INFECTIOUS MONONUCLEOSIS
An Autopsy Report *

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Infectious mononucleosis has come to be regarded as a fairly common disease, occurring sporadically or in small epidemics. The mortality from the disease has been almost negligible, with a resulting paucity of material for histopathologic study. The only previously reported case which was autopsied was that of Ziegler,[1] in which the patient died of a ruptured spleen in the fourth week. In this paper we wish to report the autopsy findings of a case of infectious mononucleosis in which the patient died accidentally in an airplane crash about 1 month after the onset of the acute illness.

The clinical entity of glandular fever was described by Pfeiffer [2] in 1889. In 1920 Sprunt and Evans [3] described "infectious mononucleosis," which a year later was shown to be identical with glandular fever by Tidy and Morley.[4] The heterophil or sheep cell agglutination was described by Paul and Bunnell [5] in 1932. This test, plus the description of the characteristic hematologic findings by Osgood,[6] Kracke and Garver,[7] and Downey and Stasney,[8] made possible accurate, objective laboratory diagnosis of infectious mononucleosis. The widespread use of these laboratory procedures, especially in the Armed Forces in which almost all patients with upper respiratory infections are hospitalized, has brought to light many cases of infectious mononucleosis which would ordinarily remain undiagnosed, and has led to the realization that it is a much more common disease than is generally appreciated.

The clinical features of infectious mononucleosis are protean, and the severity of the disease is extremely variable. The more common clinical picture includes fever, malaise, headache, sore throat, lymphadenopathy, splenomegaly, skin lesions, hepatomegaly, and gastrointestinal complaints. Jaundice during infectious mononucleosis has been observed in 3 to 5 per cent of cases. Involvement of the central nervous system associated with abnormalities in the spinal fluid has been reported by Epstein and Dameshek,[9] Thelander and Shaw,[10] and Landes, Reich, and Perlow.[11] Myocardial changes during acute infectious mononucleosis have been noted by Candel and Wheelock [12]

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who reported a case with electrocardiographic evidence of acute myocarditis, and by Logue and Hanson [13] who reported a case with first degree heart block.

The reason for the wide diversity of clinical manifestations becomes readily apparent from the autopsy report of Ziegler [1] and from the case to be described below. Infectious mononucleosis is a generalized disease with organic changes, as evidenced by cellular infiltration in almost every organ in the body. The clinical picture is the composite of the changes wrought in the affected organs, and will vary in type and severity with the organ system predominantly involved. The lymph nodes, spleen, and nasopharyngeal tissues appear to be the more usual sites of involvement, but changes can occur in the lungs, liver, kidneys, skin, heart, testes, adrenals, brain, and probably in other organs; and thus account for the occasional atypical or unusual cases.

The cause of the disease is still uncertain. The concept that "Bacillus monocytogenes" is the etiologic agent is no longer tenable. The general opinion is that the etiologic agent is probably a virus, although no specific virus has as yet been isolated.

The histologic features of infectious mononucleosis have been studied from surgical material and that taken for biopsy. Sprunt and Evans [3] stated that the histopathologic picture was not distinctive and may suggest one of the lymphomas. Fox,[14] in 1927, studied a tonsil and cervical lymph node and concluded that they showed nothing specific—only hyperplasia of the lymphoid elements with retention of the normal architecture. Pratt,[15] in 1931, reported the findings in two biopsies of cervical lymph nodes removed from himself a year apart; and found marked reticulo-endothelial hyperplasia in the first specimen. The second showed a similar but less marked hyperplasia, with some fibrosis. Downey and Stasney [16] studied lymph nodes from 8 cases of infectious mononucleosis taken at various stages of the disease. They noted extreme hyperplasia of both the lymphocytes and the reticulum, but never complete obliteration of the nodal architecture. They also concluded from imprint studies that the atypical lymphocytes present in the peripheral blood had their origin in the nodes. Gall and Stout,[17] in 1940, studied lymph nodes removed from 10 patients, and described a morphologic pattern which they considered characteristic of the disease. They emphasized again that the nodal architecture was preserved, although it was distorted in some cases. They described three predominant features which distinguished infectious mononucleosis from ordinary hyperplasia: first, marked proliferative activity in the pulp which tended to obscure the margins of the follicles; second, focal proliferative activity of the clasmatocytes, which simulated "epithe-

