# THE LESIONS OF LEAD ENCEPHALITIS IN CHILDREN

S. S. BLACKMAN, JR.

*From the Department of Pathology, The Johns Hopkins University, Baltimore, Md.*

Submitted for publication February 10, 1937

CONTENTS

1. Review ..... 1
2. The Clinical Characteristics in 22 Cases ..... 4
3. The Anatomical Material Examined ..... 8
4. The Gross Appearance of the Brain ..... 9
5. Plasma Protein in Exudate which Escapes from the Brain into the Fixing Fluid ..... 10
6. The Microscopical Lesions in the Cerebral Hemispheres ..... 11
   a. The Blood Vessels ..... 11
   b. Fresh Serous Exudate Coagulated by the Fixing Fluid ..... 13
   c. Inspissated Exudate Congulated in the Tissues about the Capillaries ..... 14
   d. Old Exudate and Old Vascular Lesions which Contain Iron and Basophilic Material Resembling Calcium ..... 15
   e. The Effect of Exudate Coagulated in the Tissue, and of Exudate Lost in the Fixative, on the Architecture of the Brain ..... 16
   f. The Neuroglia ..... 18
   g. The Nerve Cells ..... 20
   h. Foci of Necrosis ..... 21
   i. Hemorrhages ..... 22
7. The Cerebellum ..... 22
8. The Basal Nuclei, Mesencephalon, Pons, Medulla, and Spinal Cord ..... 25
9. The Meninges, Choroid Plexus, Retina and Optic Nerves, Pineal Gland, and Hypophysis ..... 29
10. Persistent Lesions and Functional Disturbances ..... 32
11. On the Pathogenesis of the Vascular Changes and the Exudate ..... 33
12. Summary ..... 34
13. Appendix I. Useful Stains for the Demonstration of Coagulated Serous Exudate in the Brain ..... 37
14. Appendix II. Case Reports ..... 38
15. References ..... 42
16. Illustrations ..... 44

## REVIEW

We are told that the clinical effects of lead poisoning on the brain were known to the ancients long before search for microscopical lesions was possible (1). The French writers, Grisolle and Tanquerel des Planches, are said to have given the first good clinical descriptions of lead encephalitis, written nearly a hundred years

ago (2, 3), and now it is familiar to all that young children with depraved appetite, or pica, may swallow plaster or chew paint from furniture, window sills, dolls and toys, and so develop symptoms of lead poisoning over a period of weeks or even months. Children, like lead workers, may develop abdominal pain, constipation and vomiting. Anaemia and basophilic stippling of red blood cells frequently develop, and sometimes a lead line appears on the gums. The urine contains not more than a good trace of protein usually, and in some instances glycosuria has been found (4). As the disease progresses the child becomes irritable and cantankerous, and finally stuporous. Visual disturbances, oedema of optic discs, elevation of blood pressure, and slow pulse may be observed. Projectile vomiting commonly occurs and convulsions generally appear for one or more days before death.

When convulsions set in, it is usually found that the pressure of the spinal fluid is increased; and the fluid contains increased quantities of protein, a few cells, and is sometimes xanthochromic (43). Lead may be demonstrated in the blood in abnormal quantity, and it was shown by Park (5) and by Vogt (6) that a curious disturbance in bone formation develops. The x-ray shows a dense shadow along the line of ossification where lead is deposited in the growing spicules of bone. The latter are found under the microscope to be more numerous than usual, and ossification is retarded. There are, too, characteristic intranuclear inclusion bodies in the kidney and liver (7).

As long ago as 1839 it was possible for Tanquerel des Planches to collect records of examinations of the brain in seventy-one instances of lead poisoning, although characteristic changes were not found to be common to all cases (8).[1] For a century the remarkably varied clinical manifestations of lead encephalitis have been recognized, and they are now perfectly familiar (2, 9). Nevertheless, examination of recent reviews on the subject and of modern textbooks of neurology and pathology shows that as yet no precise pathological lesions in the brain, responsible for the signs and symptoms, have been established as characteristic of lead poisoning (2, 10); and in a very recent monograph concerned with the clinical, anatomical and spectrographic study of the nervous system in acute metallic poisoning, Esser states that information is lacking concerning the changes caused by lead in the central nervous system of man (11).

The wide clinical interest aroused in recent years by the occurrence of acute lead encephalitis in children (12, 13, 14, 15, 16, 17, 18, 19), has been accompanied by few corresponding anatomical studies. The opportunity has lately been afforded to make systematic microscopical examination of the brain in a large series of cases which show an astonishing variety and number of lesions. Similar changes have not been described in any other disease of the central nervous system, and since they appear to be characteristic of lead poisoning, it seems

[1] No lesions were seen in some cases. Yellow discoloration was found in some, and in still others the brain was enlarged or atrophied.

worthwhile once more to review some of the literature devoted to the subject and to describe the characteristic lesions at some length.

In 1888 Westphal reviewed the cases which had been reported (3), and stated that Kussmaul and Maier in 1872 were the first to make histological examination of the brain in lead encephalitis. They examined one case and found wide homogeneous areas around blood vessels in the gray matter, interpreted as increased perivascular connective tissue (20). Von Monakow reported a case in 1879 which showed gross atrophy of the brain, and widening of the adventitial space about blood vessels, together with multiplication of nuclei, collections of cells, fat droplets and pigment. He also described hyperplasia of neuroglia, many minute haemorrhages in the white matter, and numerous abnormal ganglion cells (21). In Seifert's case, reported in 1884, the brain was atrophied and the basilar artery was sclerotic. There was abundant fluid in the subarachnoid spaces and two small gross haemorrhages were found in the brain (22). Likewise Oppenheim, describing one case in 1885, found gross cerebral haemorrhages in a patient with hemiplegia (23). Westphal could find only a small haemorrhage in the left uncinate gyrus of one case and in another several areas of softening together with sclerosis of blood vessels. He assumed that lead caused fine histological changes which could not be detected by the methods then available, though he himself made no microscopical examinations (3).

Following Westphal in 1900 Courtney reported another case with gross cerebral haemorrhages occurring in an adult (24), and in 1912 Cadwalader found a large cerebral haemorrhage in his case, without mention of the cerebral arteries. He described thickening of meninges, increased neuroglia in the cortex and chromatolysis of the Betz cells (25).

Three cases were studied microscopically and reported in 1921 by Hassin (26). Slight changes in nerve cells were found, such as fat accumulation and chromatolysis, and proliferation of endothelial cells, adventitial cells, and of new blood capillaries. Glial cells in excess along blood vessels in the cerebral cortex and cerebellum were found, and thickening of the meninges. There was some infiltration of the meninges with lymphoid cells, and granules of green pigment were found in the brain.

The whole subject of lead poisoning was reviewed at length in 1925 by Aub, Fairhall, Minot and Reznikoff who pointed out the discrepancy between the well-known clinical manifestations and the meagre anatomical findings which had so far been described in the literature (2). Changes in the spinal fluid, the presence of cells, high pressure and increased quantities of protein, were reported in several papers between 1905 and 1924; and on this basis, without examination of the brain, Suzuki and Kaneko speak of serous meningitis in children, caused by lead poisoning acquired from white powders used by Japanese mothers as a cosmetic for the skin (17). From consideration of the changes in the spinal fluid and the histological lesions reported by Hassin it was suggested in the review of Aub, Fairhall, Minot and Reznikoff, that "in so-called lead encephalopathy the meninges are primarily involved, or in other words that the disease is really a meningo-

pathy". They concluded that further information concerning the action of lead on the tissues was not possible from postmortem studies, since its action was apparently too subtle to yield to this type of investigation.

Between the years 1928 and 1934, however, several papers appeared describing new lesions which were found by independent observers. Freifeld reported two cases, lead workers, one in 1928 and one in 1933, showing focal destruction of nerve cells replaced by neuroglia in the cerebral cortex, basal ganglia and pons. She found extraordinary destruction of Purkinje cells in the cerebellum, associated in some areas with new growth of glia. Lesions in the dentate nuclei and thrombi in small vessels were described, in some instances leading to necrosis of tissue. Small perivascular calcium deposits and granules of brown pigment in phagocytic cells were found, and there were perivascular haemorrhages in all parts of the brain. She expressed the opinion that all of the lesions were dependent on vascular damage (27, 28).

In 1929 Tuthill also described focal scars of neuroglia (glial rosettes) in the cortex, basal ganglia, and cerebellum of an infant, and she too saw extensive destruction of Purkinje cells in the cerebellum and gliosis of the molecular layer (29). Scattered minute haemorrhages were found and Tuthill described for the first time lesions which were called concretions. These were scattered in many parts of the brain and cerebellum, and in the walls of blood vessels. They varied in size from small globules to large masses 100 micra in diameter, stained with basic dyes and contained iron. They were thought to be "albuminoid break-down products." It is significant that the patient, a child of 2½ years, after an initial attack of encephalitis, was free from symptoms for about two months before manifestations reappeared and death occurred.

Staemler reported a case in 1929 which he says was essentially like the first case of Freifeld (30), and in 1933 McKhann and Vogt, from consideration of the clinical signs and symptoms, suggested that they might depend on increased intracranial pressure due to intense cerebral oedema (9).

Four more cases, occurring in lead workers, were described in 1933 by Winkelman and Eckel who found lesions in the capillaries, numerous focal lesions in the gray matter of the cerebral cortex, and mentioned the presence of granular perivascular material as evidence of cerebral oedema (31).

The next year, in 1934, Rhea reported a single case in which he saw multiplication of cells in the walls of capillaries and free fluid microscopically in the meninges (32). The conspicuous appearance of the blood vessel in the brain, interpreted by some authors in the past as newly formed growing vessels (26) appeared to Rhea to depend merely on dilatation, and there were a few disseminated microscopical haemorrhages.

## THE CLINICAL CHARACTERISTICS IN TWENTY-TWO CASES

Twenty-two cases are described here, all occurring in children. The evidence of lead poisoning is clear in each instance and is shown

in Table I. Most of the cases occurred in colored infants between 13 months and 3½ years of age. One was in a boy of seven, however, and one in a girl of 6 years. Five were white children.

In most cases lead was ingested by nibbling painted articles, usually furniture. Paint may be swallowed in this manner for many months (5 to 18 months in this series) before the onset of neurological disturbances. In one case lead fumes were inhaled from old automobile battery casings burned in the cook-stove. For a period of 3 years after the original convulsions the blood lead remained elevated, and the x-ray showed lead lines in the bones. The child finally died in convulsions and the brain showed both old and fresh lesions, although no evidence could be obtained of exposure to lead fumes or ingestion of lead in the interval. In a second case the first convulsion occurred a month before death, and in a third the child lived for about 6 weeks after the onset of peripheral neuritis. The neurological signs and symptoms were of short duration in the remainder of the cases.

It is curious that 19 of the 22 cases occurred during the five months including June and October, and the tendency of lead encephalitis to appear during the summer and early fall has been mentioned before by Suzuki and Kaneko (17), and by Fukushima and Matsumoto (18), although no explanation was evident.

Complete records of the temperature from the onset of convulsions are not available, but in 21 of the 22 cases fever was present during the stay in the hospital. The temperature was usually irregular and in most cases several degrees of fever were present at times. It would seem from the microscopical sections that the lesions in the brain are sufficient to account for elevation of temperature. There is the possibility, however, discussed in another section of this paper, that fever or the elevated atmospheric temperature of summer and fall may supply the factors which initiate the vascular changes in the brain which in turn are followed by exudate of serous fluid into the tissue.

A marked leucocytosis was observed in most of the cases. The count was 30,000 or above in four of the cases, above 20,000 in eight others, between 10 and 19,000 in seven cases, and normal in two cases. In one case no white count was made, and in a case in the first group there were 58,500 white cells per cu.mm. The degree of leucocytosis

TABLE I

*Evidence of Lead Poisoning*

| AUTOPSY NUMBER | HISTORY OF LEAD INGESTION | LEAD LINE ON GUMS | ANAEMIA | STIPPLED RBC | ELEVATED BLOOD LEAD | LEAD LINE IN BONES | | NUCLEAR INCLUSIONS |
|---|---|---|---|---|---|---|---|---|
| | | | | | | X-ray | Microscopic | Kidney and liver |
| 5940 | Pica | + | + | + | No exam. | No exam. | + | + |
| 7532 | + | 0 | + | + | No exam. | No exam. | + | + |
| 10465 | + | + | + | + | No exam. | No exam. | + | + |
| 10637 | + | 0 | + | + | No exam. | No exam. | + | + |
| 10850 | + | 0 | + | + | No exam. | No exam. | + | + |
| 11766 | + | No exam. | No exam. | No exam. | No exam. | No exam. | + | + |
| 12168 | House paint on hands | 0 | + | + | No exam. | No exam. | + | + |
| 13334 | 0 | + | + | + | Elevated | + | + | + |
| 13698 | + | + | + | 0 | Elevated | + | + | + |
| 13726 | 0 | 0 | + | + | Elevated | + | + | + |
| 13795 | + | 0 | Slight | 0 | Elevated | + | + | + |
| 13830 | + | 0 | + | + | Elevated | + | + | + |
| 14057 | + | + | + | + | Elevated | + | + | + |
| 14287 | Pica | 0 | + | + | Elevated | + | + | + |
| 14307 | + | 0 | + | 0 | Elevated | + | + | + |
| 14336 | + | + | + | 0 | Elevated | + | + | + |
| 14352 | + | 0 | 0 | + | Elevated | + | + | + |
| 14354 | Exposed to lead fumes | + | + | 0 | Elevated | + | + | Few |
| 14370 | Pica | + | + | + | Elevated | + | + | + |
| 14849 | + | 0 | + | + | No exam. | + | + | + |
| 14954 | + | 0 | + | + | Elevated | + | + | + |
| 14974 | Pica | 0 | + | + | ? | + | + | + |

seems out of proportion to the anaemia in many cases, and is not apparently to be correlated with infection. At least no evident infection was discovered at autopsy in many of the cases.

The anaemia which was present in the majority of cases was not very marked, and a reduction of the haemoglobin to 50% or less was found in only eight cases. In sixteen cases basophilic stippling of red blood cells was seen in the smears, and nucleated red cells were recorded in six of the clinical histories.

Characteristic changes were seen in the bones by x-ray in all cases that were examined (15 cases), and were found in microscopical sections in every case. Eosinophilic nuclear inclusion bodies, also typical of lead poisoning, were present in liver and kidneys of all of the cases.

The familiar changes in the spinal fluid—increased pressure, increased protein, and moderate numbers of cells—were found in the present group of cases. The cells in the spinal fluid are usually said to consist chiefly of lymphocytes (42), (13), (2), in lead encephalitis. In this series, as pointed out again later, the majority of the cells in the meninges are "mononuclear" cells, but they originate from the substance of the brain and are forced out into the meshes of the meninges by exudate which distends the molecular layers of the cerebral cortex and cerebellum.

A variety of clinical manifestations appeared in many cases long before the onset of definite neurological signs and symptoms. Malaise, anorexia, loss of weight, abdominal pain, headache and constipation are all familiar. Changes in behavior were noticed in many children. Some were nervous, irritable, fretful and restless. One child was noisy and disobedient, developed enuresis and a tendency to bite and scratch. Long crying spells and screaming fits were described and a tendency to be easily frightened. One child was nervous and cranky.

Vomiting was a common complaint, and was present in twenty of the cases. It was described as projectile in a few cases. In two of the cases vomiting first appeared one to two days before death; in eight cases one to three weeks before convulsion. More often there was a history of vomiting at times for a month or more before the onset of more definite manifestations of encephalitis.

Towards the end drowsiness, stupor and a deep coma appear, usually in association with convulsions. One child fell unconscious on the

street for several minutes, regained consciousness, and later on the same day had convulsions.

