FAMILIAL OCCURRENCE OF "IDIOPATHIC" CALCIFICATION OF CEREBRAL CAPILLARIES *

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In his review of the literature in 1948, Löwenthal[1] found 32 cases of idiopathic non-arteriosclerotic intracerebral vascular calcification, or Fahr's disease, among which were 3 instances of familial occurrence. These cases were proved by x-ray demonstration of cerebral calcification, biopsy, or necropsy. The following 2 instances of this condition, one occurring in a white male child who died at the age of 33 months, and the other in a younger brother who died at 31 months, are reported because of the rare familial occurrence.

REPORT OF CASES

Family History. On the maternal side a half-brother died of unknown cause at the age of 2 years, death being ascribed either to diarrhea or pneumonia. Two sisters of the maternal grandmother each had one stillborn male infant. The mother was well at 24 years of age when the history was taken. In addition to the 2 children affected with this disease, she had had one spontaneous abortion.

On the paternal side, there were no significant data.

Case 1

A white male child was admitted to Tripler General Hospital at the age of 6 months because of convulsions of recent development. The pregnancy and birth were uneventful. The birth weight was 7 lbs. 3 oz. Shortly after birth, there developed alternating constipation and diarrhea, poor eating, and frequent episodes of vomiting. For several weeks prior to admission there was a nasal discharge associated with fever.

Physical Examination. On admission the child was malnourished, dehydrated, and weighed 9 lbs. 2 oz. The temperature was 102° F. There were enlarged anterior cervical lymph nodes, but no other positive physical findings.

Laboratory Studies. The urine contained a trace of albumin; the red blood cell count was 3.78 millions; hemoglobin, 12 gm.; white blood cells, 10,300, and the differential count was within normal limits. A stool examination was positive for fat and negative for undigested food and starch. The level of the blood cholesterol was 365 mg. per cent; the fasting blood sugar, 87 mg. per cent. Roentgenograms of the skull, long bones, chest, and gastro-intestinal tract were all within normal limits. An electro-encephalogram was interpreted as normal.

* The opinions or assertions contained herein are those of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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Course. Supportive treatment was instituted but with little improvement. Skull trephinations were performed bilaterally without giving evidence of subdural hematoma or other lesions. The child was discharged with a diagnosis of primary mental deficiency. At the age of 15 months he was re-admitted to this hospital with similar complaints, but repetition of the previous studies again was not diagnostic. At the age of 2 years and 10 months the child was examined in the Out-Patient Department of the U.S. Naval Hospital, Oakland. At that time he gave evidence of further mental and physical retardation, the level of development being considered at less than 2 years. His diet, which had always been poor, now consisted mostly of milk. There had been fever and vomiting 6 days prior to admission; he had then developed right-sided paralysis.

On admission his weight was 21 lbs. He had a tendency to hold his head to the left. His left arm was spastic. He was unable to move the right arm and leg, yet the deep tendon reflexes were active and equal and there were no pathologic reflexes.

Laboratory Studies. The serum sodium was 135 m.eq. per liter; calcium, 11.4 mg. per cent; potassium, 4.1 m.eq. per liter. The serum cholesterol was 330 mg. per cent. Phosphorus was 7.04 mg. per cent and chlorides 634 mg. per cent. Repeated examinations of the urine revealed 4 to 8 red blood cells with 10 granular casts per high-power field. The total serum protein was 6.3 gm., albumin being 2 gm. and globulin 4.3 gm. The white blood cell count was 18.000 with a normal differential. A blood culture was reported as negative. The spinal fluid contained 6 red blood cells and 3 white blood cells per high-power field. The protein in the spinal fluid was 38.4 mg. per cent; sugar, 83 mg. per cent; chlorides, 880 mg. per cent; Pandy's test, negative. Roentgenograms of the skull and other bones again were negative. The hospital stay of approximately 1 month was characterized by episodes of fever, increased spasticity, and finally coma terminating in death.

Necropsy Findings

Gross Examination. At necropsy the brain weighed 767 gm. It was obviously reduced in size, but showed, externally, only diffuse swelling and engorgement of the pial vessels. Coronal sections demonstrated enlargement of the lateral ventricles which measured 18 mm. in width at the level of the anterior horns. The most conspicuous gross change was the presence of symmetric areas of softening and hyperemia, having a granular or sandy consistency. These were located in the centrum semi-ovale of the frontal and parietal white matter (Figs. 1 and 2) and in the superior aspect of the lenticular nuclei. In the white matter of the parietal and occipital lobes there were no areas of softening, but a similar granularity was palpated. There were no changes in the brain stem, but granular areas were noted also in the white matter of the cerebellum.

