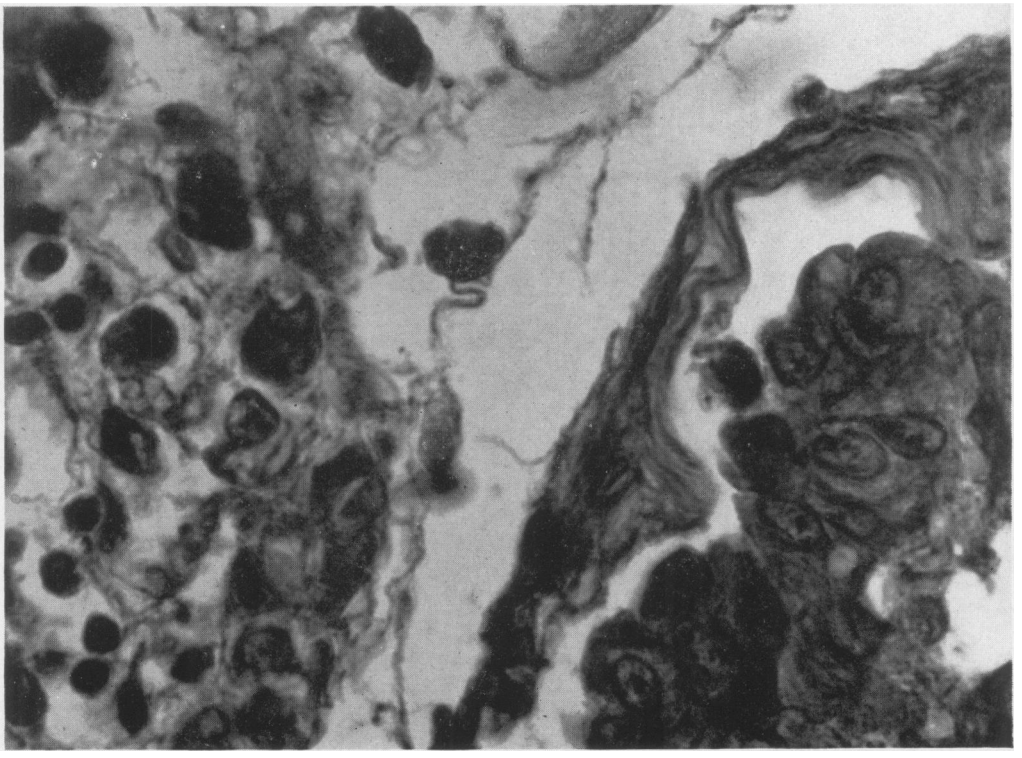

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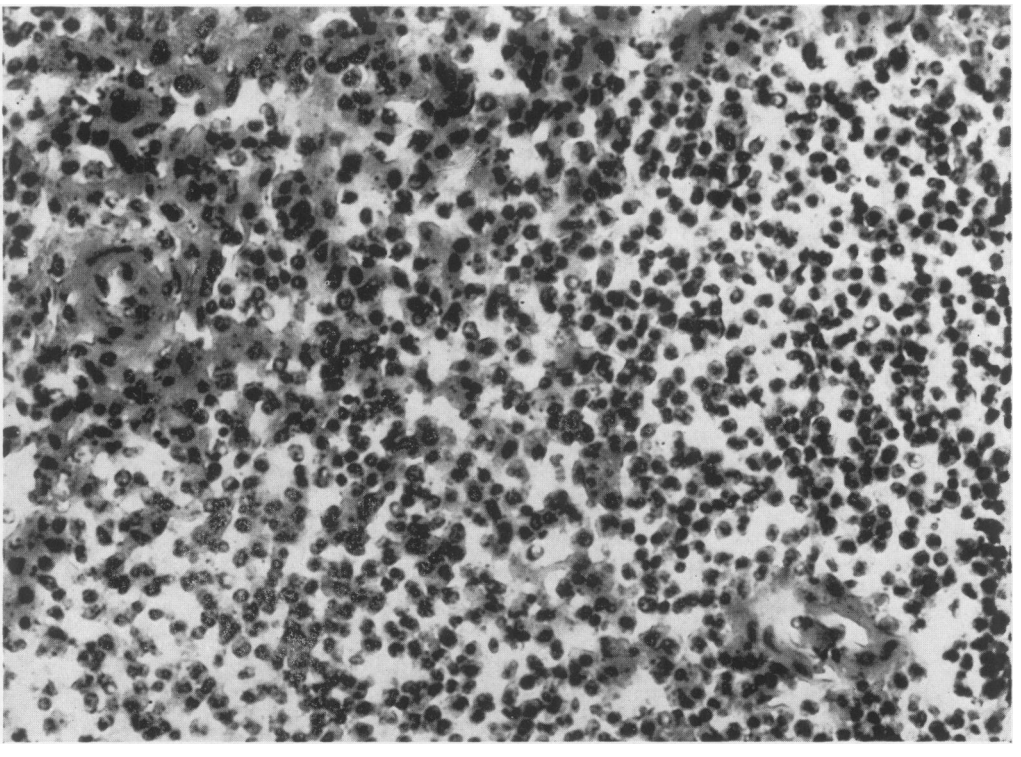

French Histopathologic Changes with Sulfonamides

PLATE 137

FIG. 13. Focal necrosis in a lymph node, with hyperplastic reticulo-endothelial cells. Acidophilic histiocytes are striking components of the cellular infiltration in the necrosed areas. × 350. A.I.P. neg. 79043.