Generalized clonic convulsions developed in nearly all cases, but one child showed nothing more than alternate periods of spasticity and flaccidity. In some cases, after attacks of vomiting, the children were described as becoming limp and then comatose.

In most instances the convulsions became generalized and were frequently repeated. At first, however, they were unilateral in some cases, or one side and then the other was affected before the convulsions became generalized. Strabismus and nystagmus were frequently observed in association with convulsions.

The pulse was slow in some cases, rapid and irregular in others. The blood pressure was not studied in general, but was found elevated in a few cases. Respirations were often slow, sometimes irregular, and were described as gasping in some cases.

In two cases there was clinical evidence of peripheral neuritis in addition to encephalitis. The peripheral nerves were not examined at autopsy in one of these, but the other showed widespread peripheral lesions, as described elsewhere (33).

## THE ANATOMICAL MATERIAL EXAMINED

In ten of the cases relatively few sections of the brain and spinal cord have been available for microscopical examination, since at autopsy few (from 2 to 11) blocks of tissue were cut. This number in two instances includes a section of each retina.

Many blocks were prepared, however, from all lobes of the cerebral hemispheres of the twelve cases autopsied in recent years. The number of blocks varied from 30 to 65 in the different cases. In each instance blocks of the cerebellum varying in number from 4 to 11 were cut at autopsy and the corresponding microscopical sections were examined. The basal ganglia, mesencephalon, pons and medulla of the recent cases were examined and sections were made from a number of blocks (table II). One or two blocks were taken from the cervical part of the spinal cord in most cases and in three cases sections from the cervical, thoracic and lumbar portions of the cord were examined microscopically.

In most instances the body was embalmed with the brain *in situ*, the fluid containing about 3 per cent of formalin. After removal the brains were hardened in 10 per cent formalin and blocks were then cut, dehydrated, and embedded in paraffin. In a few cases additional blocks were fixed in Zenker-formol at autopsy after the body was embalmed.

In order to determine whether or not the fluid exudate found microscopically in the brain and the distortion of the normal architecture were influenced by the

embalming and dehydrating processes, the brain was removed before the embalming was begun in three cases (Nos. 17, 18 & 21), and blocks were cut immediately and fixed in 10 per cent formalin; and the blocks from one unembalmed case (No. 18) and from two of the embalmed cases (Nos. 20 & 22) were dehydrated very slowly, beginning with 30% alcohol and increasing the strength of alcohol 10% with each period of dehydration. In these control cases coagulated exudate and abnormal distortion of architecture are found as in the others. The disturbances in the architecture are the result of exudate which escapes into the tissues from damaged blood vessels and is partly dissolved in the fixing fluid. The lesions are described below in detail.

The posterior half of each eye was removed and fixed in Bouin's fluid in five of the cases, and microscopical sections were made showing the retina and optic disc. Blocks of the hypophysis were fixed in Zenker-formol at autopsy in seventeen cases, and the pineal body, usually fixed in formalin, was examined microscopically in eight cases.

## THE GROSS APPEARANCE OF THE BRAIN

It has long been recognized that in acute lead encephalitis associated with convulsions, the brain at autopsy may appear large and soft with broad, flat convolutions, and narrow, obliterated sulci. In some of the cases of Tanquerel des Planches the convolutions were flattened, and the depressions between them had disappeared (8). Traube, in 1870, said that Tanquerel des Planches found the brain to be anaemic and swollen (34), and it is said by McKhann that Chvostek in 1897 described a case with swollen brain, flattened convolutions and medulla pressed into the spinal canal (19). The swollen appearance of the brain has become familiar and, without any clear microscopical descriptions of the tissue, it has been inferred from the external appearance that the brain is oedematous (35, 36). McKhann and Vogt (9) especially have pointed out that the clinical signs of encephalitis may depend on accumulations of fluid in the brain.

In this series of 22 cases it was often but not always recognized at autopsy that the brain was larger and softer than normal. Unusually broad, flattened convolutions, and narrow sulci, more or less obliterated, were described in the protocols in many of the cases. In many instances a well marked pressure cone was recognized at the base of of the cerebellum, like that described by Blackfan (44) in association with acute nephritis in children.

These external changes have been observed in all of the twelve cases

autopsied in the past two years, and in addition certain other manifestations of the presence of fluid in the substance of the brain. The gray matter has been found to be thicker and more translucent than normal and the freshly cut surface of the brain very wet.

The gross specimen may be pale and has frequently been so described in the literature. The external surface may be hyperaemic and inflamed in appearance, however, and this has been observed in a number of the cases. On section, too, minute dilated blood vessels in the white matter have been conspicuous in some cases, and may be difficult to distinguish from punctate haemorrhages. In one case such haemorrhages were very numerous and distinct in the gross specimen, and they were readily recognized because microscopically each haemorrhage forms a ring about a central area of necrotic tissue which is usually associated with a capillary thrombus.

### ON THE PRESENCE OF PLASMA PROTEIN IN EXUDATE WHICH ESCAPES FROM THE BRAIN INTO THE FIXING FLUID

The gross appearance of the brain indicates that it is distended with fluid, and microscopical sections show a part of the fluid coagulated about the blood vessels and far out in the tissue. The exudate is identical in appearance with serum in the blood vessels, and both the serum and fresh exudate are evidently coagulated by the fixing fluid.

A portion of the exudate, however, escapes into the fixing and dehydrating fluids. If several blocks of the unembalmed or freshly embalmed brain are dropped into a small jar of alcohol, the latter, by virtue of its dehydrating action, rapidly withdraws the serous fluid and a milky precipitate forms at once, thus indicating the protein content of the exudate.[1]

Microscopical sections of material thus fixed in alcohol show less of the exudate coagulated in the tissue than is seen in sections of material fixed in formalin. But the latter has an abnormal vacuolated and distorted architecture in many places, indicating that the thinner watery portion of the exudate, poor in coagulable protein, is either slowly dissolved by the formalin or extracted later by the dehydrating fluids.

[1] Blocks of the normal brain produce a faint cloudiness in alcohol.

Staining methods useful for the detection of coagulated serous exudate in the brain are described in Appendix I (p. 37).

## THE MICROSCOPICAL LESIONS IN THE CEREBRAL HEMISPHERES IN ACUTE CASES

On microscopical examination very numerous lesions and a variety of changes are found which affect the blood vessels, the gray matter, and the central white matter of many convolutions. Dilated and narrowed capillaries, necrotic vessels and capillary thrombi, minute haemorrhages, fresh and old serous exudate permeating, stretching and tearing the tissues, small foci of necrosis, fat-laden cells, necrotic cells and other lesions are all present; and the same variety of lesions is found in each case. It is to be emphasized, however, that each type of lesion is not usually seen in every microscopical section, and in some sections few changes may be recognized. All of the lesions are indeed somewhat patchy and irregular in distribution in every case, but examination of many sections shows that actually there are widespread lesions of like appearance in many parts of the brain. The intensity of the damage, the number of microscopical lesions, and the quantity of visible exudate are not the same, however, in every case.

In order to see the thinner films of perivascular exudate, and to fully appreciate the changes in nerve cells and in the nuclei of cells in the walls of capillaries, it is necessary to examine the sections carefully, and under the oil-immersion lens.

*The Blood Vessels.* Most of the lesions in the brain seem to be directly dependent on damage to the arterioles and capillaries. The changes in the vessels are like those caused by many other injurious agents, and they are quite like the vascular alterations ordinarily found at the site of any acute and subacute inflammation. Vessels in the meninges and in the gray and white matter are affected, and in the white matter all of the lesions are especially pronounced in the apical portion of the central white tissue of each convolution. Lesions in the vessels and exudate in the tissue are much less abundant far out towards and directly in the more densely packed fibres of the centrum semiovale, in the compact internal capsule, and in the corpus callosum.

Many capillaries are filled with red blood cells and look dilated;

and not infrequently, on examining many sections, dilated capillaries stuffed with polymorphonuclear leucocytes are found. Such dilated vessels may be surrounded by thin irregular films or wider rings of serous exudate in which rarely one or two polymorphonuclear leucocytes are found. In some cases, perhaps the most acute, the dilatation of the capillaries is very conspicuous.

In other cases some capillaries are dilated, but many more have narrow lumina which may contain no red blood cells for a long distance and are filled with serum. These narrow capillaries are probably contracted, and some of the nuclei in the walls of many of them are swollen, while some are necrotic, pyknotic and broken into several fragments. About many of them there are films, rings, or droplets of exudate.

In most of the cases a few necrotic capillary loops occluded by thrombi are found in gray and white matter, and in some occluded necrotic little vessels are very numerous. The nuclei in the walls of the occluded loops are pyknotic and fragmented. Usually fresh or older films of exudate and droplets of exudate are found in clusters about the occluded capillary loops.

The nuclei of cells in the adventitia of many arterioles, and in the walls of the dilated and narrowed capillaries which are not necrotic are in general swollen and vesicular in appearance. There is evidence of multiplication of these nuclei, and one can readily find groups of three or four at a point where one nucleus should normally be found. Rarely, too, a mitotic figure may be seen in such a nucleus.

Most of the swollen nuclei and the new clumps of nuclei project outward from the walls of the capillaries, not into the lumina. This may be observed especially in segments of small vessels which are closed, with opposite walls in contact. We have found no evidence of sprouting or actual new formation of capillaries, however, as described by Hassin (26), and Winkelman and Eckel (31). The vascular appearance of the tissue which is seen in some cases can be accounted for by dilatation of the capillaries, as already suggested by Rhea (32).

Aside from dilatation and narrowing of the capillaries, and the swelling, multiplication and necrosis of nuclei, it may be pointed out that the thinner films of exudate about the vessels may give the appearance of thickened capillary walls. The irregular outer margins of the fluid,

the variable thickness about a given capillary, and the identity of its appearance with the exudate which forms wider pools about vessels, all go to show that the thin films are composed of coagulated exudate. The walls of the capillaries seem to be permeated by the fluid, however, as well as surrounded by it and may therefore appear to be continuous with the exudate.

Occasional small arteries are found in some of the cases with areas of hyaline necrosis of the media and pyknosis and fragmentation of the nuclei of the muscularis. Such arterioles may contain thrombi, and exudate and new glial cells are found in the spongy tissue about them.

*Fresh Serous Exudate Coagulated by the Fixing Fluid.* Most of the exudate consists of fluid which has the appearance of serum and stains precisely like serum in the blood vessels. From this it may be inferred that during life this portion of the exudate, like the blood, was in a fluid condition, and that both the serum in the vessels and the serous exudate outside are coagulated by the formalin used to fix the blocks of tissue. The exudate generally contains no fibrin (phosphotungstic acid-haematoxylin), and only occasional polymorphonuclear leucocytes are found in it. The freshly coagulated exudate is found about blood vessels in all of the cases, and in fifteen cases there are large areas in the gray or white matter diffusely permeated by serous fluid.

The perivascular fluid forms narrow rings and wide pools which surround capillaries and arterioles and vary in width. The fluid about numerous capillaries forms exceedingly thin films with irregular wavy margins, or, when more abundant, it may extend outward for a distance of 2 or more micra. The collections of exudate are wider around arterioles, and are especially conspicuous in the central and apical white matter where the fibres are relatively few in number and the tissue is less compact and more readily pushed aside by fluid than in the denser grey matter. The rings of homogeneous exudate about vessels in the white matter may extend outward for a distance of 150 or 200 micra. Diffuse exudate appears under the high power of the microscope as fine granular material between and adherent to the fibers. In the meninges the exudate may be very abundant, and often extends far out from the vessels on the surface, while the sulci may be more or less completely filled.

Irregular microscopical foci of variable size, whole microscopical fields, and confluent patches occupying most of the grey matter of a given convolution, may be diffusely infiltrated by the protein-filled exudate. Such areas stain very deeply and irregularly with eosin and may be recognized under the microscope and also by the naked eye. Microscopically they are homogeneous and hyaline in appearance, and the normal striation dependent on the parallel arrangement of the cells and fibres is distorted. The use of safranin and light green brings out the red color of the diffuse exudate in a surprising way, and in contrast to the neighboring grey matter which is not infiltrated and consequently stains green. (See Appendix I for Staining Methods.)

*Inspissated Exudate Coagulated in the Tissues about the Capillaries.* Besides the fresh serous exudate there is, in addition, a perivascular material in the form of small drops which differ somewhat in appearance from the serum coagulated by the formalin, and are especially numerous about narrowed capillaries in the gray matter. Their perivascular location and association with damaged capillaries, and their staining properties, indicate that they represent somewhat older inspissated exudate, coagulated in the brain before the blocks of tissue were fixed by the formalin.

Rows and clusters of these small round drops of exudate are found in the gray matter on one side and along the margins of many capillaries in most of the cases, and some are also found about vessels in the white matter. A single drop may completely surround a capillary segment, and the origin of some of the droplets from the fresh serous fluid may be observed. Occasionally there are small drops incompletely separated from the margin of a film or wider ring of fresh perivascular serous exudate. These little drops, caught in the process of forming, have round margins but remain attached at one point to the main mass of perivascular serum; and they stain almost exactly like the serous fluid fixed by the formalin.

Most of the droplets, however, are somewhat more deeply stained with eosin than the fresh exudate, and they are a little more homogeneous, hyaline, and refractive. They are variable in size and number. Numerous minute drops, less than 1 micron in diameter, may be found closely applied to the wall of a capillary. More often the droplets along one margin of a capillary form clusters, 50 to 60 micra in diameter,

in which the individual drops may vary from 1 to 20 micra or more in size. Some clusters of irregular outline measure 80 or more micra in largest diameter, and in general there is great variation in the size of the clusters and individual drops of exudate. Many droplets are 4 to 12 micra in diameter. Larger ones, 20 to 30 micra in size, are quite numerous, and some measure 50 micra in diameter.

Droplets of exudate are found especially about the damaged capillaries which look narrowed and show swollen or pyknotic and fragmented nuclei. They are also found about necrotic capillary segments filled with hyaline thrombi. The fresher films and rings of exudate are found more especially around dilated capillaries.

In one of the cases (No. 17) there are a few large masses of granular exudate 70 micra in largest diameter, which contain pyknotic nuclear fragments and a few polymorphonuclear leucocytes. These masses resemble old fibrinous exudate but contain no fresh threads of fibrin. Serofibrinous exudate was found in only one of the cases (No. 4) in which intense capillary damage was evident and necrotic capillary segments were very numerous.

*Old Exudate and Old Vascular Lesions which Contain Iron and Basophilic Material Resembling Calcium.* It is evident that the round drops of perivascular exudate originate from the serous fluid which escapes from the damaged blood vessels. The apparent increased density of the drops, and their somewhat inspissated appearance, suggest that they were hardened or coagulated in the tissue before death. Further proof of their antemortem coagulation is offered by the changed appearance of the perivascular droplets in cases of long duration.

In this series of cases the clinical evidence of marked cerebral damage (coma and convulsions) usually appeared several days or a few hours before death occurred, and in these the droplets of exudate appear to be somewhat older than the very fresh rings of serous exudate. In one of the cases, however (No. 5), the first convulsion had appeared a month before the child died. Most of the perivascular droplets in the brain are slightly basophilic, staining purplish-red with haematoxylin and eosin. In other respects they resemble the eosinophilic droplets of exudate found in the cases of short duration. In two cases of still longer duration (No. 7 and No. 18) there are very

numerous deeply basophilic drops about many small blood vessels. In haematoxylin stains they look precisely like calcium salts and contain iron (Prussian blue reaction). With increasing basophilia they show a series of concentric circular strata. In their perivascular location, their predominance about vessels in the gray matter and in their variation in size, they are quite like the eosinophilic droplets which occur in the cases of short duration. From this it seems clear that the collection of stainable iron in the drops and their basophilic calcium-like appearance represent changes which have gradually developed over a considerable period of time. Such changes do not occur in perfectly fluid serous exudate, and it seems evident that by means of an unknown mechanism the perivascular eosinophilic droplets are coagulated in the brain where they may remain for months or years, gradually accumulating iron and basophilic material which stains like calcium salts. The clotting of fibrin is not concerned in the process, for no fibrin can be demonstrated in the freshest serous fluid in the majority of the cases.