lioid cells" and formed small nodules (no necrosis or giant cells were ever noted); and third, the presence in the nodes of many "infectious mononucleosis cells." These cells they described as large, with "abundant, slightly foamy, cerulean blue cytoplasm," identical on imprint preparation and supravital staining with the characteristic cells found in the circulating blood. These cells they considered almost pathognomonic of the disease, and seen best with Zenker's fixation and the phloxine-methylene blue stain. King,[18] in 1941, reported a case of spontaneous rupture of the spleen in infectious mononucleosis. Microscopic study of the spleen and appendix removed at laparotomy revealed nothing distinctive. Straus,[19] in 1942, reported a case in which an appendix, removed during acute infectious mononucleosis, showed morphologic changes in the lymphoid tissue identical with those seen in a lymph node removed at the same time, and similar to those described by Downey and Stasney, and Gall and Stout. Darley, Black, Smith, and Good [20] reported spontaneous rupture of the spleen in infectious mononucleosis. Examination of the spleen revealed an increase in lymphoid elements and the presence of an atypical cell similar to the characteristic lymphocytes found in the peripheral blood. An additional case of traumatic rupture of the spleen was reported by Milne.[21] The preliminary microscopic diagnosis was Hodgkin's disease, but further study revealed infectious mononucleosis.

Ziegler,[1] in his report of a fatal case with autopsy, described changes in the liver, kidneys, lungs, and spleen. The lesions in the liver, kidneys, and lungs consisted of focal infiltrations of mononuclear cells, with reticulocyte proliferation and necrosis. The changes in the spleen were more diffuse than focal in character.

Report of Case *

H. S., a white, American Army Air Forces pilot, 23 years old, was admitted to a small station dispensary on about May 11, 1945, because of malaise and fever. He was kept in bed, given two "sulfa" tablets four times a day, and penicillin for 1 day before being admitted to a station hospital on May 18. He had previously been in excellent health and physical condition. Family history and previous personal history were not significant. He had had no serious illness or injury.

At the time of admission to the station hospital he was complaining of headache, and was febrile. There was no cough. Physical examination was negative. The skin was clear, and there was no significant glandular enlargement. The lungs were clear; the heart, normal. There were no signs of disease of the nervous system. Blood taken at the time of admission showed a red cell count of 4,500,000; hemoglobin, 80 per cent (Sahli); 11,450 white blood cells with 14 per cent neutrophils, 77 per cent lymphocytes, 9 per cent monocytes. The urine was negative.

A roentgenogram of the chest taken on the day after admission showed a definite increase in the vascular and peribronchial markings on the right side. The hilar

* The clinical record was obtained through the courtesy of Capt. William C. Weir, M.C.

markings were also increased in prominence. In the lower aspect of the right lung an early peribronchial infiltration was noted. These findings suggested the diagnosis of primary atypical pneumonia.

Blood taken on May 22, 4 days after admission and about 11 days after the onset of the illness, showed a heterophil antibody titer of 1:896. On May 25, he complained of sore throat, was found to have a red and edematous pharynx, and was given 50,000 units of penicillin with marked improvement in the following 2 days. He was asymptomatic and afebrile after May 27.

On May 28, the white blood cell count was 10,000, with 30 per cent neutrophils and 61 per cent lymphocytes. A further report (undated) gave a differential count of 13 per cent neutrophils, 83 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils, with the remark that the lymphocytes were atypical and characteristic of infectious mononucleosis. The heterophil antibody test was repeated on May 28, and the titer was again found to be 1:896.