Other significant findings at necropsy were: atrophy of the testes, thyroid gland, and thymus. Each testis weighed 3 gm.; the thyroid gland, 2 gm.; and the thymus, 5 gm. There was also an incomplete congenital stricture of the lower third of the right ureter with a mild right hydro-ureter and hydronephrosis. A Meckel's diverticulum,

measuring 3.5 cm. in length and 1 cm. in diameter, was present 115 cm. proximal to the ileocecal valve.

Microscopic Observations. Sections of the brain revealed a striking picture of calcification of the capillaries and, to a lesser extent, of the arterioles and venules in both the cerebral gray and white matter. The changes occurred in foci, predominantly in the central white matter (Fig. 3), but also in segments of the cortex lying in troughs of the sulci; in the latter, only the deep layers were involved. A similar change was present in the various parts of the thalamus (Fig. 4), but particularly in its lateral nucleus, in the major part of the putamen (Fig. 5), and to a lesser extent in the globus pallidus. The mildest change was noted in the dentate nucleus (Fig. 6) and adjacent white matter of the cerebellum. In all of these areas the capillary bed was prominent by virtue of deposition of a lime-like substance, varying from discrete droplets to homogeneous fused masses. This substance stained blue-black with hematoxylin and eosin, black with von Kossa's method, red with iron-carmine, and deep blue with Holzer's crystal violet[1a] method. These histochemical reactions suggested that the deposited material was calcium rather than iron or amyloid. Variable changes were noted in the underlying tissues, such as gliosis by astrocytes and their fibers, and areas of necrosis with fat-containing gitter cells. These changes, however, were mild to moderate and became apparent only where the calcification was most pronounced, suggesting that they were secondary to the vascular disorder.

Other pathologic findings included: Amyloid deposits in the arterioles of the splenic corpuscles; mild hyperplasia of the parathyroid glands, which were composed mostly of principal cells, a rare oxyphilic cell, and an occasional uninucleated or multinucleated giant cell; degeneration of the convoluted tubular epithelium of the kidneys with droplet formation, necrosis, and many hyaline casts, particularly in the collecting tubules and most striking in the right kidney. The thyroid gland was composed mostly of follicles of small to moderate size which were lined with columnar epithelium and had a poor colloid content. The pituitary gland was not remarkable.

Comment

This case is a classical example of so-called idiopathic calcification of the cerebral vessels. The lesions were characteristically symmetric and involved predominantly the central white matter of the frontal lobes, the basal ganglia, the thalamus, and dentate nuclei of the cere-

bellum. There was no clinical or chemical evidence of parathyroid deficiency and histologically the parathyroid glands showed a mild hyperplasia. The nephrosis probably had been present for some time since there was mild albuminuria at the age of 6 months and granular casts later, persistently high normal blood cholesterol, and a reversal of the albumin-globulin ratio. The amyloidosis of the spleen probably was secondary to the nephrosis. Other findings were underdevelopment of the tnymus, thyroid gland, and testes, and congenital anomalies in the form of partial stricture of the right ureter, a Meckel's diverticulum, and an accessory spleen.

Case 2

The younger brother of the patient designated as case 1 was admitted to Tripler General Hospital at the age of 2 months with complaints of constipation, fever, and vomiting. The child weighed 6 lbs. 13 oz. at birth. During pregnancy the mother had mild bleeding during the first 3 months but continued to a full-term, spontaneous delivery. The child did not breathe spontaneously immediately after birth and considerable assistance was necessary to start respiration. Bouts of fever with elevation of temperature to 101° and 120° F. had been present daily for 1 week. The vomiting had become more forceful 3 days prior to admission.

Physical Examination. On admission the child was pale, poorly developed, and weighed 7 lbs. 12 oz. There was moderate dehydration and poor turgor of the skin. There were no other physical abnormalities.