Besides the basophilic drops of old exudate there are basophilic areas in the intima and media of arterioles in three cases (Nos. 7, 17 and 18). Similar lesions were seen in the case reported by Tuthill (29), and they are precisely like foci of necrosis and calcification commonly seen in association with arteriosclerosis. Such delayed changes developing slowly after the initial injury serve to emphasize the harmful effects of lead on the cerebral blood vessels; but proof is lacking that the basophilic precipitate in the vessels and exudate is actually calcium since it is not readily dissolved by weak acids and since crystals of gypsum (calcium sulphate) do not appear when the sections are treated with sulphuric acid. Furthermore, as in the case reported by Tuthill, it has been found impossible in the present series of cases to demonstrate the presence of lead in the basophilic exudate by means of the histo-chemical methods now available.

*The Effect of Exudate Coagulated in the Tissue and of Exudate Lost in the Fixative on the Architecture of the Brain.* Microscopical sections of the normal brain fixed in formalin and stained with haematoxylin and eosin show the nerve cells of the cerebral cortex arranged in regular vertical columns parallel to each other. Likewise it is evident under the high power of the microscope that the majority of the fibres

in the gray and white matter, while not specifically stained by eosin, are arranged in vertical parallel rows. The architecture is therefore characterized by a delicate striation determined by the direction of the majority of the cells and fibres. The striation in the gray matter is very delicate and the parallel lines are compact and very close together. In the central white matter of each convolution, on the other hand, the striation is coarser and less compact in appearance and the actual fibrous nature of the striae can be seen in sections stained with haematoxylin and eosin.

The outpouring of exudate into the brain produces a marked disturbance of the normal architecture. The fibres are separated, stretched and torn by the infiltrating fluid, and the orderly arrangement of cells and fibres in parallel columns is lost. Where the exudate is coagulated and stained, the tissue looks smooth and homogeneous instead of striated. In areas from which the fluid has disappeared the normal striated tissue has been converted into a tissue of spongy texture in which the cells are irregularly scattered.

In most of the cases the gray and white matter of many individual convolutions exhibit such a porous architecture in a diffuse or patchy way except in the areas which are filled with coagulated exudate. There are, in addition, certain zones where the change is especially marked and the porous texture is especially coarse. These areas are found about arterioles in the white matter, in circumscribed foci about capillaries scattered irregularly in the gray and white matter, in a long narrow zone at the junction of gray and white matter, in the superficial part of the molecular layer of the gray matter, and in large portions of the whole central white matter of single convolutions from which the exudate has more or less disappeared.

The perivascular accumulations of serous fluid and of older droplets of exudate coagulated about the capillaries push the cells and fibres away from the walls of the vessels. The width of the gaps produced and the distortion of the architecture depend on the quantity of exudate. Perivascular pools of fluid about arterioles are especially wide in the white matter, and usually a little neuroglia, together with frayed, torn adventitial fibres, is left near the walls of the arterioles and scattered in the fluid exudate. Outside these periarteriolar rings of fluid the white matter in a circular zone of varying diameter is often ex-

tremely porous. Many fibres have disappeared, leaving the remainder widely separated from each other. Similarly, in some cases much of the whole central white matter or its apical portion in some convolutions may be diffusely altered in the same way. In both perivascular and diffuse areas many of the remaining axis cylinders are poorly stained and broken into numerous irregular fragments (Bodian's silver stain for axis cylinders). Indeed the tissue that remains is necrotic and disintegrating and the glial nuclei are pyknotic.

In many of the cases there are conspicuous sharply circumscribed clusters of holes in the gray and white matter. They are usually found grouped around or at the margin of a capillary, and vary from 20 to 600 micra in longest diameter. The individual vacuoles in a given group vary from 2 to 50 micra in diameter. In many of the clusters some of the vacuoles contain coagulated serous exudate, while most of them are empty. The tissue at the margins of the clusters and between the holes in each group is compressed and stretched, and some fibres are obviously torn.

A similar irregular porous change of finer texture is often found diffusely in a long zone 200 to 400 micra wide at the junction of the gray and white matter of many convolutions. Here, too, some of the spaces may contain coagulated serous exudate, while the majority are empty. The fibres between the spaces are compressed, stretched, and torn.

In all of the acute cases there are numerous superficial patches in the molecular layer of the cortex where the tissue is very coarsely vacuolated. These patches vary in size and are found on the surface and deep in the sulci. Here again some of the spaces contain coagulated exudate which escapes from capillary vessels penetrating the brain from the meninges. The collection of fluid in these superficial patches lifts up and tears the inner layer of the pia mater from the brain, and propels glial cells into the subarachnoid space. In many places the pia may be elevated from 25 to 50 micra above its original level.

*The Neuroglia.* In association with the lesions produced in the fibres of the white matter by the presence of exudate, certain characteristic changes in the cells are also usually found. New cells, damaged cells with fat-laden cytoplasm and necrotic cells may all be recognized.

In the spongy patches of the molecular layer there are numerous small groups of abnormal glial cells. The arrangement of the cells in groups and the presence of occasional mitotic figures indicate that there is proliferation of neuroglia. Most of the cells resemble fibrous astrocytes. They are large, and may measure 12 micra in diameter. The cytoplasm of many is homogeneous and hyaline, and the nuclei are large and vesicular. In sections stained with haematoxylin and eosin processes are readily seen emerging from the angular margins of the cells, and specific stains (phosphotungstic acid-haematoxylin) show the processes to be neuroglia fibres. The cytoplasm of some of the cells is foamy and vacuolated in appearance due to the presence of fat droplets (Scharlach R; osmic acid), and occasional cells contain fine yellowish-brown granules of pigment. Some cells are rounded and apparently are no longer connected with neuroglia fibrils. Some of these have foamy fat-laden cytoplasm and many of them are necrotic, with pyknotic nuclei. Such necrotic cells may be found lying free in the meshes of the meninges, evidently dislodged and forced outwards by the fluid which stretches and tears the fibres of the molecular layer and lifts up the pia mater.

These damaged and necrotic glial cells make up the great majority of the cells found in the meninges in all of the cases. In the cases in which the cells found clinically in the spinal fluid were most numerous, 25 to 66 per cu.mm., the microscopical sections show a good many of the altered glial cells in the meshes of the pia mater, and practically no leucocytes of any kind. This suggests that most of the so-called lymphoid cells in the spinal fluid in lead poisoning are not leucocytes from the blood; and certainly many of them are cells dislodged from the surface of the molecular layer.

Somewhat similar changes are found in the glial cells of the central white matter of many convolutions. The abnormal cells are especially conspicuous in the apical part of the central white matter and in the narrow spongy zone at the junction of the gray and white matter. Scattered more or less diffusely in these zones there are: (1) large astrocytes with vesicular nuclei, hyaline cytoplasm, angular bodies, and evident neuroglia fibrils; (2) occasional cells in mitosis; (3) some foamy fat-laden cells; and (4) round necrotic cells with pyknotic nuclei. In the cases in which the white matter is diffusely saturated with very abundant coagulated serous fluid, many of the glial cells are necrotic,

and few of the new swollen astrocytes are found (Cases 6, 15, and 19). In other cases where the central white matter is particularly spongy and distorted by fluid which was evidently poor in protein and dissolved in the fixing agent, many of the large swollen astrocytes are found and relatively few necrotic cells (Cases 11, 21 and 23).

In most of the cases foamy fat-laden cells and a few cells which contain granules of yellowish-brown pigment are found about arterioles in the white matter. Very few are to be seen in some cases, while in others the cells may be present in moderate numbers about many little arteries. They are apparently damaged glial cells and are identical in appearance with the foamy and pigmented cells in the spongy patches of the molecular layer. The origin of the foamy fat-laden cells from damaged neuroglia can be seen in many places where the fluid which collects in rings and pools about arterioles tears a gap in the perivascular tissue, leaving a narrow ring of neuroglia attached to the adventitia of the blood vessels. In the zone of glial cells and fibres left attached to the vessel some cells look normal, some are a little vacuolated, while others are rounded, detached from the rest of the tissue, and are full of fat globules.

A few of the foamy cells also contain clumps of minute yellowish-brown granules of pigment, and occasional cells are uniformly filled with such pigment. The nature and origin of the pigment is not clear. It is a lipochrome (Scharlach R; osmic acid), and gives negative reactions for iron (Prussian blue reaction) and lead (39). In older cases, after the fluid exudate has disappeared, these pigmented cells about the blood vessels in the white matter and meninges persist and may be quite numerous (Case 18). Both foamy cells filled with fat and pigmented cells are occasionally found in the gray matter about vessels which extend from the surface into the central white matter.

*Nerve Cells.* Various changes are found in the nerve cells. Since the number of abnormal cells and the degree of damage vary in different cases and in different areas of a given brain, it is necessary to examine sections from many parts of the brain in each case.

There is, first, mechanical displacement of the cells by the serous exudate. A few cells in localized areas may be displaced by perivascular rings of exudate and by clusters of coagulated drops of older exudate, but the arrangement of many nerve cells is disordered in the

larger fields of the gray matter which are diffusely saturated with serous fluid.

Nerve cells in areas filled with coagulated exudate have vague outlines, and the cytoplasm is not sharply demarcated from the surrounding tissue. The cytoplasm is more basophilic than normal, and distinct Nissl granules can scarcely be made out. The whole cell body stains diffusely with Nissl stains (gallocyanin, thionin, cresyl violet). The nuclei are more basophilic than normal, nearly pyknotic in appearance, and the nucleoli are indistinct.

Many of the nerve cells in the torn spongy areas from which exudate escapes resemble the cells in areas filled with coagulated exudate. In the vacuolated areas the nerve cells tend to be smaller than normal, however, and many are represented by altered nuclei and very thin rings of cytoplasm, the whole cell lying at one edge of a large empty space. In the areas which are extremely porous many completely necrotic cells are usually found. Such changes may be seen in any part of the gray matter, including Ammon's horn.

Necrotic cells are scattered irregularly in all of the cases. They are very numerous in many, and some are found in practically every microscopical section in most cases. Necrotic cells are much smaller than normal. They are sharply outlined and the cytoplasm is homogeneous, hyaline, and stains bright pink with eosin. The nuclei are pyknotic, solid black, and may be fragmented. Often they are found triangular in shape, like the cell itself. Some of the necrotic cells may be surrounded by several neuroglia cells, the so-called neuronophagia, but numerous necrotic nerve cells may be found without any increase in the surrounding neuroglia.

Most of the changes in the nerve cells seem to be related to the vascular lesions and consequent presence of exudate in the tissues. It is not evident as yet that lead acts directly on the cells.

*Foci of Necrosis.* Small circumscribed foci of necrosis in the cerebrum were found in 12 of the 22 cases. In some cases they were seen only in the gray matter, in others only in the white matter, and in 5 cases they were present in both the gray and white matter. In one of the cases (No. 20) haemorrhagic lesions of this type are very numerous and readily visible in the gross specimen. The lesions vary in size from about 40 to 200 micra in diameter, and are characterized by

pyknosis and fragmentation of the cells and granular disintegration of the fibres. There is usually a ring of multiplying glial cells, some in mitosis, about the necrotic foci, and the smaller ones may be diffusely infiltrated by glial cells. In addition to the peripheral rings of neuroglia there may be circular haemorrhages about some of the necrotic areas, and in some instances more or less diffuse infiltration of the necrotic tissue by red blood cells and neuroglia.

The small areas of necrosis are apparently minute infarcts. In the cases which contain many there are also numerous necrotic capillary segments and capillary thrombi; and often a necrotic capillary segment occluded by a thrombus is found within or at the margin of the necrotic tissue. The demonstration of a causal relationship between capillary thrombi and each of the foci of necrosis could only be determined by cutting many serial sections.

*Haemorrhages.* Three types of haemorrhage have been found in this series of cases. Minute rings of blood surrounding arterioles and capillaries are present in the gray and white matter of most of the cases. They are usually more numerous in the white matter than in the gray cortex and are variable in size, some measuring 60 x 120 micra. The perivascular haemorrhages are independent of the rings of serous exudate which usually contain no red blood cells whatsoever. In some cases few perivascular haemorrhages are found, while in others they are numerous. No apparent relation exists, however, between the occurrence of convulsions and the number of haemorrhages. This is illustrated by Case 21 in which there were no convulsions and perivascular haemorrhages are as numerous as in other cases characterized clinically by the occurrence of many convulsions.

Haemorrhages of a second variety are shown by the circular rings of blood which are frequently found about the periphery of small foci of necrotic tissue described above. Larger haemorrhages have rarely been observed in this group of cases. In one case (No. 12) a confluent group of haemorrhages 5 to 6 mm. in diameter was found in the white matter, and in another (No. 18) several small thin microscopic films of blood were found under the meninges.

### THE CEREBELLUM

The cerebellum is intensely affected in lead encephalitis, and the same variety of lesions occurs in both cerebellum and cerebral

hemispheres. In the cerebellum, too, the lesions are patchy in distribution, and so it is important to examine sections from many areas. In this series from 4 to 12 blocks of the cerebellum were cut in 12 cases. In six of the earlier cases the cerebellum was not examined microscopically, and in four the microscopical sections were made from single blocks of tissue.

It is not necessary to describe again in detail the changes in the capillaries and arterioles, the old and fresh exudate about the vessels and far out in the tissues, the disordered architecture, and the necrotic cells and tissue, since these are similar in the cerebellum and cerebral hemispheres. On account of the peculiar architecture of the cerebellum, however, there are certain particular lesions which should be described.

It is well known that cells of the marginal embryonic stratum, nervous elements resembling the cells of the granular layer, persist on the surface of the molecular layer just under the meninges of the cerebellum for several years after birth (40). In the cases of lead encephalitis in which this layer of cells persists, the serous exudate about the capillaries and in spongy patches in the surface of the molecular layer dislodges many of the cells and forces them out into the meshes of the meninges, just as neuroglia cells are forced into the meninges from the molecular layer of the cerebral cortex. The cells found free in the meshes of the meninges of the cerebellum consist almost entirely of small round cells from the marginal embryonic stratum, and it is evident that they too may be found in the spinal fluid taken for clinical examination.

In the cerebellum, lesions in the molecular layer are numerous and conspicuous in most of the cases. Damaged capillaries, capillary thrombi, perivascular little foci of necrosis, haemorrhages, and thin films of serous exudate about many capillaries, are commonly found. About many capillaries, for some distance, often stretching from near the meninges to the Purkinje layer, the tissue is very coarse and porous. Some of the spaces may contain coagulated serous exudate. The nerve fibres are stretched and separated, some have disappeared, and a good many new glial cells and fibres are found loosely arranged in the spongy perivascular areas.

The large nerve cells in the Purkinje layer are especially subject to damage and are found vacuolated and even necrotic. In most cases

many of them have disappeared. The whole Purkinje cell layer is stretched and spongy, and in some of the cases it is filled here and there with coagulated serous exudate. With disappearance of the nerve cells, their dendrites in the molecular layer disappear, and also the axones of basket cells which normally terminate about the Purkinje cells.

In five cases there are several extremely and diffusely atrophied folia. In these five cases from 4 to 8 blocks of the cerebellum were cut, and it is evident that the recognition of the extreme changes in isolated scattered folia was a matter of chance depending on the number of blocks cut. The diffusely affected folia are very small, and each layer is thin. Most of the Purkinje cells and many of the granular cells have disappeared. Many dendrites of Purkinje cells are missing, so that the molecular layers, composed principally of these fibers, become very coarse-meshed, and new glial cells and fibres are found both in the molecular and granular layers. Thick cuffs of lymphocytes may be found about small blood vessels in the meninges over these extremely altered folia, and in one case there are clumps of minute basophilic granules in the molecular layer which suggest fragments of necrotic calcified fibres.