Roentgenograms of the lungs on May 31 showed no abnormalities. The patient was discharged to duty on June 1. On June 10, approximately 1 month from the onset of illness, and 2 weeks after the remission of clinical symptoms, he crashed while piloting an airplane, and was dead when pulled from the plane a few minutes later. Autopsy was performed 30 hours after death.

AUTOPSY FINDINGS

The gross findings were essentially those of severe trauma. There were multiple fractures of the skull and facial bones, and compound fractures of the left femur and right hand. There was a moderate amount of subdural and subarachnoid hemorrhage, and occasional petechial hemorrhages were present in the brain substance. There was also extensive pulmonary hemorrhage. The liver, spleen, kidneys, and remaining viscera were of normal size and weight, and showed no gross abnormalities, with the exception of the retroperitoneal and hilar lymph nodes, which were discrete and grossly enlarged, measuring up to 3 cm. in greatest dimension.

Microscopic Examination

All tissues except the brain were fixed in Zenker's solution; the brain was fixed in 10 per cent formalin. All sections were stained with hematoxylin and eosin.

Liver. The liver parenchyma was studded with small, discrete, focal areas of cellular infiltration (Figs. 1 and 2). Many of these infiltrates were perilobular in distribution, but just as many were scattered through the lobules with no characteristic localization. The cellular infiltrations consisted almost exclusively of rather large mononuclear cells, with oval or rounded nuclei, a few of which were reniform. Varying numbers of lymphocytes, and an occasional neutrophil, were present. Definite vacuolization of the cytoplasm of the mononuclear cells could not be made out. In the areas of infiltration the liver cells had mostly disappeared. The liver cells immediately surrounding these areas showed some degree of atrophy and no evidence of regeneration.

Kidney. Scattered throughout the renal cortex and medulla were many small, focal areas of mononuclear infiltration similar to those described above. There were atrophy, degeneration, and disappearance of the tubules in some of these areas (Fig. 4).

Heart. The heart showed a few interstitial collections of mononuclear cells and lymphocytes (Fig. 5). These collections were small to moderate in size. There was no atrophy or replacement of the muscle fibers.

Lung. There were many red blood cells, considerable edema fluid, and the usual numbers of "heart lesion" cells in the alveoli and bronchi. Many nodular collections of mononuclear cells and lymphocytes, similar to those previously described, were seen (Fig. 3). These were in relation to bronchi and blood vessels, and often within the interstitial tissues. Anthracotic pigment was present in the usual quantities in the peribronchial lymphoid tissue, but was not present in the nodules.

Testis. A moderate number of focal collections of mononuclear cells were seen within the interstitial tissue of the testis and the tunica albuginea (Fig. 6). These were quite large and were morphologically similar to those previously described. Spermatogenesis and the cells of Leydig were within normal limits.

Adrenal. There were a few foci of mononuclear infiltration present chiefly in the adrenal medulla, occasionally in the cortex and capsule (Fig. 7). These were not too unlike the lymphoid collections often found in this organ, and may not have been the result of infectious mononucleosis.

Brain. An occasional blood vessel in the cerebral cortex showed heavy cuffing of mononuclear cells, mostly lymphocytes (Fig. 8).

Spleen. The splenic architecture, follicles, and pulp were essentially normal. Moderate numbers of eosinophils were present, consistent with the sudden death. The sinusoids were prominent, and there was some proliferation of reticulo-endothelial cells.

Lymph Nodes. The nodal architecture was preserved. The sinusoids were unusually prominent, but aside from a moderate degree of hyperplasia of the reticulo-endothelial cells there was no striking abnormality.

Other Organs. Sections of aorta, pancreas, esophagus, pylorus, jejunum, ileum, appendix, urinary bladder, prostate, diaphragm, thymus, pituitary body, and costal bone marrow showed no abnormalities except for post-mortem autolytic changes. However, it is possible that if larger amounts of tissue had been preserved and more sections taken for study, additional foci of cellular infiltration might have been encountered.