Laboratory Studies. The red blood cell count initially was 2.8 millions but with treatment rose to 4.57 millions. The differential count was 30 per cent neutrophils and 70 per cent lymphocytes. Urinalysis was normal; the serum sodium was elevated to 329 mg. per cent. The spinal fluid was normal, showing a total protein of 24 mg. per cent; sugar, 62 mg. per cent; no cells; a normal colloidal gold curve; and a negative Wassermann test. Studies for toxoplasmosis were negative. Adrenal insufficiency was considered, but the addition of sodium chloride to the feeding formula produced no clinical improvement. Dural taps at the age of 2½ months revealed no evidence of subdural hematoma. A pneumo-encephalogram done at the age of 3½ months was interpreted by one observer as showing "left cerebral atrophy and a small cyst of the 5th and 6th ventricles," and by another observer, as being within normal limits.

Course. The further course was characterized by repeated vomiting, constipation, and fever. At the age of 4½ months, the infant weighed 8 lbs. 6 oz., and he was discharged from the hospital with a diagnosis of mental deficiency, cause undetermined.

The patient was first seen at the U.S. Naval Hospital, Oakland, California, at the age of 11 months with complaints of poor gain in weight, poor eating, constipation, and intermittent convulsions. His physical development was delayed, as evidenced by the fact that he could not hold his head up until the age of 6 months and at the age of 11 months (on admission) he could not sit up. He had four teeth. Fever had been almost constant. At that time the child weighed 9 lbs. 2½ oz. He was poorly nourished but seemed happy and followed objects with his eyes. The circumference of the head was 16 inches; that of the chest, 14 inches; and the anterior fontanelle was 3 by 2 cm. There was a slight discharge from the nose and a mild congestion of the tonsils and pharynx. The abdomen was soft and doughy. The heart and lungs

were negative. The testicles were descended. Neurologic examination revealed hyperactive deep tendon reflexes.

Laboratory Studies. Non-protein nitrogen was 83 mg. per cent; creatinine, 0.625 mg. per cent; sodium, 161 m.eq. per liter; and potassium, 5.0 m.eq. per liter. A complete blood count was negative except for mild anemia. Urinalysis was negative. Roentgenograms, including a skull plate, were negative. Subdural taps were performed but were unrevealing. Intravenous pyelograms showed poor concentration of the dye. The patient was discharged 1 month after admission.

The third admission to the same hospital was at the age of 12½ months. The child then weighed 9 lbs. 10 oz. There had been no change in the clinical course. The serum sodium remained at the high level of 165 m.eq. per liter. The blood calcium levels were normal. Chlorides were 114 m.eq. per liter; cholesterol, 243 mg. per cent; non-protein nitrogen, 42 mg. per cent. Spinal fluid sugar was 55 mg. per cent and protein, 38 mg. per cent.

At 2 years of age the child suffered an ear and throat infection with a fever of 105° F. He was examined and treated elsewhere and his weight was then 9 lbs. Since that time he had improved considerably in nutritional status so that at 2½ years of age his weight was 16 lbs. He could also stand but was unable to walk.

He was admitted to another activity at the age of 31 months with a history of fever of 104° F., and episodes of convulsions for 3 days. Physical examination was negative and the following day he improved considerably. On the third hospital day there was a recurrence of the fever to 102° F. with onset of tonic convulsions and generalized rigidity which was more marked on the right side. He developed cyanosis, tachycardia, and slow, deep, regular respirations. The remaining physical examination at that time was negative. There was progressive coma with death occurring on the fourth hospital day.

Laboratory Studies. The urine was alkaline, with negative albumin and 2 to 4 white blood cells per high-power field. Spinal fluid was clear, with sugar 50.6 mg. per cent; chlorides, 734 mg. per cent. No organisms or cells were seen on microscopic examination. The white blood cell count was 5,850 with 85 per cent segmented cells and 15 per cent lymphocytes. Red blood cell count was 3.84 millions with hemoglobin of 10.5 gm.

Comment

The clinical course of this child closely resembled that of his older brother. In both cases there were mental and physical retardation, persistent febrile episodes, constipation, convulsive seizures, and laboratory evidence of high normal serum cholesterol. In case 1 there was proved nephrosis while in case 2 there was evidence of renal disease as revealed by poor concentration of the dye for the pyelogram. In both cases roentgenograms of the head failed to demonstrate cerebral calcification.