Noteworthy changes occur in the dentate nucleus, where a good many necrotic nerve cells are usually found, some surrounded by clusters of glial cells. In some cases there are little rosettes, nodules which may measure 50 micra in diameter, composed of 30 to 40 glial cells. In some parts of the dentate nucleus more widespread loss of nerve cells may be found and a corresponding more or less diffuse infiltration with glial cells. Changes in the capillaries are conspicuous, and there are thin rings and small drops of fluid coagulated about many capillaries. The tissue about a good many capillaries is coarse and porous, the fibers stretched and distorted, and there is pericapillary infiltration with neuroglia. Where capillary thrombi occur, small round foci of necrosis may result, with peripheral rings of red blood cells and glial cells.

In the white matter of the cerebellum wide pools of perivascular serous exudate are often found, and other large areas from which much of the tissue has disappeared, leaving a coarse network of stretched, torn and necrotic fibres. Perivascular foamy fat-laden

cells and pigmented cells are found in the cerebellum as in the cerebral cortex.

THE BASAL NUCLEI, MESENCEPHALON, PONS, MEDULLA AND SPINAL CORD

In this series the same variety of lesions and changes of identical character are found throughout the entire central nervous system. In the basal nuclei and mesencephalon, the pons, medulla and spinal cord, however, the intensity of injury is less marked; the quantity of exudate is less abundant; and the distortion of architecture less evident than in the cerebral hemispheres and cerebellum. But it is important to point out that microscopical examination of numerous sections of the basal nuclei, brain stem, and spinal cord shows small lesions of one kind or another at nearly all levels and in many of the sections. Actually there are very numerous widely scattered small lesions, although the changes in a single microscopical section may appear to be slight (Table II).

To summarize briefly, the lesions are more numerous in the grey matter than in the fibre tracts, and they are less evident in the spinal cord than elsewhere. Swelling and multiplication of nuclei in the walls of capillaries and adventitia of arterioles, necrosis of capillary segments and capillary thrombi are found on careful examination of the sections. Likewise, films and small drops of exudate coagulated about scattered capillaries are fairly numerous, and wider pools of serous exudate are seen about occasional arterioles. There are large fields diffusely saturated with serous exudate in the putamen in two cases and in the caudate nucleus in three. Serous fluid is rarely found in the meninges. Older drops of perivascular exudate showing various degrees of basophilia were encountered, usually in the caudate nucleus, corpus striatum and thalamus, in six of the acute cases, excluding the three cases of longer duration already mentioned. In some of these six cases similar basophilic areas resembling calcium were found in the walls of small blood vessels.

Spongy porous areas of distorted tissue, damaged glial cells and proliferating neuroglia are likely to be seen in the superficial molecular layer of neuroglia of the mesencephalon and brain stem; and there is a similar distortion of the architecture about many capillaries and arterioles, together with serous exudate in some of the porous peri-

TABLE II

*Necrotic Nerve Cells, and Foci of Necrotic Tissue with Glial Reaction in Basal Nuclei, Mesencephalon, Pons, Medulla, and Spinal Cord*

| CASE NO. | NUMBER OF SECTIONS EXAMINED | NECROTIC NERVE CELLS WITH FEW NEUROPHAGOCYTES | FOCI OF NECROTIC TISSUE | NODULES OF NEUROGLIA ABOUT NECROTIC CELLS OR REPLACING NECROTIC TISSUE |
|---|---|---|---|---|
| 1 | 1 | Spinal cord | 0 | 1 in lateral horn of cord |
| 2 | 4 | Spinal cord, nu. cuneatus, inf. olives, sub. nigra, red nu., geniculate body, corpus striatum and thalamus | 3 in lateral columns of cord | Numerous in geniculate body and thalamus |
| 3 | 1 | Inferior olive | 0 | 0 |
| 4 | 5 | Spinal cord, thalamus, corpus striatum, caudate nucleus | 1 in thalamus and 1 in globus pallidus | 2 in anterior horn of cord |
| 5 | 1 | Spinal cord | 0 | 0 |
| 6 | 6 | Cord, post. colliculi, geniculate body, thalamus, putamen, caudate nucleus | 12 in gray matter of medulla at decussation; 2 in thalamus | Several in geniculate body and thalamus |
| 7 | 3 | Cord, nuclei gracilis and cuneatus, post. colliculi, inf. olives | 0 | 1 in pyramidal tract at decussation |
| 8 | 2 | Spinal cord and nuclei pontis | 0 | 0 |
| 9 | 1 | Spinal cord | 0 | 0 |
| 10 | 1 | Sub. nigra, paraventricular nuclei, and thalamus | 0 | Several in thalamus |
| 11 | 17 | Cord, inf. olive, nuclei pontis, gracilis and cuneatus, inf. colliculus, thalamus, corpus striatum, and caudate nucleus | Several in inferior olives | 1 in cord; several in inf. olive, nuclei gracilis and cuneatus, and in thalamus |
| 12 | 11 | Cord, nuclei gracilis and cuneatus, inf. olive, nuclei pontis, the colliculi, hypothal. nu., thalamus, putamen, and caudate nu. | 1 in thalamus (infarct of 7 mm.). Several in nu. cuneatus | Several in the inferior olives. |
| 13 | 15 | Cord, nu. cuneatus, nuclei of nerves 5, 6, 7; the olives, nuclei pontis, sub. ferruginea, red nu., thalamus, caudate nu., and corpus striatum | 1 in geniculate body | 1 in dorsal column of cord. Several in geniculate body. Many in the inferior olives |



| | | | | |
|---|---|---|---|---|
| 14 | 20 | Cord, nu. of Schwalbe, nu. of nerves 7 and 12, inf. olives, nu. pontis, hypothalamic nu., geniculate body, and thalamus | 1 in thalamus (infarct of 4 mm.) | 1 in gray matter of lumbar cord. Several in nu. of Schwalbe, 1 in nu. of tract. solitarius, several in geniculate body, numerous in thalamus |
| 15 | 16 | Spinal cord, nuclei gracilis and cuneatus, inf. olives, nu. of several cr. nerves, nuclei pontis, the colliculi, red nu., sub. nigra, and thalamus | 1 in triangular nu. vest. nerve | 1 in nuclei pontis; 1 in sup. colliculus, several in thalamus |
| 16 | 15 | Cord, nuclei gracilis and cuneatus, inf. olives, triangu. nu., vestib. nerve, nu. of N. 12, nuclei pontis, the colliculi, sub. nigra and ferruginea, red nu., and thalamus. | 0 | 2 in nucleus gracilis |
| 17 | 19 | Cord, nu. gracilis and cuneatus, the olives, nu. lateralis, nuclei pontis, inf. colliculi, sub. nigra, red and hypothal. nuclei, thalamus, corpus striatum, and caudate nucleus. Nuclei of Schwalbe and of cranial nerves 4, 5, 7, 8, and 12 | Nucleus of Schwalbe (1), inferior and dorsal acces. olives (several), thalamus (several) | Ant. horn of cord (several), nu. cuneatus (several), inf. olive (many), restiform body (1), reticular sub. of pons (1), nu. of N. 4 (1), hypothal. nu. (several) |
| 18 | 22 | Cord, nuclei gracilis and cuneatus, nu. of N. 12, inf. olives, thalamus, corpus striatum | Nu. cuneatus (1), motor nu. N. 5 (1), nu. of sp. br. of N. 5 (1), brachium conjunctivum (1) thalamus (1) | 2 in nu. of N. 3, several in inf. olives, 1 in nu. of N. 12, and 2 in reticular sub. of pons |
| 19 | 18 | Cord, nuclei gracilis and cuneatus, nuclei of nerves 4, 5, 7, 8, and 12; nu. of Schwalbe, the olives, inf. colliculi, nuclei pontis, thalamus, candate nucleus, corpus striatum | Several in ant. horns of cord at decussation | Ant. horn of cord (1), nuclei gracilis and cuneatus (several), nu. of N. 8 (several), restiform body (1), nuclei pontis (1), nu. of Schwalbe (2), ret. sub. of pons (1), nu. N. 4 (1), inf. olive (several), globus pallidus (1), thalamus (1) |
| 20 | 15 | Cord. inf. olives, inf. colliculi, thalamus, caudate nucleus | Cord at decussation (2), nu. of N. 8 (several), inf. olives (several), sup. olive (1), fibres of ventral pons (2), nu. of N. 12 (several), inf. colliculus (1); red and hypothal. nu., geniculate body, thalamus, corp. striatum (many) | Sup. olive (1), retic. sub. of pons (1), thalamus (few) |
| 21 | 12 | Cord, nuclei gracilis and cuneatus, nu. sp. br. N. 5, nu. N. 6, the olives, nuclei pontis, sub. ferruginea, hypothal. nu., thalamus, corpus striatum, caudate nucleus | Nuclei gracilis and cuneatus (several) | Reticular sub. of medulla (3), inf. olives (several), reticular sub. of pons (several), hypothal. nu. (several) |
| 22 | 19 | Cord, nu. sp. br. N. 5, nuclei gracilis and cuneatus, nuclei of nerves 6, 7, and 12; sup. and inf. olives, sub. ferruginea, thalamus | Reticular sub. at decussation (1) | Pyramidal tract at decussation (1), nu. cuneatus (1), inf. olives (few) |

vascular areas. Pigmented cells and fat-laden cells about blood vessels are found at various levels, and a few small perivascular haemorrhages in the basal nuclei, brain stem, and spinal cord in eighteen of the cases.

Necrotic nerve cells, focal areas of necrotic tissue, and older circumscribed nodules of neuroglia replacing normal structures form the most conspicuous lesions, although regularly associated with vascular changes and evidence of exudate in the tissue. The numbers of these lesions and their distribution in the present series may be seen in Table II.

Necrotic nerve cells are scattered in small numbers in many nuclei (Column 1, Table II). In most instances few necrotic cells are found in a given microscopical section. Several glial cells are usually found immediately about the necrotic nerve cells, but in the inferior olives, the geniculate bodies, and in the thalamus it is not uncommon to see scattered solitary necrotic cells with bright pink hyaline cytoplasm, no Nissl granules, and pyknotic nuclei.

In the spinal cord the smaller nerve cells of the lateral horns seem more susceptible to injury than others, and in general large cells like those in the anterior horns, in the substantia nigra, and locus caeruleus, are apparently the more resistant. In the spinal cord and in the nuclei of gracilis and cuneatus, in nuclei of cranial nerves and in the nuclei pontis, in the colliculi, red nucleus, putamen and caudate nucleus some of the nerve cells undergo karyolysis and fade away. The cytoplasm of the injured cells disappears, while their nuclei are left better preserved, surrounded by neurophagocytes.

The foci of necrotic tissue resemble those in the cerebral hemispheres and cerebellum. They are associated with marked changes in closely related capillaries, and in many instances they contain necrotic capillary segments and capillary thrombi. Most of the areas are more or less rounded and vary from 40 to 80 micra in diameter. Some are 100 to 200 micra in size, and in two cases small infarcts, 4 and 7 mm. in diameter, were found in the thalamus, each surrounded by acute inflammatory exudate (Nos. 12 and 14). The smaller foci of necrosis usually show a ring of glial cells and red blood cells in a peripheral zone of spongy vacuolated tissue, and they may contain recognizable shadows or nuclei of necrotic nerve cells.

The changes in nerve cells and in small foci of the tissue described

above have the appearance of fresh lesions. Similar lesions, which are evidently older, are found in most of the cases and are listed in Columns 3 of Table II. They correspond in size and distribution to the fresher lesions from which they differ chiefly in containing more abundant, and more mature neuroglia. The older lesions vary from 25 to 200 micra in diameter, although most measure 40 to 80 micra. There are a good many of large size, however, 120 to 160 micra in longest diameter, and in one case a nodule of fibrous tissue and neuroglia measuring 250 x 400 micra was found in one of the dorsal columns of the spinal cord (Case No. 13).

Listed among the older lesions are, first, single necrotic nerve cells or fragments surrounded by numerous closely packed glial cells forming nodular rosettes. They are found especially in the inferior olives, geniculate bodies and thalamus. Secondly, there are many small nodules of neuroglial tissue composed of nuclei and fibres which replace normal tissue. These occur in both gray matter and fibre tracts. The glial nuclei are loosely arranged, not closely packed together, in the little nodules of fibres. They are most numerous in the inferior olives, and are probably formed by the growth of neuroglia in foci of tissue once necrotic, lesions like the fresh foci of necrosis described above.

### THE MENINGES, CHOROID PLEXUS, RETINA AND OPTIC NERVES, PINEAL GLAND AND HYPOPHYSIS

*The Meninges.* No especial primary lesions of the meninges have been found in any of the cases in this series and none of the microscopical lesions confirm the suggestion that in lead poisoning there is a primary meningopathy (2). The changes which do occur concern the blood vessels, and are like the vascular lesions in the gray and white matter. They are readily seen in small branches which penetrate the molecular layer from larger vessels above in the meninges. These arterioles and capillaries show dilatation and narrowing, swelling and multiplication of nuclei, and necrotic pyknotic nuclei as observed in the gray and central white matter. Capillary thrombi in meningeal vessels, however, have rarely been found in any of the cases.

The outpouring of serous exudate produces the spongy patches in the molecular layer as already described, and some of the exudate may

remain coagulated about the vessels and in the tissue. The escape of fluid from the vessels pushes the inner layer of the pia mater up and tears many of its fibres from their moorings. There is some evidence, too, of slight proliferation of cells in the displaced and torn meninges; and, as already described, a good many damaged and necrotic glial cells and cells of the marginal embryonic stratum of the cerebellum are forced from the surface of the molecular layer and come to lie free in the meshes of the pia mater. Besides these cells, in a few cases very small numbers of polymorphonuclear leucocytes have been found in the meninges, and there may be small lymphocytes about vessels in the meninges overlying the localized folia in the cerebellum which are extremely altered as described above. In the majority of the cases, however, there is no evidence of any diffuse leucocytic reaction in the meninges.

In addition to the exudate about the meningeal vessels penetrating the molecular layer, in most of the cases there is evidence of abundant serous fluid about small vessels between the two layers of the pia mater. The exudate is usually found in patches on the surface of convolutions and deeper in the sulci. In some cases the sections made show little fluid, but in many cases it is very abundant. It is identical in appearance with serum within the blood vessels coagulated by the fixing fluid, and apparently escapes from damaged blood vessels in the meninges. It is therefore not abnormal cerebrospinal fluid, since it is not a secretion from the choroid plexus, but rather an exudate.

*The Choroid Plexus.* Microscopical sections of the choroid plexus of fifteen of the cases were examined, and no definite lesions in the epithelial cells were recognized. In all of the cases examined, however, there is a patchy separation of the epithelium from the underlying blood vessels, and vacuolization of the stroma. In three cases narrow rings of serous exudate remain coagulated about very few vessels. Demonstrable changes in the walls of the blood vessels are slight, but there is some swelling of the nuclei in the walls of some of the capillaries and arterioles.

There is no microscopical evidence therefore that in lead encephalitis the cerebrospinal fluid secreted by the choroid plexus is either increased in amount or abnormal in composition. The changes in the blood vessels of the brain and meninges, and the abundant serous

fluid in both locations show clearly that the increased intracranial and intracerebral pressure and the protein found in the spinal fluid clinically result from widespread vascular damage and consequent outpouring of serous inflammatory exudate which escapes principally from the blood vessels of the brain and meninges.