Comment

This patient had clinical infectious mononucleosis 2 to 4 weeks prior to death. The diagnosis was established beyond reasonable doubt by the clinical picture, hematologic findings, and the strongly positive heterophil antibody test on two separate occasions. It is therefore logical to assume that the microscopic lesions noted are those of a late stage of infectious mononucleosis. They are very similar in type and distribution to the visceral lesions described by Ziegler.[1] Unfortunately, the body was not obtained for autopsy until 30 hours after death, and had not been refrigerated during relatively hot weather. The tissue changes which ensued obscured the precise histologic details of the lesions. In addition, infectious mononucleosis was not suspected at the time of autopsy, and it was not until several weeks later that the clinical record was obtained. Had we been aware that the patient had just recovered from acute infectious mononucleosis, more careful search for lymph nodes would have been made, and special studies, such as imprint smears and supravital stains, would have been attempted.

This case emphasizes again the basic concept suggested by Ziegler [1] and others that infectious mononucleosis is a generalized disease, with lesions in many, and possibly all, organs of the body. The lesion consists essentially of a focal infiltration of mononuclear cells, including variable numbers of small lymphocytes, which in some cases crowds out and replaces the normal parenchyma. No evidence of fibrosis of the lesions was noted. It may be that the mononuclear cells are identical with the atypical lymphocytes seen in the peripheral blood and described by Gall and Stout [17] in affected lymph nodes, but we could not ascertain this from our sections.

Focal microscopic infiltrations were seen in the liver, kidneys, heart, lungs, testes, adrenals, and brain. The lesions in the adrenals are somewhat questionable, as similar collections of lymphoid tissue are frequently encountered in this organ. It is quite remarkable that the lymph nodes and spleen, which are usually most profoundly affected in infectious mononucleosis, were in this case relatively uninvolved. It is possible that in this particular case these organs were less involved than usual, or that they returned to normal more rapidly than other tissues.

The lungs are of considerable interest in this case. On the basis of the roentgenologic evidence, a tentative diagnosis of "primary atypical pneumonia, etiology unknown" was made—the nomenclature used in the Army to label so-called "virus" pneumonia. Since this patient did have definite clinical infectious mononucleosis at the time the roent-

genogram was made, it is possible that the nodular infiltrations in the lungs were those of infectious mononucleosis, rather than of a less likely co-existing independent disease involving the respiratory tract. It may very well be that infectious mononucleosis can produce a clinical and radiographic picture simulating "virus" pneumonia, as has been suggested by Halcrow, Owen, and Rodger.[22]

The brain in this case presented the first opportunity, to our knowledge, to study sections of the central nervous system in infectious mononucleosis. As mentioned previously, clinical involvement of the central nervous system, with spinal fluid changes, has been reported several times. Histologic study of the brain in this case, which had no clinical symptoms referable directly to organic changes in the central nervous system, revealed a few blood vessels, chiefly in the cortex, with perivascular infiltrations of lymphoid tissue. The histologic picture was similar to that seen in mild virus encephalitis. It thus appears likely that the central nervous system shares with the other viscera the generalized involvement in infectious mononucleosis.

Histologic changes in the heart in infectious mononucleosis have not been described previously, but have been postulated on the basis of electrocardiographic findings. The interstitial infiltrations seen in the heart in this case are compatible with conduction changes demonstrable by electrocardiograms, assuming that the infiltrations may occur in any part of the cardiac muscle and may involve important conduction fibers.

The presence of microscopic infiltrations in the liver and kidneys furnishes the organic background to explain those occasional cases of infectious mononucleosis in which "hepatitis" or "nephritis" dominates the clinical picture. It is probable, due to the diffuse nature of the disease, that these organs are involved to some degree in almost every case, although rarely with sufficient alteration of function to be clinically detectable.

SUMMARY

Necropsy was done in a case of infectious mononucleosis, in which the patient had died 2 to 4 weeks after the acute illness as a result of an accident. Focal cellular infiltrations, similar to those previously described in infectious mononucleosis, were found in the liver, kidneys, heart, lungs, adrenals, testes, and brain. Cerebral and cardiac lesions, not previously described, were found.