FIG. 14. A paravascular focus in the wall of the gallbladder which is granulomatous and resembles the lesions of periarteritis nodosa. The predominant cell is the acidophilic histiocyte. × 330. A.I.P. neg. 79130.

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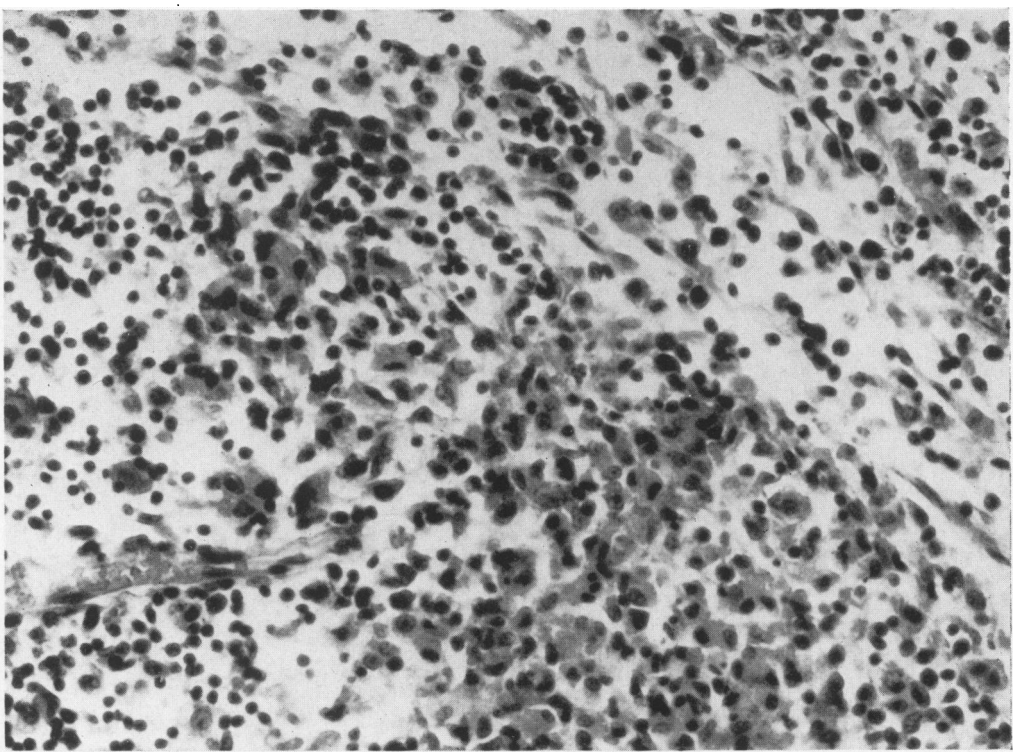

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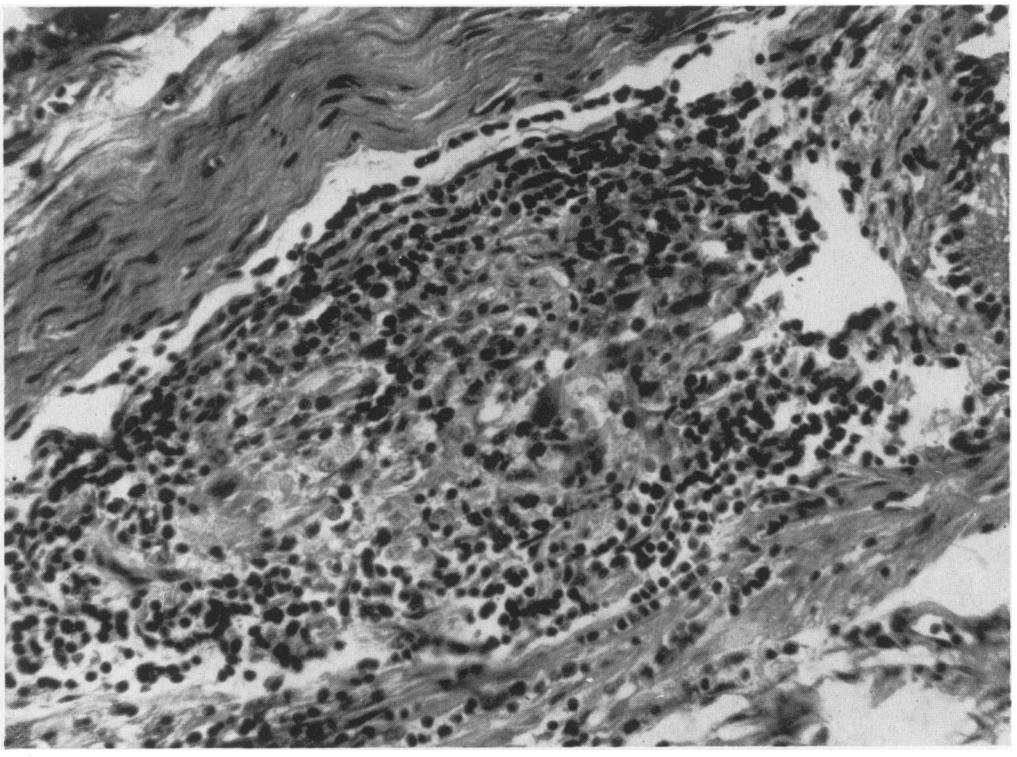

French Histopathologic Changes with Sulfonamides