*The Retina and Optic Nerves.* The retina, optic discs and nerves were examined microscopically in five cases. In each instance there are spongy, vacuolated patches, especially along margins of capillaries, in the nerve, optic disc, and in the nerve fibre layer of the retina. In three cases patches of serous fluid were coagulated on the surface of the nerve fibre layer.

Microscopical sections of the optic chiasm and nerves were made in eight other cases. Five of these show spongy patches about capillaries. In another case there are, in addition, occasional perivascular rings of coagulated serous exudate, and small perivascular haemorrhages occur in three cases.

*The Pineal Gland.* In eight of the cases single blocks were made from the pineal gland at autopsy and one microscopical section was prepared from each, stained with haematoxylin and eosin. In most cases the gland was torn in removal, and the sections are somewhat faulty. Three, however, show irregular gaps in the tissue, each filled with serous fluid, and in several of the cases there is some irregularity and increase in the size of some of the nuclei. It seems probable that further study of material prepared more carefully would show more definite and more numerous changes in the pineal gland.

*The Hypophysis.* The hypophysis was examined microscopically in seventeen of the cases. Changes which were slight in most instances were found in the anterior lobe in twelve cases. In nine there is serous exudate about some of the capillaries. In most of these only a little perivascular fluid is found about a few vessels. In one case (No. 22) the exudate is quite abundant in patches in the central part of the anterior lobe, and produces some tearing of the tissue and displacement of the cells.

A few irregularly scattered necrotic cells and groups of two to five necrotic cells are found in the anterior lobe of seven cases; and in two others there are larger microscopical foci of necrosis. Small haemorrhages are present in two cases. In a good many there are occasional

cells in the anterior lobe with greatly enlarged hyperchromatic or pale vesicular nuclei.

### PERSISTENT LESIONS AND FUNCTIONAL DISTURBANCES

Children may recover from lead encephalitis and live on with a variety of permanent functional disorders which will vary in character with the location and intensity of the original lesions in the brain. McKhann described a case in which blindness, spastic left hemiparesis, and occasional convulsions were present three years after the acute encephalitis occurred; and a ventriculogram showed evidence of atrophy on the right side of the brain (13). In the present group of 22 cases there are three somewhat similar examples.

In one case (No. 5) a week after the original convulsions the child showed generalized spasticity, spastic paralysis on the left, constant purposeless movements of the head, face, tongue and right arm; and there was evident disturbance of mentality. These signs persisted and a month later the child died with convulsions. Several atrophied cerebral convolutions were found on each side of the brain at autopsy. The microscopical sections show fresh vascular changes and fresh exudate together with older lesions. There are perivascular collections of old exudate with basophilic changes and iron content; and in the gray matter many nerve cells are atrophied and whole fields of cells concentrated together from loss and collapse of the tissue.

In a second case (No. 7), for about a year there were periods of abdominal pain, constipation, vomiting, and crying spells. Peripheral neuritis finally developed, with flaccid paralysis of all the extremities, paralysis of the trunk and diaphragm, and almost complete loss of sensation. For several hours before death there was high fever and coma, together with convulsive movements of the muscles of the neck and face. Microscopically, both fresh and old lesions are found in the brain and also the lesions of peripheral neuritis. Many large microscopical fields in the cortex show extensive destruction and a loss of tissue, and there is abundant old perivascular exudate. Few blocks of the brain were prepared, and the possible relation between the lesions in the brain and the loss of sensation must remain in doubt.

In the third case (No. 18), three years elapsed between the original convulsions and the final attack of lead encephalitis. Examination

made two years after the first attack showed quite marked mental retardation, but no other definite functional disorders were recognized. The microscopical sections of the brain show fresh lesions and exudate, and very abundant old basophilic perivascular exudate scattered everywhere in the cerebral cortex. Old areas of perivascular encephalomalacia and more diffuse loss of tissue in the central white matter of some convolutions are evident; and in the cerebellum there are extensive old lesions.

### ON THE PATHOGENESIS OF THE VASCULAR CHANGES AND THE EXUDATE

Experimental lead encephalitis is readily produced in laboratory animals, and the lesions found by various writers have been reported. A good review is that of Farraro and Hernandez (41). In their own experimental animals these authors found lesions in blood vessels, nerve cells and fibres, and in neuroglia, but no fluid exudate was described. Weller and Christensen (42) reported the occurrence of oedema of the brain in experimental lead encephalitis, describing spongy vacuolated areas in the tissue as oedema. We have found no experimental reports, however, in which the presence of exudate coagulated in the tissues has been recognized.

It seems evident from the familiar swollen appearance of the brain which has been often described in the literature, and from the present series of cases in which there is abundant serous exudate about blood vessels and diffusely infiltrating the brain, that vascular damage and exudate of fluid which may coagulate in the brain, or partly dissolve in the fixative, are characteristic of acute lead encephalitis. The spongy porous changes pictured by Weller and Christensen (42) in the brain of the experimental animal indicate that the experimental disease is similar in these respects to the disease in man.

Lead encephalitis is said to be purely a "degenerative" disease without evidence of inflammation (41). But as a matter of fact, the vascular changes, the haemorrhages, and the exudate of serous fluid are inflammatory lesions of a particular type. They differ in intensity from more familiar examples such as sero-fibrino-purulent peritonitis and meningitis.

It appears, then, that the lesions in the brain are for the most part dependent on vascular damage and the collection of exudate. But

the precise relation between lead in the tissues and the pathogenesis of the vascular phenomena is not clear. It seems likely, however, that the usual occurrence of lead encephalitis in children during the warm months of summer and fall, and the presence of fever in most cases, may be significant factors in initiating the changes in the cerebral blood vessels which are followed by widespread serous exudate and tearing of tissue. The question requires further investigation, but at this point experiments in support of this view may be mentioned briefly.

Twenty-four rabbits were given daily subcutaneous injections of 1 cc. of basic lead acetate for 7 weeks without exhibiting any signs of encephalitis. Eight of them were then placed in the incubator at 37°C., which produced an elevation of 3 or 4°C. in the temperature of the animals. Four of the rabbits died within 24 hours; the others lived for 38, 53, 60 and 102 hours, respectively. The controls injected with lead and kept at room temperature were killed and autopsied. Normal controls were killed after living for two weeks in the incubator at 37°C., with a temperature 3° to 4° above normal. The rabbits which were injected with lead and placed in the incubator all developed pulmonary oedema, and microscopical sections show serous exudate about capillaries in the meninges and molecular layer of the cortex, spongy porous areas in the surface of the molecular layer, and upward displacement of the inner layer of the pia mater—lesions which are characteristic of lead encephalitis in children. These lesions were not found in either set of control animals.

The experiment and the fact that acute lead encephalitis usually occurs in the summer and fall suggest that lead acts on the blood vessels of the brain in such a way that they become more permeable than normal when they are dilated by agents such as rising atmospheric temperature and fever.

## SUMMARY

In acute lead encephalitis the brain is swollen, and may be hyperaemic or pale. When blocks of fresh tissue are placed in alcohol, a milky precipitate is formed by plasma protein in the exudate which escapes.

Lesions are found throughout the entire central nervous system.

They are most abundant in the cerebral hemispheres and cerebellum. All of the changes are patchy in distribution, but examination of many sections shows the presence of numerous lesions.

The microscopical changes are those of a serous inflammation. Vascular lesions are found, including capillary necrosis and thrombi, together with abundant exudate, tissue damage, and evidence of repair. Most of the injury to the nervous tissue seems dependent on the accumulation of exudate.

The exudate is composed of serous fluid, usually without fibrin. A part is coagulated in the brain by the formalin; some is older, inspissated in appearance, and coagulated in the tissue before death; and a portion is extracted by the fixing and dehydrating agents.

The freshly fixed serous exudate is found about blood vessels and in the meninges in all cases; and in many cases large fields of tissue in many convolutions are diffusely saturated with the exudate.

The older inspissated exudate is found especially about capillaries in the gray matter in the form of small droplets. After periods of weeks and years they become basophilic, accumulate iron, and stain like calcium. The mechanism by which this exudate is coagulated remains obscure, and the clotting of fibrin is not concerned. Similar basophilic areas are found in the walls of blood vessels after elapse of months and years.

The fresh serous exudate and the older droplets cause distortion of the architecture of the brain, depending on the location and quantity of the fluid. Fields in the gray and white matter diffusely saturated with exudate contain many damaged and necrotic nerve and glial cells, and there is marked tearing and necrosis of fibres. The necrotic nerve cells may be surrounded by several glial neurophagocytes.

The portion of the exudate which escapes in the fixing and dehydrating fluids leaves stretched and torn areas in the tissue like those in which coagulated fluid remains. Large confluent spongy areas are found in the gray matter and in the central apical white matter; and there are certain other characteristic zones and foci which are especially coarse and porous.

Very coarse torn spongy patches regularly occur in the superficial part of the molecular layer of the brain and cerebellum. The exudation of fluid into these areas tears and pushes up the inner layer of

the pia mater, and scatters necrotic neuroglia cells and cells of the marginal embryonic stratum of the cerebellum into the meshes of the meninges. These glial cells and embryonic cells constitute the majority of the cells free in the meninges and they appear also, no doubt, in the spinal fluid.

Especially coarse spongy tissue is also found in a narrow zone at the junction of the gray and white matter of many convolutions, and there are similar circumscribed foci about arterioles and capillaries. Some of the spaces in the vacuolated zones and foci generally contain coagulated serous exudate, although most are empty.

Small perivascular haemorrhages in variable numbers occur in most cases, and small focal areas of necrosis may be found in any part of the brain, usually in association with necrotic capillary segments or capillary thrombi. They may be surrounded or diffusely infiltrated by haemorrhage and glial cells. Damaged and necrotic glial cells and new astrocytes are found, especially in the spongy porous molecular layer, in the apical central white matter and about arterioles in the white matter.

Lesions of similar character are scattered in the cerebellum and are especially evident in the molecular layer, the Purkinje layer, and in the dentate nucleus. On making sections from many parts of the cerebellum, extreme changes affecting whole folia and single lobules are likely to be found.

In the basal nuclei, brain stem, pons, medulla and spinal cord, the lesions are small, few in number in a given section, and scattered at wide intervals. In these structures small rosettes of glial cells about necrotic nerve cells, foci of necrotic tissue, and nodules of neuroglial cells and fibres replacing the damaged tissue, are conspicuous. Slight changes were found in this series of cases in the choroid plexuses, the retina and optic nerves, pineal gland, and hypophysis.

In patients who recover after the initial convulsions, functional disorders varying from mental retardation to spastic paralysis may be expected, depending on the intensity and location of the injuries. Microscopically, there is a corresponding loss of tissue in the gray and white matter of the brain and cerebellum. Remnants of old coagulated exudate are found, basophilic in appearance like calcium, and basophilic plaques in the walls of blood vessels.

Fever and marked leucocytosis were present in most of the cases in this series, and the signs of encephalitis appeared during the hot months of summer and fall in 19 of the 22 cases. In another patient, dying in January, the encephalitis appeared in association with widespread lobular pneumonia caused by the Type II Pneumococcus. It is suggested that factors which cause vasodilatation, such as fever and the temperature of summer weather, may be important in precipitating the lesions in the brain. Experimental evidence is cited in support of this idea.

## APPENDIX I. USEFUL STAINS FOR THE DEMONSTRATION OF COAGULATED SEROUS EXUDATE IN THE BRAIN

The exudate is eosinophilic like blood serum, and the perivascular accumulations are readily seen in ordinary sections stained with haematoxylin and eosin. Large areas in the gray and white matter diffusely saturated with the exudate are stained more intensely with eosin than other areas, and inspection of the stained sections with the naked eye will show the deeply stained, dark red areas in sharp contrast to the paler porous tissue which contains less exudate. Under the microscope one can see the pink-stained fluid coagulated between the fibres in the white matter, and areas in the gray matter saturated with exudate look very hyalin, homogeneous and smooth.

The precipitated protein in the exudate may be demonstrated by a variety of stains. It appears as black granular material in Weil's myelin-sheath stain (37). Even after the differentiation has been carried too far and the myelin sheaths are no longer stained, much of the exudate remains as a black precipitate. Bodian's silver method (38) for axis cylinders stains the exudate which appears as fine purplish granules.

These methods are unsatisfactory because the contrast between the color of the fluid and that of the tissues may be slight. By the use of safranin and light green the blood serum and the serous exudate are stained red. Areas in the gray and white matter which are not filled with exudate turn green, and by this method the serous red fluid in the vessels, around the vessels, and in the tissues is brought out in sharp contrast against a green background.

### *Technique*

1. Fix thin blocks in formalin. Dehydrate, embed in paraffin and cut sections in the usual way.
2. Remove paraffin with xylol, pass through alcohol, and wash in water.
3. Stain for half an hour at 40° to 50°C. in a saturated aqueous solution of safranin Y.
4. Wash in water and quickly saturate section in 95 per cent alcohol.
5. Differentiate in saturated alcoholic solution of light green. This step

requires care. If the section remains in light green too long, the blood serum, the exudate and all of the tissue, will be stained dark green. Differentiation requires only a few seconds. The section should be dipped quickly in and out of the light green. Proper differentiation is reached when the tissue which does not contain the exudate turns pale green and the areas filled with serous fluid look very dark green *to the naked eye.*

6. Wash in water and examine under the microscope. If necessary, differentiate further.

7. Dehydrate quickly in graded alcohols and xylol.

8. Mount in balsam.

## APPENDIX II. CASE REPORTS

*Case 1.* Autopsy No. 5940. A colored boy, 3 years old. History of pica, malaise for a month, and repeated convulsions for one day. Lead line on gums. Stippled red blood cells. Haemoglobin 60 per cent. *Spinal fluid:* Pandy +, cells 15 per cu.mm. *Temperature:* 99.8° to 101.2°F. *Leukocytes:* 19,000. *Died* in July. Lead line in microscopic sections of ribs. Nuclear inclusion bodies in liver and kidneys.

*Case 2.* Autopsy No. 7532. A white girl, 2 years old, who ate the paint from window-sills and toys. She was easily frightened and startled and had screaming spells for two months. Vomiting present at times for one month. Coma, nystagmus, and convulsions for a day. *Blood:* Haemoglobin 45 per cent. Stippled and nucleated red blood cells. *Spinal fluid:* Pandy 3+. Cells, 12 per cu.mm. *Temperature:* 100° to 105°F. *Leukocytes:* 58,500. *Died* in June. Slight lobular pneumonia. Lead line in microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidney.

*Case 3.* Autopsy No. 10465. A colored boy, 3 years old, who ate house paint. History of vomiting, strabismus, and convulsions off and on for a week. Lead line on gums. *Blood:* Red blood cells 3,950,000. Stippled red cells. *Spinal fluid:* Pandy +. Cells, 5 per cu.mm. Pressure increased (1+). *Temperature:* 38° to 39.6°C. *Leukocytes:* 15,400. *Died* in July. Lead line in microscopical sections of ribs. Intranuclear inclusion in liver and kidneys.

*Case 4.* Autopsy No. 10637. A white boy 22 months old, who chewed painted furniture for six months. Later constipation, projectile vomiting, and drowsiness appeared for three weeks. He had convulsions and strabismus for three days. *Blood:* Haemoglobin 50 per cent. Stippled red blood cells. *Temperature:* 37° to 38.8°C. *Leukocytes:* 16,400. *Spinal fluid:* Pandy +. Cells 9 per cu.mm. Pressure increased (4+). *Died* in October. Purulent bronchitis, microscopical lead line in ribs, and nuclear inclusions in liver and kidneys.