This case emphasizes again that infectious mononucleosis is a generalized disease, and may produce organic changes in many viscera, thus explaining the wide diversity of clinical manifestations which are encountered.

It is suggested that infectious mononucleosis may produce a clinical and radiographic picture simulating "primary atypical pneumonia."

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[*Illustrations follow*]

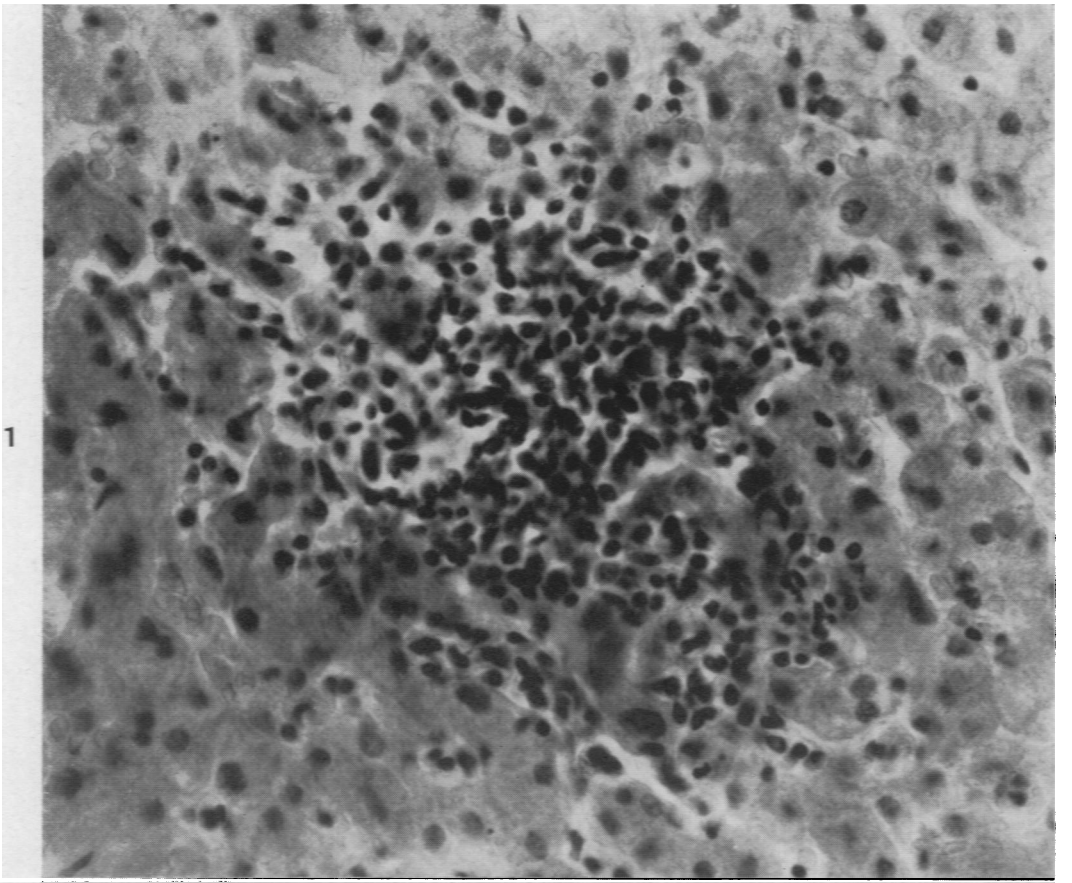
DESCRIPTION OF PLATES

PLATE 77

All sections were stained with hematoxylin and eosin. × 120 except for Figure 1.

FIG. 1. Liver, high power. Focal mononuclear infiltration, with replacement of liver cells. × 450.

FIG. 2. Liver, low power. Focal collections of mononuclear cells.