Necropsy Findings

The brain, in its fresh state, weighed 1000 gm. and showed diffuse symmetric swelling. Sections prepared from limited material available showed scattered calcareous deposits in capillaries, particularly in the subcortical white matter (Fig. 7) and in the putamen and globus pallidus (Fig. 8). Sections from the spinal cord, pons, and cerebellum showed no such deposits. There were no parenchymal changes.

Discussion

In reviewing the literature, it is apparent that the condition of "idiopathic" calcification of cerebral capillaries is not a disease entity. It can occur at different age periods. In the adult form it usually presents a picture of organic psychosis,[2] often with extrapyramidal signs[3] while in the infantile form it frequently manifests itself as a convulsive disorder. As stated before, of the 32 cases summarized by Löwenthal,[1] there were only 3 familial instances.

In recent years, Eaton[4,5] and his associates have presented clinical and chemical evidence of parathyroid deficiency in some of these cases and, moreover, favorable response to therapy with calcium and parathormone has been stressed in such instances. However, in the 2 cases reported here there was no clinical evidence to suggest hypoparathyroidism. Furthermore, in case 1, examination of the parathyroid glands showed no demonstrable pathologic condition. This would be in keeping with the consideration that some cases of Fahr's disease are probably due to other, and perhaps local, disturbances of metabolism rather than to a general disturbance in blood calcium brought about by parathyroid insufficiency. The familial occurrence in these cases would suggest inheritance of a specific metabolic difficulty similar to the familial occurrence of, for example, lipid metabolic disorders.

Summary

The rare familial occurrence in two male siblings of non-arteriosclerotic idiopathic calcification of the cerebral vessels, or Fahr's disease, is reported. The complete findings at necropsy are included in the case report of the older brother who died at the age of 33 months, plus the findings in the brain of the younger brother who died at the age of 31 months.

It is my opinion that this condition is not a disease entity. Although some cases appear to be due to hypoparathyroidism,[5] others may be on the basis of local disturbances of calcium metabolism. Still others, as in the cases presented here, appear to be the result of an inheritance of a specific metabolic disorder.

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[Illustrations follow]

LEGENDS FOR FIGURES

FIG. 1. Case 1. Coronal section of frontal lobes, showing symmetric areas of granular softening in the centrum semi-ovale.

FIG. 2. Case 1. Enlarged view of the gross appearance of the right centrum semi-ovale as shown in Figure 1. Small beads of calcium stand out in the vascular areas. × 5.

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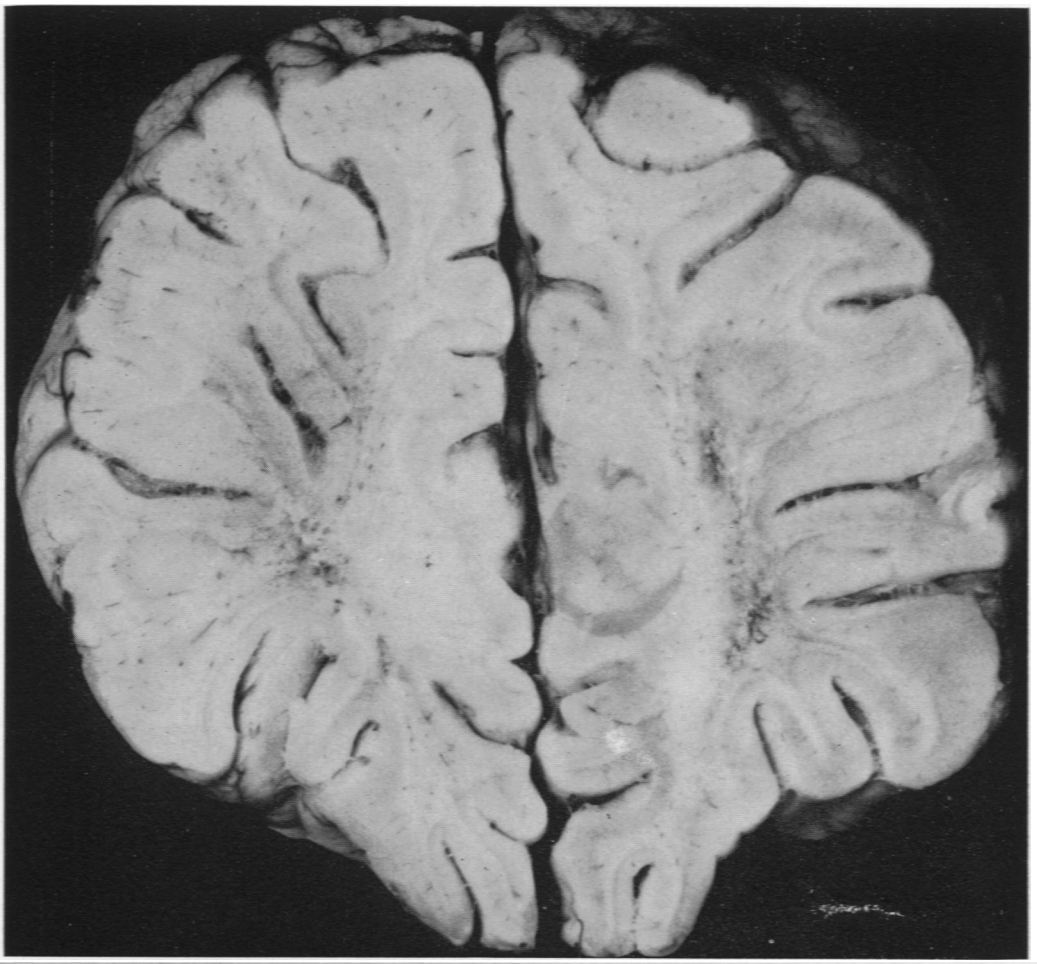