*Case 5.* Autopsy No. 10850. A white boy, 13 months old, who gnawed painted furniture for four months. Had a cold and convulsions with fever (104°) for two days a month before death. The first convulsion appeared after the third of a series of daily injections of "cold" vaccine. Later there was spastic paralysis

on the left, and the head and right arm were in constant motion. He was mentally retarded. Several missing teeth and ulcerated gums. *Blood:* Haemoglobin 54 per cent. Stippled red blood cells. *Spinal fluid:* Negative. *Temperature:* 38° to 42°C. *Leukocytes:* 12,300. *Died* in April. Purulent bronchitis and lobular pneumonia. Microscopical lesions of lead poisoning in ribs, and intranuclear inclusions in liver and kidneys.

*Case 6.* Autopsy No. 11766. A colored boy, 2 years old, who liked to chew paper, plaster, and clothes. For two weeks he was noisy, fretful and disobedient. Enuresis appeared and a tendency to bite and scratch. Occasionally he vomited, and had nystagmus and convulsions for one day. *Spinal fluid:* Pandy 3+. Cells 66 per cu.mm. Pressure increased (1+). *Temperature:* 98 to 105°F. *Died* in December. Lead line in x-ray and in microscopical sections of ribs. Nuclear inclusions in liver and kidneys.

*Case 7.* Autopsy No. 12168. A colored girl, 3½ years old. Over a year before death there were several periods of vomiting, abdominal pain, constipation, and crying spells. Later she was seen with house paint on her hands and face and a week afterwards vomited persistently for 3 days. This was followed by ascending paralysis, difficulty in speech and swallowing, and dysphagia. Paralysis of extremities and muscles of lower trunk and diaphragm was complete. Weakness of pharyngeal muscles. Occasional convulsive movements of facial muscles. Complete anesthesia to touch and pain over extremities and trunk. Finally, fever, coma and convulsions of facial muscles for several hours before death. *Spinal fluid:* Negative. *Blood:* Haemoglobin 60 per cent. Stippled red blood cells. *Leukocytes:* 19,500 to 22,000. *Temperature:* 37.6° to 38.4°C. *Died* in September, about six weeks after the onset of symptoms. Lead line in x-ray and microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys. Demyelinization of peripheral nerves.

*Case 8.* Autopsy No. 13334. A colored boy, 3½ years old. History of vomiting for two days. Coma, brachycardia and convulsions for one day. *Blood:* Haemoglobin 45 per cent. Stippled red cells. *Temperature:* 37.4° to 39°C. Leukocytes: 28,000. Blood lead: 0.1 to 0.2 mgm. per cent. Lead line on gums. *Spinal fluid:* Pandy 3+. Cells, 16 per cu.mm. Pressure increased (1+). *Died* in October. Lead line in x-ray and microscopical sections of ribs. Nuclear inclusions in liver and kidneys.

*Case 9.* Autopsy No. 13698. A colored boy, 2 years old, who ate plaster, ashes, and paint from window-sills. Had abdominal pain and was constipated. History of vomiting for a month. Comatose for four days and had convulsions for one day. Lead line on gums. *Blood:* Haemoglobin 50 per cent. *Blood lead:* 0.5 to 1.0 mgm. per cent. *Temperature:* 37.4° to 38.4°C. *Leukocytes:* 12,880. *Spinal fluid:* Pandy 2+. Cells 30 per cu.mm. *Died* in June. Lead line in bones (x-ray and microscopical). Intranuclear inclusion bodies in liver and kidneys.

*Case 10.* Autopsy No. 13726. A colored girl, 2 years old, troubled with vomiting for two months. Convulsions chiefly on left side and nystagmus for two days. *Blood:* Haemoglobin 58 per cent. Stippled and nucleated red cells.

*Blood lead:* 0.1 mgm. per cent. *Spinal fluid:* Pandy 4+. Cells 45 per cu.mm. Pressure increased (2+). *Temperature:* 38.6° to 41°C. *Leukocytes:* 26,350. *Died* in July. Lead line in x-ray and microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys.

*Case 11.* Autopsy No. 13795. A colored girl, 2 years old, who ate the paint from her dolls for 2 months. Abdominal pain, constipation and vomiting present for two weeks, and convulsions for a day. *Temperature:* 38° to 40.6°C. *Leukocytes:* 25,500. *Haemoglobin:* 78 per cent. *Blood lead:* 0.5 mgm. per cent. Lead line in x-ray and microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys. *Spinal fluid:* Pandy 3+. Cells, 6 per cu.mm. Pressure increased (2+). *Died* in August.

*Case 12.* Autopsy No. 13830. A colored girl, 3 years old, who sucked painted toys. History of abdominal pain and vomiting for one month, and long period of crying. Stuporous, with spontaneous motion of head and hands, and right-sided convulsions for one day. Gasping respirations. *Temperature:* 35.4° to 40.2°C. *Leukocytes:* 39,000. *Blood:* Haemoglobin 48 per cent. Stippled and nucleated red blood cells. *Blood lead:* 0.5 to 1.0 mgm. per cent. Lead line in x-ray and in microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys. *Spinal fluid:* Pandy 4+. Cells, 11 per cu.mm. Pressure increased (2+). *Died* in September.

*Case 13.* Autopsy No. 14057. A colored boy, 7 years old. Chewed crayon and chalk. Was drowsy for five weeks and had pain in abdomen and back of head. Vomited at times for four weeks. Two days before death he fell twice on the street and was unconscious for a few minutes. He later became comatose and had convulsions. *Temperature:* 37.4° to 39.5°C. *Leukocytes:* 38,800. *Blood:* Red cells 3,720,000. Normoblasts and stippled red cells in blood smears. *Blood lead:* 0.5 mgm. per cent. Lead line on gums. Lead line in x-ray and in microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys. Widespread bilateral lobular pneumonia (pneumococcus type II). *Spinal fluid:* Pandy 4+. Cells 25 per cu.mm. Pressure 600 mm. of water. *Died* in January.

*Case 14.* Autopsy No. 14287. A colored girl 3 years old. History of pica. Vomiting, headache, and drowiness for five weeks. Coma, nystagmus and convulsions for one day. Tachycardia, extrasystoles and elevated blood pressure. *Temperature:* 36 to 40.6°C. *Leukocytes:* 25,700. *Blood:* Haemoglobin 62 per cent. Stippled red blood cells. *Blood lead:* 0.5 mgm. per cent. Lead line in x-ray and microscopical section of ribs. Intranuclear inclusion bodies in liver and kidneys. *Spinal fluid:* Pandy 2+. Cells 25 per cu.mm. Pressure increased. *Died* in June.

*Case 15.* Autopsy No. 14307. A colored boy, 18 months old, who ate flakes of dry paint from the walls. Had anorexia and was fretful for six weeks. Vomited for a week. Cried almost constantly and held hands to head and abdomen for four days. Convulsions for one day. *Spinal fluid:* Pandy 2+. Cells, 15 per cu.mm. *Blood:* Haemoglobin 50 per cent. *Blood lead:* 0.5 to 1.0 mgm. per cent.

*Temperature:* 37.4 to 39°C. *Leukocytes:* 8,200. *Died* in July. Lead line in bones (x-ray and microscopical). Intranuclear inclusion bodies in liver and kidneys.

*Case 16.* Autopsy No. 14336. A colored boy, 19 months old, who ate plaster and was constipated for 2 or 3 months. He was fretful and restless, and lost appetite and weight. For a week he was drowsy and vomited. Had convulsions for one day. Lead line on gums. *Blood:* Haemoglobin 35 per cent. *Blood lead:* 0.2 mgm. per cent. *Spinal fluid:* Pandy 2+. Cells 9 per cu.mm. Pressure increased (1+). *Leukocytes:* 10,000 *Temperature:* 37° to 38.4°C. *Died* in July. Lead line in x-ray and in microscopical sections of ribs. Nuclear inclusion bodies in liver and kidneys. Slight lobular pneumonia in right middle lobe.

*Case 17.* Autopsy No. 14352. A colored boy, 18 months old, who chewed paint from an icebox and sucked an indelible lead pencil. He was constipated and irritable for two weeks, and vomited at times for a week. Had screaming attacks and convulsions for three to four days. *Spinal fluid:* Pandy 2+. Cells 0. Pressure increased (630 mm. of water). *Blood:* 87 per cent. *Leukocytes:* 8,600. *Temperature:* 37.2° to 40.6°C. *Died* in August. Lead line in x-ray and microscopical sections of ribs. Nuclear inclusion bodies in liver and kidneys.

*Case 18.* Autopsy No. 14354. A colored girl, 6 years old, poisoned by inhaling fumes from battery casings burned for fuel. She had lead encephalitis with convulsions first in July, three years before death. She recovered, though retarded mentally thereafter. A month before death symptoms reappeared and there were anorexia, cough and fever. One week before death she had a single convulsion, and vomited almost daily afterwards. There were frequent violent convulsions for sixteen hours before death. Lead line on gums. *Spinal fluid:* Pandy 3+. Cells 11 per cu.mm. *Blood:* Haemoglobin 75 per cent. Blood lead elevated for three years (0.2 to 0.5 mgm. per cent). *Temperature:* 38.6° to 40°C. *Leukocytes:* 29,000. *Died* in August. Slight lobular pneumonia. Lead line in x-ray of bones three years ago, at intervals afterwards, and on final admission. Lead line in microscopical sections of ribs. Intranuclear inclusion bodies in liver and a few in kidneys.

*Case 19.* Autopsy No. 14370. A colored girl, 2½ years old, with a history of pica. Vomiting for a week and convulsions for one day. Lead line on gums. *Spinal fluid:* Pandy 2+. Cells 11 per cu.mm. Pressure increased. *Blood:* Stippled and nucleated red blood cells. Haemoglobin 65 per cent. *Blood lead:* 0.2 to 0.5 mgm. per cent. *Leukocytes:* 24,500. *Temperature:* 39° to 41°C. *Died* in August. Lead line in bones on fluoroscopic examination and in microscopical sections. Intranuclear inclusion bodies in liver and kidneys.

*Case 20.* Autopsy No. 14849. A white girl, 3 years old, who gnawed painted furniture for 18 months. History of vomiting for three months. She was irritable, nervous, cranky and lethargic for a month. Drowsiness and coma appeared during the last two days of life, and finally convulsions. *Spinal fluid:* Pandy 2+. Cells 11 per cu.mm. *Blood:* Haemoglobin 76 per cent. Stippled red cells. *Blood lead:* 0.55 mgm. per 100 gms. *Temperature:* 37° to 40.4°C.

*Leukocytes:* 31,500. *Died* in June. Lead line in x-ray and in microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys.

*Case 21.* Autopsy No. 14954. A white boy 2 years old chewed the paint from woodwork and toys for three months. Attacks of vomiting appeared five weeks before the present illness and again for about one day before death. For about twenty hours he was drowsy and had episodes of spasticity and flaccidity, slow respirations, choked discs, stiff neck, ankle clonus and hyperactive reflexes. Finally, deep coma and death. *Spinal fluid:* Pandy 3+. Cells 10 per cu.mm. *Blood:* Haemoglobin 63 per cent. Stippled red cells. *Blood lead:* 0.41 mgm. per cent. *Temperature:* 36.2° to 37.4°C. *Leukocytes:* 21,320. *Died* in September. Lead line in x-ray and microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys.

*Case 22.* Autopsy No. 14974. A colored girl, 2½ years old, with history of pica from 9 to 12 months of age. Had projectile vomiting several times the day before death. Became limp and comatose after vomiting, and a little later convulsions appeared, first on the left and then on the right side. Repeated clonic convulsions at half-hour intervals for thirteen hours until death. *Spinal fluid:* Pandy 2+. Cells 5–10 per cu.mm. *Blood pressure:* 105/70. *Pulse:* Irregular. *Respirations:* Irregular and shallow. *Blood:* Haemoglobin 45 per cent. Red blood cells 2,700,000. Stippled red cells. *Temperature:* 38.2° to 39.2°C. *Leukocytes:* 20,940. *Died* in October. Lead line in bones (x-ray and microscopical). Nuclear inclusions in liver and kidneys. Purulent tonsillitis. Few minute tubercles in one lung and confluent tubercles in a bronchial lymph node. Large crusted pustular lesions on extremities like those of impetigo (present for two weeks).

## REFERENCES

(1) ALDERSON: *Lancet*, 1852, **2**, 73 and 95.
(2) AUB, *et al*: *Medicine*, 1925, **4**, 1.
(3) WESTPHAL: *Arch. f. Psych.*, 1888, **19**, 620.
(4) MCKHANN: *Amer. Jour. Dis. Child.*, 1926, **32**, 386.
(5) PARK, JACKSON AND KADJI: *Ibid.*, 1931, **41**, 485.
(6) VOGT: *Amer. Jour. Roentgenol.*, 1930, **24**, 550.
(7) BLACKMAN: *Bull. J. H. H.*, 1936, **58**, 384.
(8) DANA: Lead Diseases: Translation from the French of Tanquerel des Planches, 1848.
(9) MCKHANN AND VOGT: *Jour. A. M. A.*, 1933, **101**, 1131.
(10) BAKER: *Arch. of Path.*, 1935, **19**, 213.
(11) ESSER: *Dtsch. Ztschr. f. d. Gesammte Gerichtliche Med.*, 1936, **26**, 430.
(12) KATO: *Amer. Jour. Dis. Child.*, 1932, **44**, 569.
(13) MCKHANN: *Arch. Neurol. and Psych.*, 1932, **27**, 294.
(14) VOGT: *Jour. A. M. A.*, 1932, **98**, 125.
(15) WILCOX AND CAFFEY: *Ibid.*, 1926, **86**, 1514.
(16) THOMAS AND BLACKFAN: *Amer. Jour. Dis. Child.*, 1914, **8**, 377.

(17) SUZUKI AND KANEKO: *Jour. of Oriental Med.*, 1924, **2**, 55.
(18) FUKUSHIMA AND MATSUMOTO: *Oriental Jour. Dis. of Child.*, 1928, **3**, 27.
(19) MCKHANN: *Trans. Amer. Neurol. Assoc.*, 1931, 183.
(20) KUSSMAUL AND MAIER: *Disch. Arch. f. klin. Med.*, 1872, **9**, 283.
(21) VON MONAKOW: *Arch. f. Psych. u. Nervenheilk.*, 1879–80, **10**, 495.
(22) SEIFERT: *Berliner Klin. Wchnschr.*, 1884, **21**, 555.
(23) OPPENHEIM: *Arch. f. Psych. u. Nervenheilk.*, 1885, **16**, 476.
(24) COURTNEY: *Boston Med. and Surg. Jour.*, 1900, **142**, 136.
(25) CADWALADER: *Jour. of Nervous and Mental Dis.*, 1912, **39**, 153.
(26) HASSIN: *Arch. Neurol. and Psych.*, 1921, **6**, 268.
(27) FREIFELD: *Virch. Arch.*, 1928, **268**, 456.
(28) FREIFELD: *Ibid.*, 1933, **287**, 549.
(29) TUTHILL: *Bull. Buffalo Gen. Hosp.*, 1929, **7**, 15.
(30) STAEMMLER: *Klin. Wchnschr.*, 1929, **81**, 1210.
(31) WINKELMAN AND ECKEL: *N. Y. State Jour. Med.*, 1933, **33**, 427.
(32) RHEA: *Internat. Clinics*, 1934, **1**, 203.
(33) GOODWIN: *Bull. J. H. H.*, 1934, **55**, 347.
(34) TRAUBE: Gesammelte Beiträge, 1870, **2**, 551.
(35) GRINKER: Neurology, 1933, 895.
(36) BRAIN: Disorders of the Nervous System, 1933, 584.
(37) WEIL: Text-Book of Neuropathology, 1933, 314.
(38) BODIAN: *Anat. Record*, 1936, **65**, 89.
(39) OKKELS: *C. r. Soc. de biol.*, 1930, **102**, 1089.
(40) KEIBEL AND MALL: Human Embryology, 1912, **2**, 74.
(41) FERRARO AND HERNANDEZ: *The Psychiatric Quart.*, 1932, **6**, 121.
(42) WELLER AND CHRISTENSEN: *Arch. Neurol. and Psych.*, 1925, **14**, 327.
(43) GINANDES: *J. of Mount Sinai Hosp.*, 1935, **2**, 74.
(44) BLACKFAN AND HAMILTON: *Boston Med. and Surg. Jour.*, 1925, **193**, 617.