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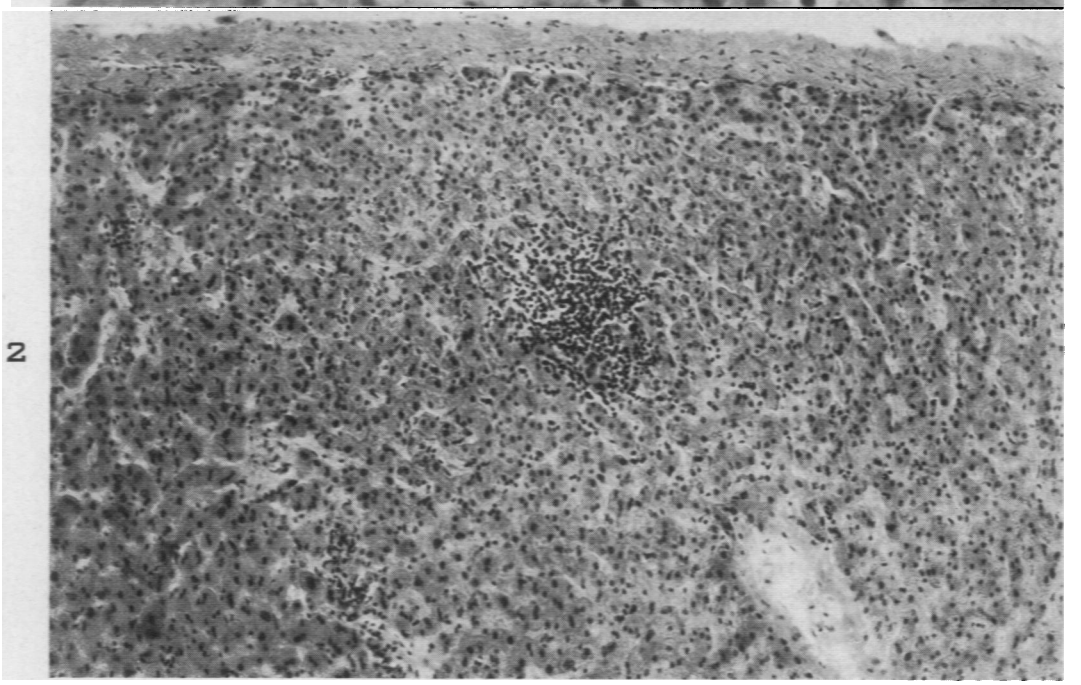

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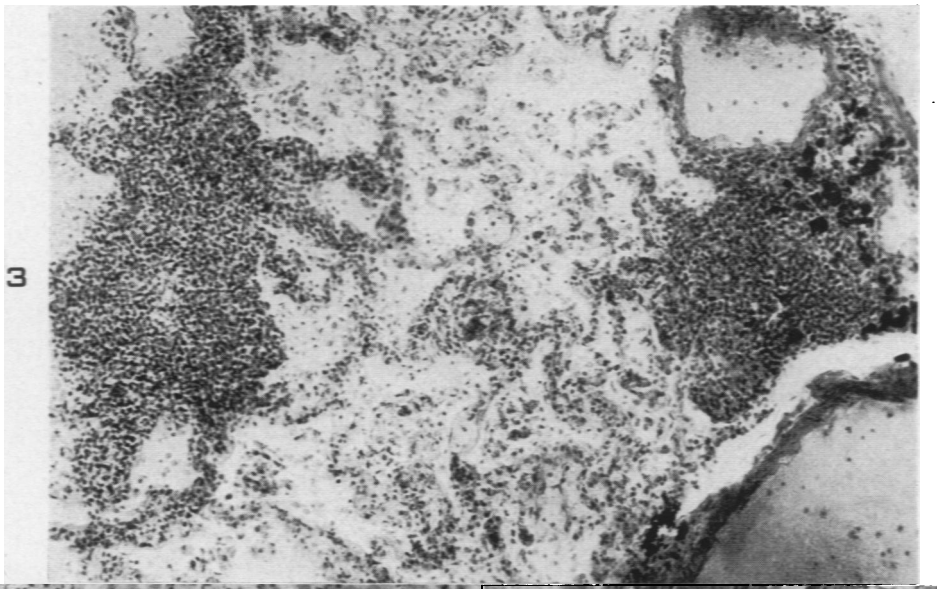
PLATE 78

FIG. 3. Lung, low power. Nodular perivascular and interstitial infiltrations of mononuclear cells.