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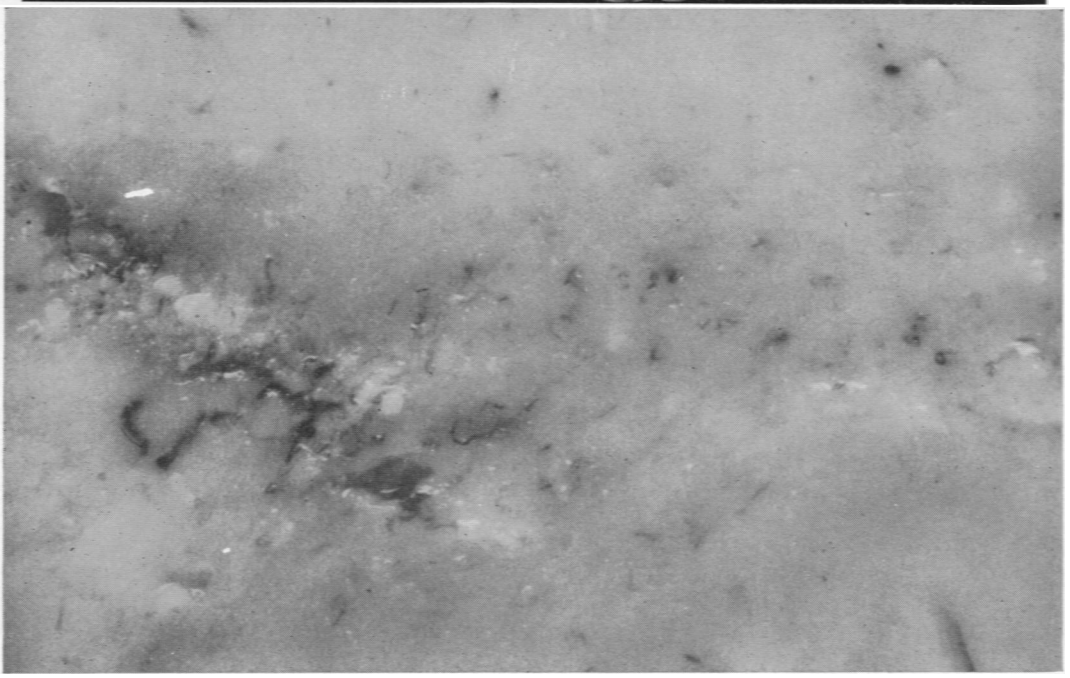


FIG. 3. Case 1. Cerebral (frontal) white matter, deep layers of cortex, showing striking calcification of the capillary bed, with deposition varying from discrete droplets to homogeneous fused masses. Von Kossa's method for calcium. × 100.