## EXPLANATION OF ILLUSTRATIONS

(Photographs by Mr. Milton Kougl)

PLATE 1. (Hematoxylin and eosin stains)

FIG. 1. Dilated capillaries in the white matter of a cerebral convolution. There is a little serous exudate along the lower margin of vessel at the top in the centre. Case 14. ×100.

FIG. 2. Dilated capillaries in the gray matter of the cerebral cortex. The smooth homogeneous spot within the circle is diffusely filled with serous fluid. Case 12. ×100.

FIG. 3. A mitotic figure in a nucleus in the wall of a capillary in the molecular layer of the cerebellum. Cass 11. ×1170.

FIGS. 4 AND 6. Clumps of swollen nuclei in the walls of capillaries in the molecular layer of the cerebellum. Case 22. ×1170.

FIG. 5. Swollen nuclei in the wall of a capillary in the inferior olive. They project outward, not into the lumen of the capillary. There is a thin irregular film of serous exudate in the tissue outside the vessel. Case 22. ×1170.

FIG. 7. A capillary in the gray matter of the cerebral cortex. The upper horizontal segment is necrotic and occluded. Along the vessel at several points are clusters of minute droplets of exudate in the spongy tissue. Case 16. ×390.

FIG. 8. An arteriole in the gray matter of the cerebral cortex. The wall is necrotic and partly fragmented along the left side. The lumen contains thrombus material. Case 17. ×390.


1
2
3
4
5
6
7
8

## Plate 2

Fig. 1. The arrows point to a single drop of serous exudate completely surrounding a segment of a capillary in the molecular layer of the cerebellum. Case 16. H. and E. stain. ×400.

Fig. 2. The arrows point to several drops of exudate coagulated along one margin of a capillary in the gray matter of the cerebral cortex. Case 16. H. and E. stain. ×390.

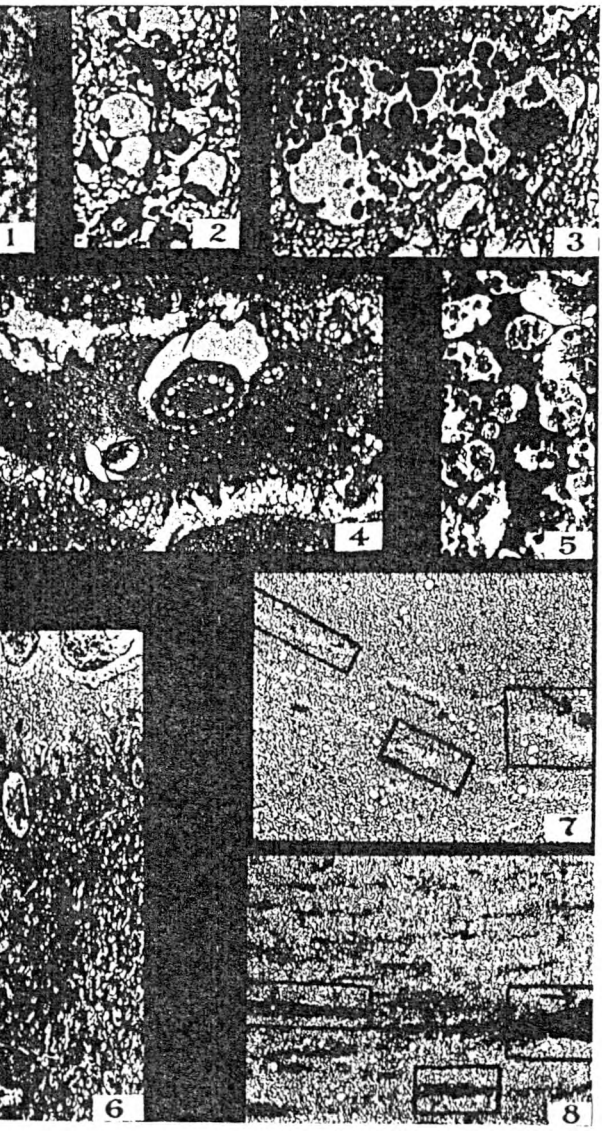
Fig. 3. A large cluster of drops of exudate about a capillary in the gray matter of the cerebral cortex. Case 12. H. and E. stain. ×390.

Fig. 4. Serous exudate in the meninges of a sulcus between two cerebral convolutions. The exudate is identical in appearance with blood serum in the vessels. Case 19. H. and E. stain. ×100.

Fig. 5. Serous fluid between acini of cells in the anterior lobe of the hypophysis. Case 22. Mann's stain. ×200.

Fig. 6. A large area in the gray matter of the cerebral cortex diffusely infiltrated with serous exudate. The molecular layer at the top is not infiltrated. Case 12. Safranin and light-green stain. ×65.

Figs. 7 and 8. Consecutive serial sections stained by different methods to show perivascular serous exudate in the white matter. The section in Fig. 7 is stained with hematoxylin and eosin; in Fig. 8 with safranin and light-green. The sections were mounted at different angles on the slides, but arrows point to the same little vessel in each section, and identical collections of exudate are bracketed with ink. Case 15. ×80.


1
2
3
4
5
6
7
8

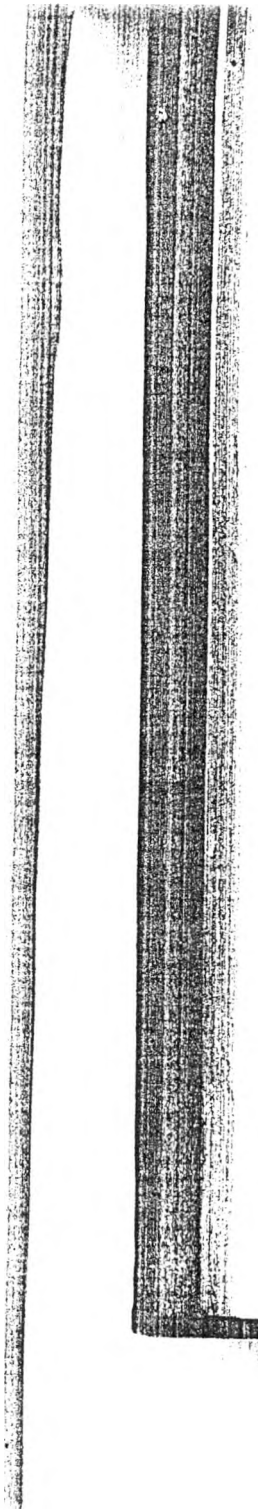


PLATE 3

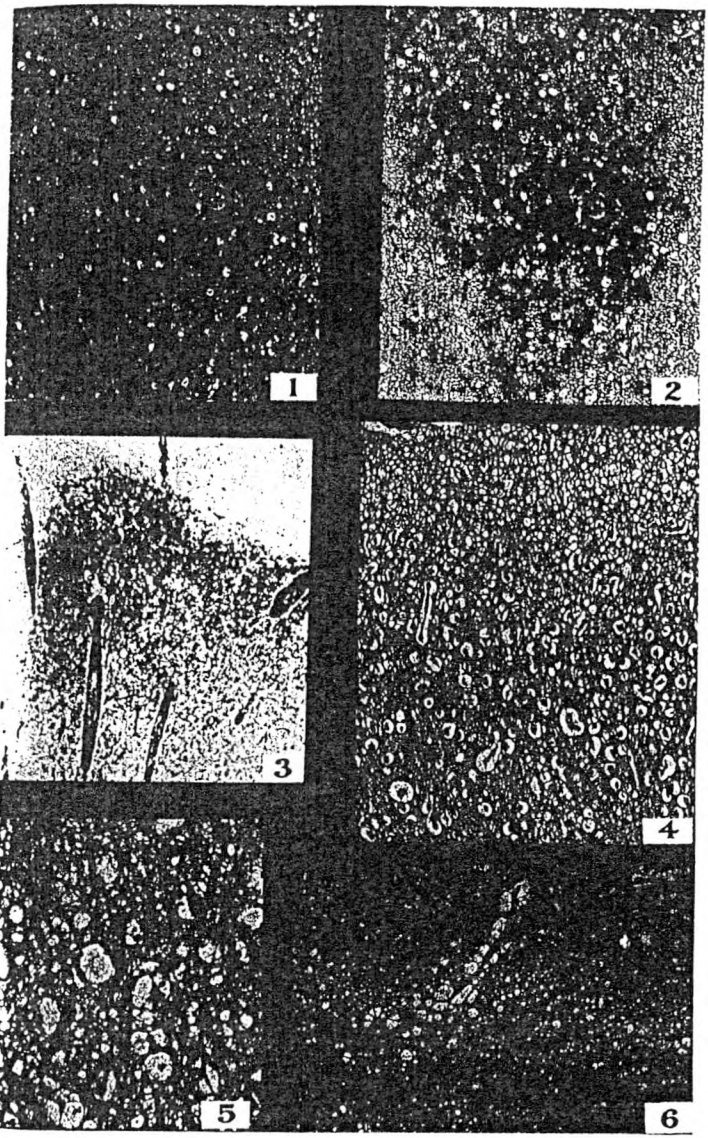
FIGS. 1 AND 2. Perivascular and diffuse exudate in the central white matter of a cerebral convolution. In Fig. 1 the section is stained with hematoxylin and eosin. It was decolorized and the exudate shown to better advantage when stained with safranin and light-green (Fig. 2). The arrows point towards a ring of exudate about an arteriole. There is a narrow strip of tissue about the vessel composed of neuroglia and adventitia, torn loose by the exudate. Case 12. ×90

FIG. 3. A low magnification of the whole apical part of the central white matter of one cerebral convolution. The apical white matter is diffusely infiltrated with serous exudate and there is perivascular fluid in gray and white matter. Case 12. Safranin and light-green. ×20.

FIG. 4. Gray matter of the cerebral cortex. In the upper part of the figure extremely porous and vacuolated tissue is shown where most of the nerve cells are necrotic. Case 11. H. and E. stain. ×100.

FIG. 5. Diffuse distortion of the architecture of the gray matter of the cerebral cortex. The fibres are stretched and torn. The parallel arrangement of cells is lost. Case 2. H. and E. stain. ×200.

FIG. 6. Marked disturbance of architecture in a narrow zone at the junction of gray and white matter. Case 16. H. and E. stain. ×100.


1
2
3
4
5
6

## PLATE 4

FIG. 1. The meninges and molecular layer of the cerebral cortex. A narrow superficial zone of tissue is extremely spongy. Fibres are stretched and torn. The inner layer of the pia mater is torn loose and pushed upward. There is some perivascular serous exudate which is continuous with a number of little streams of fluid in the spongy molecular layer. Case 14. H. and E. stain. ×100.

FIG. 2. A torn distorted superficial zone in the molecular layer of the cerebral cortex. The pia mater is displaced. In the centre small confluent collections of serous fluid and several pyknotic glial nuclei are shown. Case 16. H. and E. stain. ×200.

FIG. 3. A group of large astrocytes with swollen nuclei in the molecular layer of the cerebral cortex. Case 11. H. and E. stain. ×200.

FIG. 4. Fat laden glial cells in the molecular layer of the cerebral cortex. Case 11. Osmic acid stain. ×200.

FIG. 5. Low magnification of the central white matter of a cerebral convolution. There are numerous localized foci of extremely porous torn tissue. Case 19. H. and E. stain. ×35.

FIG. 6. Higher magnification of similar torn tissue about a capillary in the gray matter of the cerebral cortex. Case 19. H. and E. stain. ×200.

FIG. 7. A localized area of torn spongy tissue still partly filled with serous exudate. Case 19. H. and E. stain. ×200.

FIGS. 8 AND 10. A pool of exudate (Fig. 8) has torn through the white matter leaving a narrow strip of damaged fat-laden glial cells attached to the adventitia of the arteriole. Single cells and clumps of cells lie free in the fluid. Case 14. H. and E. stain. In Fig 10 (Case 14) the fat-holding cells are shown stained with osmic acid. ×200.

FIG. 9. Low magnification of central white matter of a cerebral convolution. There is loss of tissue in wide zones about blood vessels. The fibres that remain in the spongy areas are necrotic and fragmented. Case 14. Weil's stain for myelin sheaths. ×80.

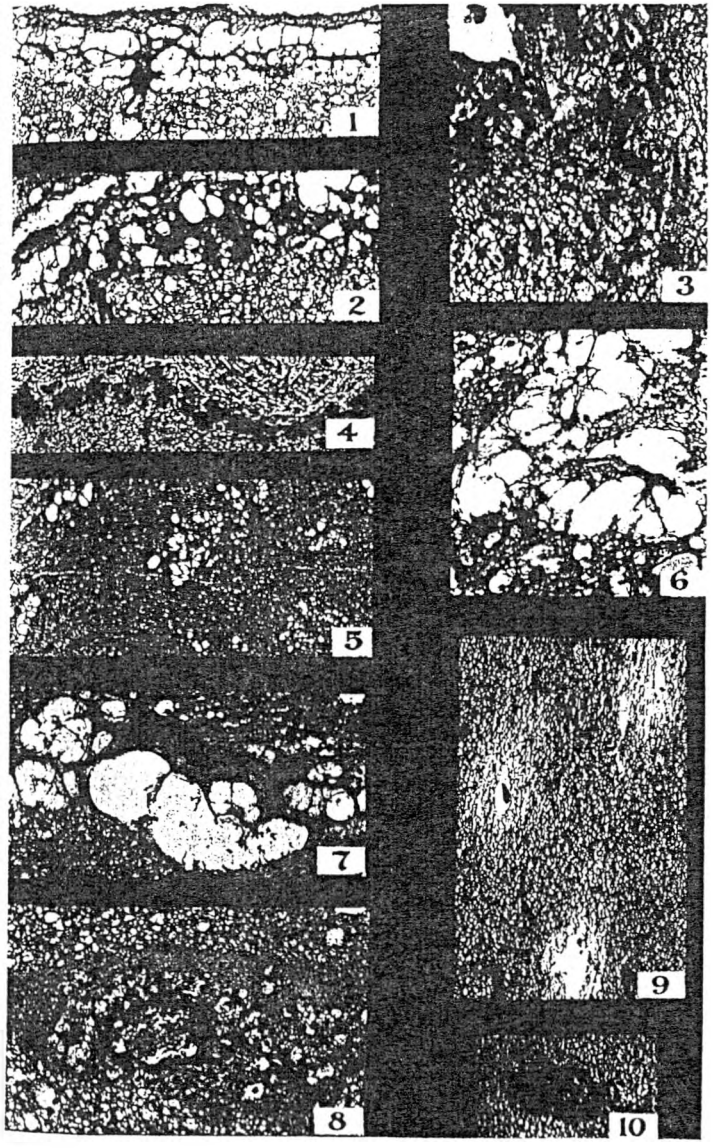


PLATE 5. (Hematoxylin and eosin stains)

FIG. 1. A small focus of necrotic tissue and peripheral haemorrhage in the motor nucleus of the 5th cranial nerve. Case 18. ×200.

FIG. 2. An area of necrosis with peripheral growth of glial cells in the white matter of the insula. The arrow points to a mitotic figure. Case 4. ×390.

FIG. 3. Two necrotic nerve cells in the thalamus. There are four or five neurophagocytes about the upper nerve cell and more numerous ones about the lower cell. Case 10. ×390.

FIG. 4. A small focus of necrosis, and glial cells in the peripheral spongy tissue in the cerebral cortex. Case 20. ×200.