FIG. 4. Kidney, low power. Mononuclear infiltrate in the cortex, with atrophy and replacement of the renal tubules.

FIG. 5. Heart, low power. Interstitial infiltration of mononuclear cells.



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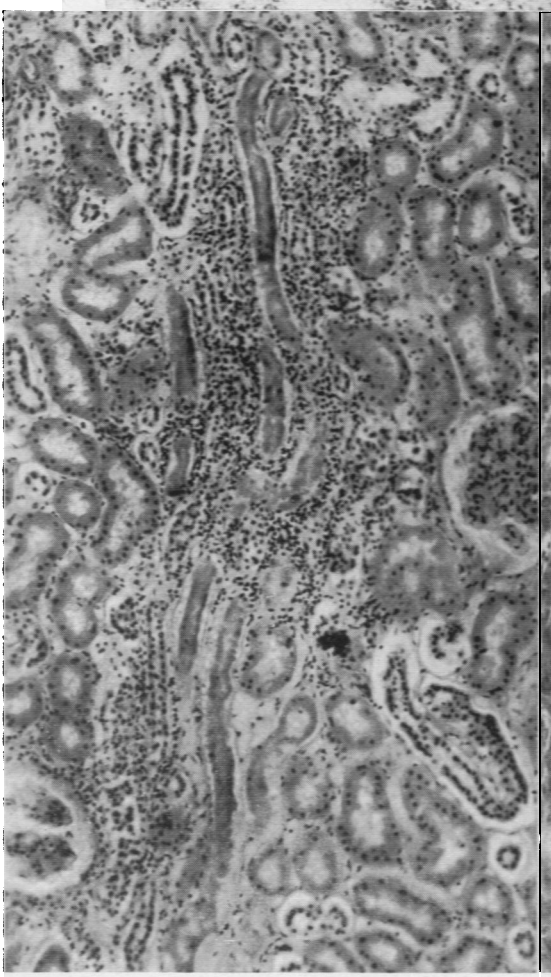

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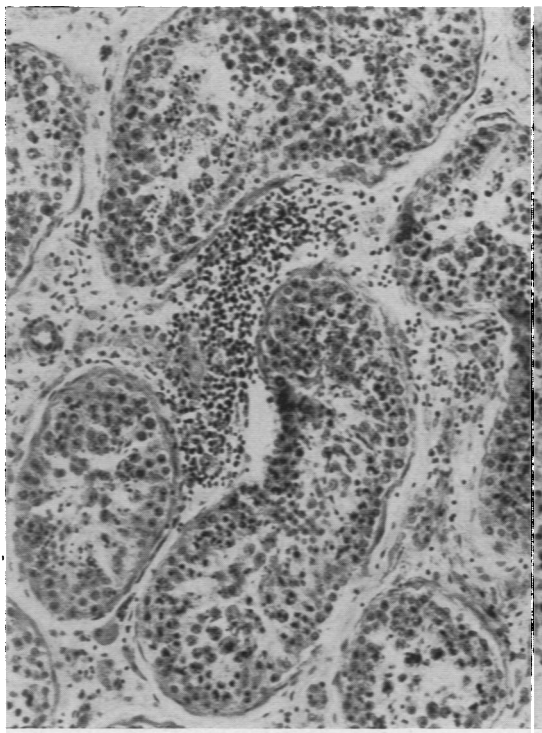
PLATE 79

FIG. 6. Testis, low power. Focal interstitial infiltration of mononuclear cells.

FIG. 7. Adrenal, low power. Focal infiltration of mononuclear cells in medulla.