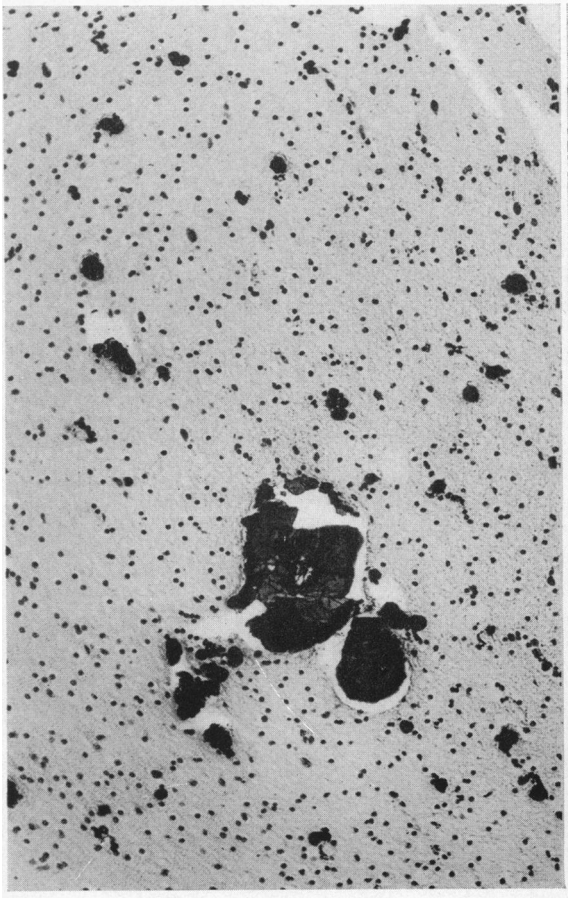
FIG. 4. Case 1. Thalamus. A change similar to that in Figure 3 is present. Cresyl violet (Nissl) stain. × 100.

FIG. 5. Case 1. Putamen and globus pallidus. Abundant calcification. Cresyl violet (Nissl) stain. × 40.

FIG. 6. Case 1. Dentate nucleus. Calcification is present although less marked than in the region illustrated in Figure 5. Weil's myelin stain. × 100.

FIG. 7. Case 2. High power view of area of the cerebral cortex, showing fused masses of calcium within small capillaries. Hematoxylin and eosin stain. × 420.

FIG. 8. Case 2. Putamen and globus pallidus, showing deposits of calcium in small capillaries and in the wall of a small vein. Hematoxylin and eosin stain. × 560.



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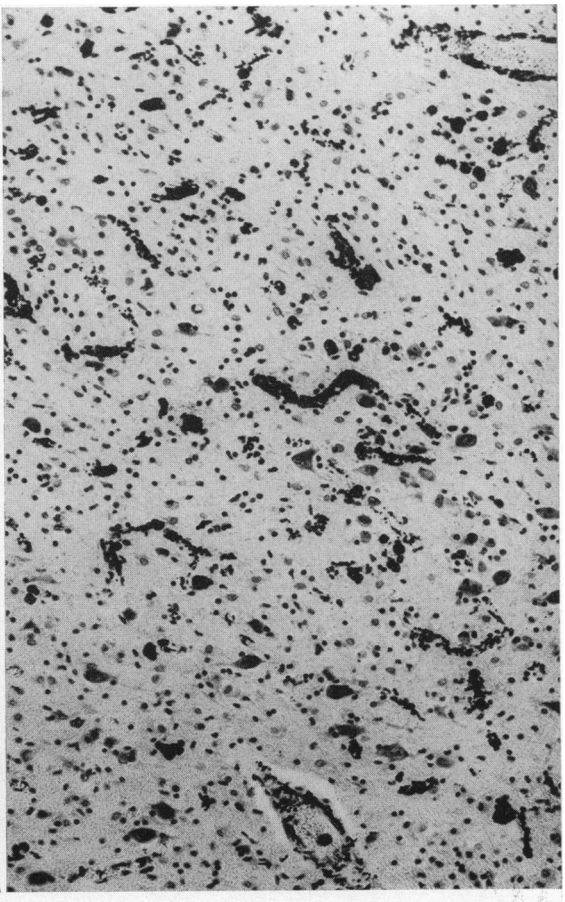