FIG. 5. A fresh area of necrosis and peripheral haemorrhage in the cerebral white matter. Case 20. ×200.

FIG. 6. A rosette of neuroglia about a centrally placed necrotic nerve cell in one of the geniculate bodies. Case 2. ×390.

FIG. 7. Distorted architecture and numerous large astrocytes in the apical white matter of a cerebral convolution. Case 11. ×200.

FIG. 8. A rosette of glial cells about a necrotic nerve cell in the thalamus. Case 14. ×390.

FIG. 9. A single necrotic nerve cell in the cerebral cortex without appreciable glial reaction. Case 20. ×390.

FIG. 10. A nodular collection of neuroglia in a focus of necrotic tissue in the gray matter of the cerebral cortex. Case 17. ×200.

FIG. 11. A small focus of necrotic tissue and peripheral gliosis in the white matter of the spinal cord. Case 2. ×390.

FIG. 12. Focus of necrotic tissue and peripheral glial cells in the brachium conjunctivum. Case 18. ×390.

FIG. 13. The arrow points to the nucleus of a necrotic nerve cell accompanied by neurophagocytes in one anterior horn of the lumbar spinal cord. Case 14. ×390.

FIG. 14. On the right a normal nerve cell in the thalamus is shown. On the left is the remnant of a necrotic nerve cell surrounded by a few glial cells. Case 10. ×390.

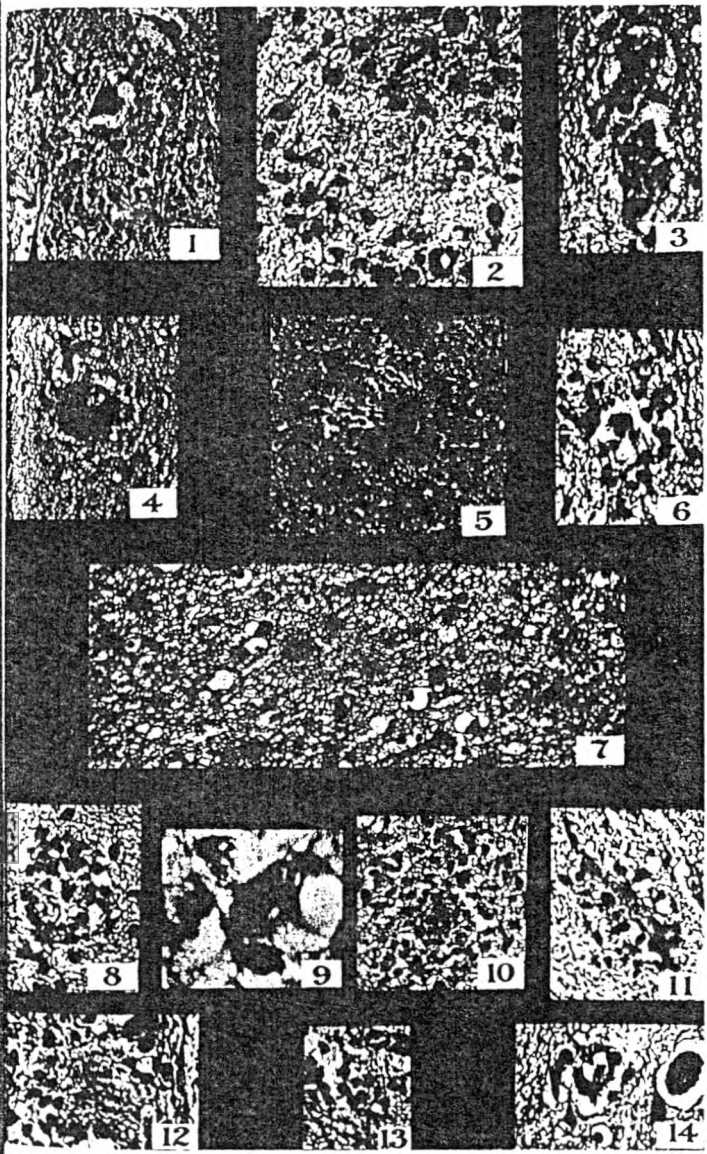

1
2
3
4
5
6
7
8
9
10
11
12
13
14

PLATE 6. (Hematoxylin and eosin stains)

FIG. 1. Perivascular serous exudate in the white matter of the cerebellum. Case 14. ×50.

FIG. 2. Serous exudate and torn necrotic tissue in the Purkinje layer of the cerebellum. Case 19. ×200.

FIG. 3. Extensive necrosis and loss of tissue in the white matter of the cerebellum. Case 14. ×50.

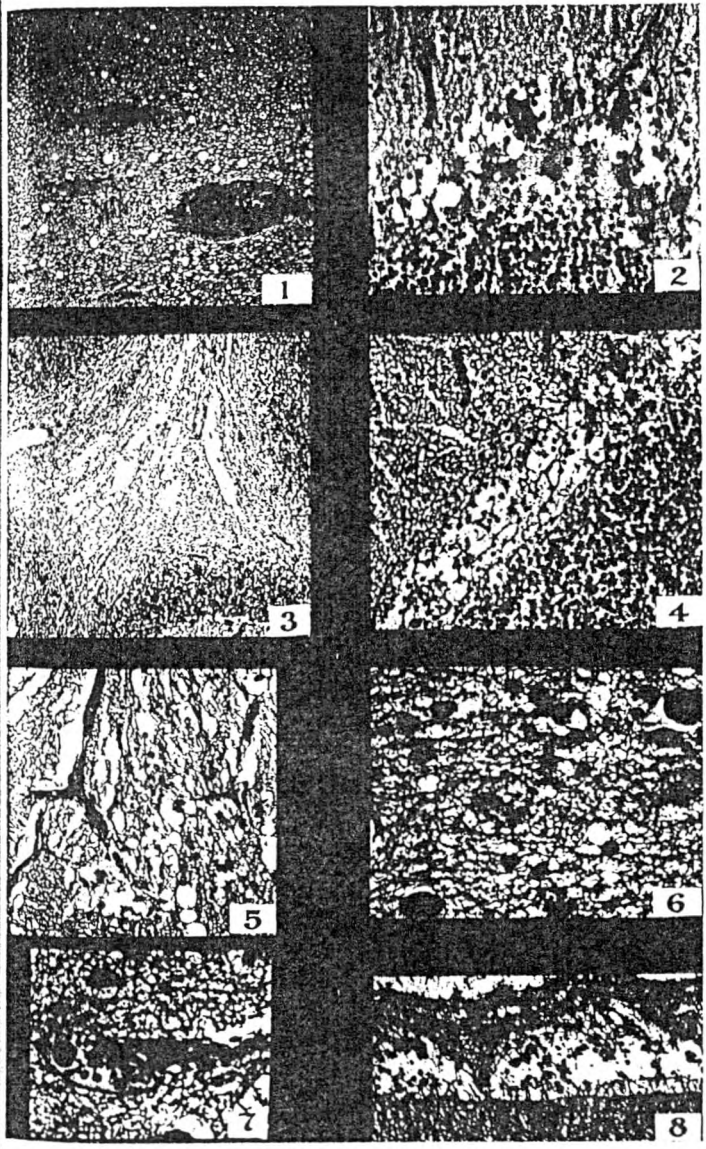
FIG. 4. The arrows point to necrotic Purkinje cells. The rest of the Purkinje layer is stretched and torn and devoid of nerve cells. Case 15. ×200.

FIG. 5. Distorted architecture and new glial cells in spongy patches of the molecular layer of the cerebellum Case 17. ×200.

FIG. 6. Necrotic glial cells scattered in the white matter of the cerebellum. Case 14. ×390.

FIG. 7. A thrombus in a necrotic capillary segment in the cerebral cortex. Within the circle are minute and larger droplets of inspissated exudate. Case 16. ×390.

FIG. 8. Shows (1) a narrow superficial zone of torn spongy tissue in the molecular layer of the cerebellum, (2) small round cells of the marginal embryonic stratum and the inner layer of pia mater torn from the surface and forced outward, (3) serous exudate in the subarachnoid space at the top of the figure. Case 14. ×200.


1
2
3
4
5
6
7
8

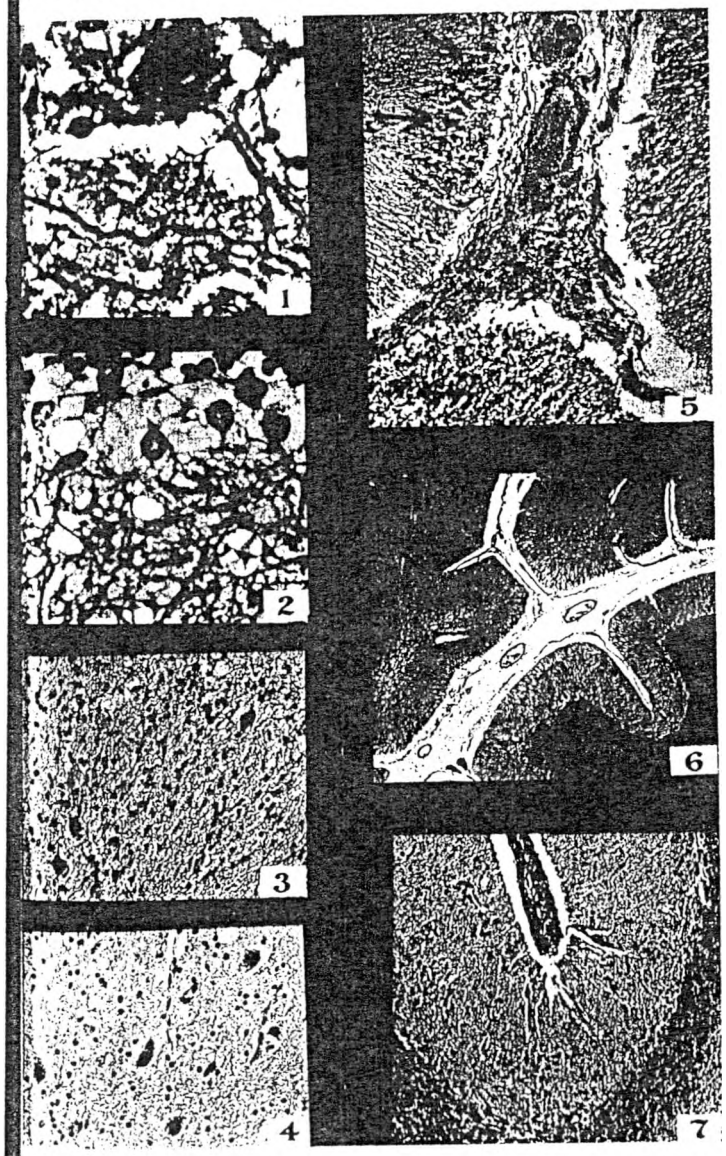



PLATE 7

FIGS. 1 AND 2. Cerebellum, Case 14. Bodian's silver stain for axis cylinders. Figure 1 shows a normal Purkinje cell and fibres of basket cells which run horizontally in the molecular layer and end around the Purkinje cells. In Fig. 2 is shown an area from which the Purkinje cells and the dendrites of basket cells have disappeared. ×670.

FIGS. 3 AND 4. Dentate nucleus of cerebellum, Case 2. H. and E. stain. Fig. 3 shows loss of many nerve cells and diffuse new growths of neuroglia. In Fig. 4 a more normal area in the same dentate nucleus is shown for comparison. ×200.

FIG. 5. Extensive destruction of tissue in the molecular layer of three folia of the cerebellum. Most of the remaining tissue is composed of neuroglia. The arrows point to collections of basophilic material resembling calcium. The adjacent meninges are somewhat scarred and are infiltrated with lymphocytes. Case 19. H. and E. stain. ×100.

FIG. 6. Diffuse atrophy, loss of cells and fibres, and gliosis affecting several folia of the cerebellum. More normal folia are shown below at the right. Case 18. H. and E. stain. ×25.

FIG. 7. Irregular growth of neuroglia in patches in the molecular layer of the cerebellum. Only a single Purkinje cell remains. Lymphocytes about a blood vessel in the meninges. Case 19. H. and E. stain. ×100.

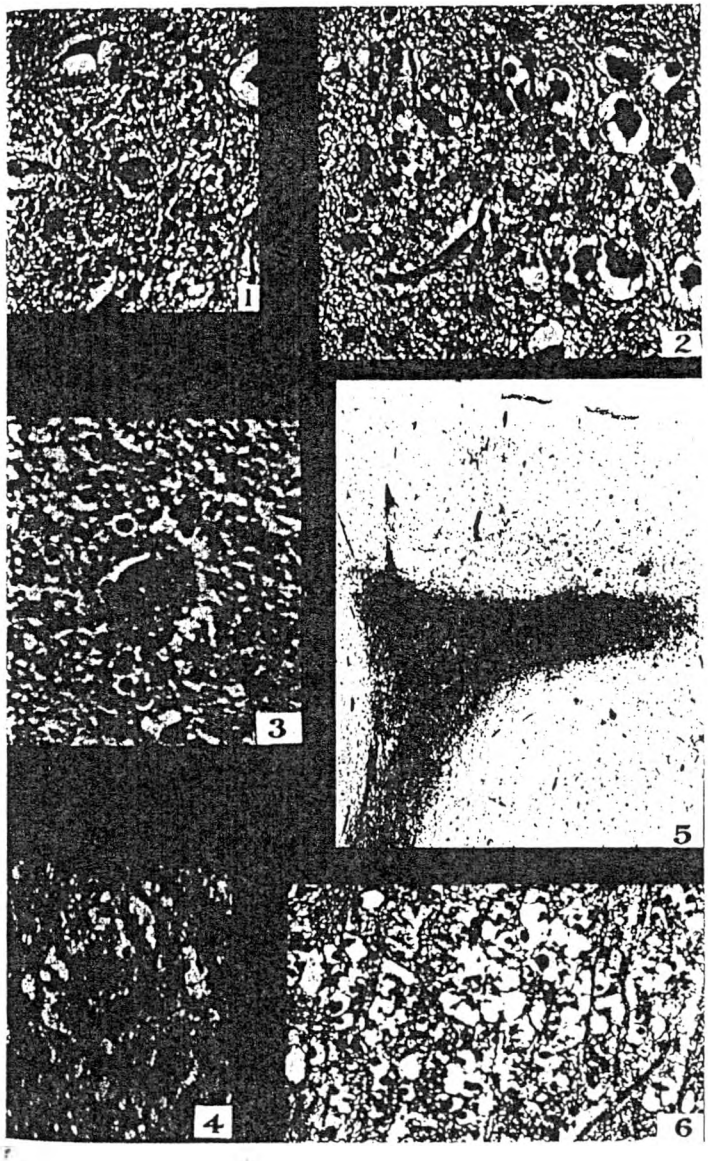



PLATE 9

FIG. 1. A fresh area of necrosis in the inferior olive with a central capillary thrombus and peripheral ring of haemorrhage. Case 20. H. and E. stain. ×390.

FIG. 2. A larger nodule in the inferior olive composed of neuroglia which has replaced the normal tissue. Nerve cells may be seen at the right. None are left in the glial nodule. Case 17. H. and E. stain. ×390.

FIG. 3. A thrombus in an arteriole. Glial reaction in the tissue immediately about the vessel. Case 18. H. and E. stain. ×390.

FIG. 4. Capillary thrombus and focus of necrotic tissue without haemorrhage in the cerebral white matter. Case 20. H. and E. stain. ×390.

FIG. 5. A cerebral convolution in which the central white matter is diffusely saturated with serous exudate. Perivascular fluid may be seen in the gray matter. Case 12. Safranin and light-green stain. ×12.

FIG. 6. Cerebral cortex of a child dying a year and a half after onset of the original symptoms. There is extensive patchy destruction and loss of tissue. Case 7. H. and E. stain. ×200.