FIG. 8. Brain, low power. Cortical vessel with perivascular cuff of mononuclear cells.



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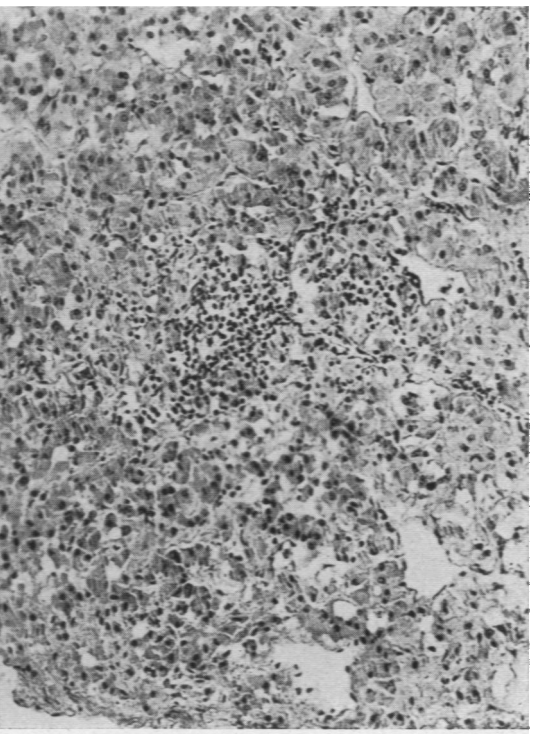

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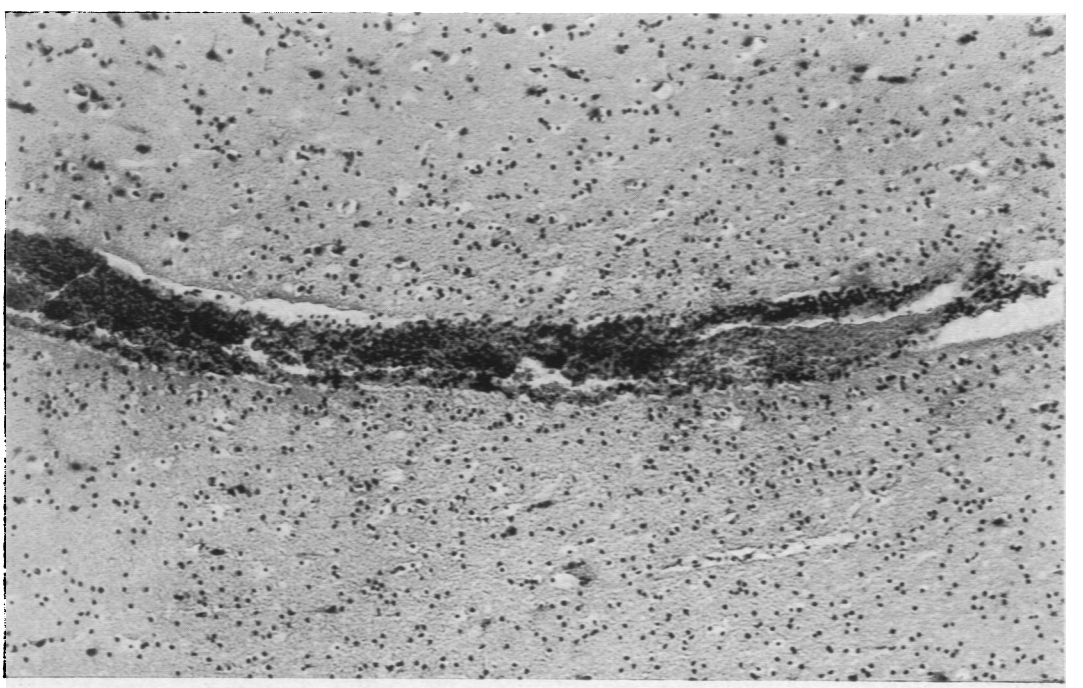

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