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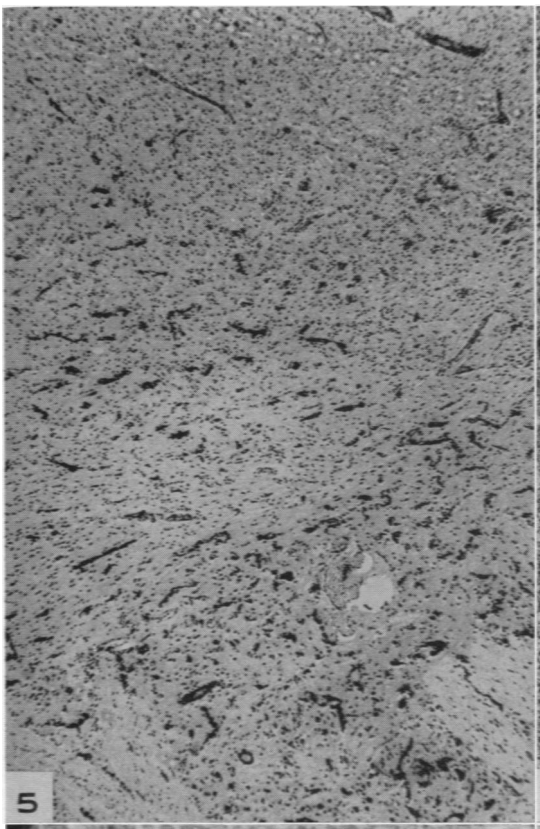
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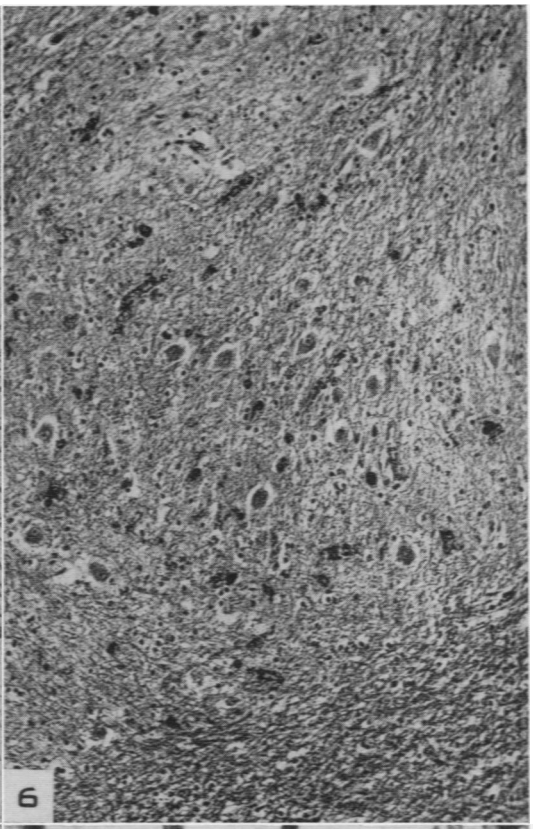
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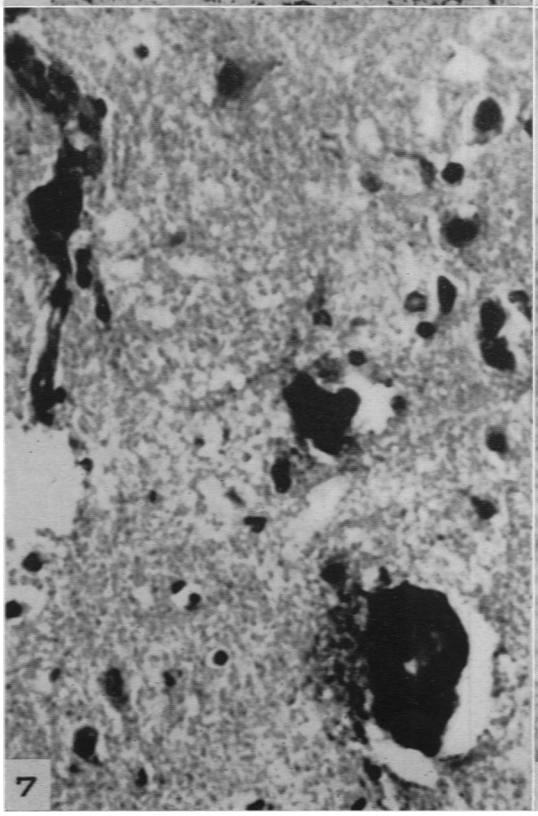
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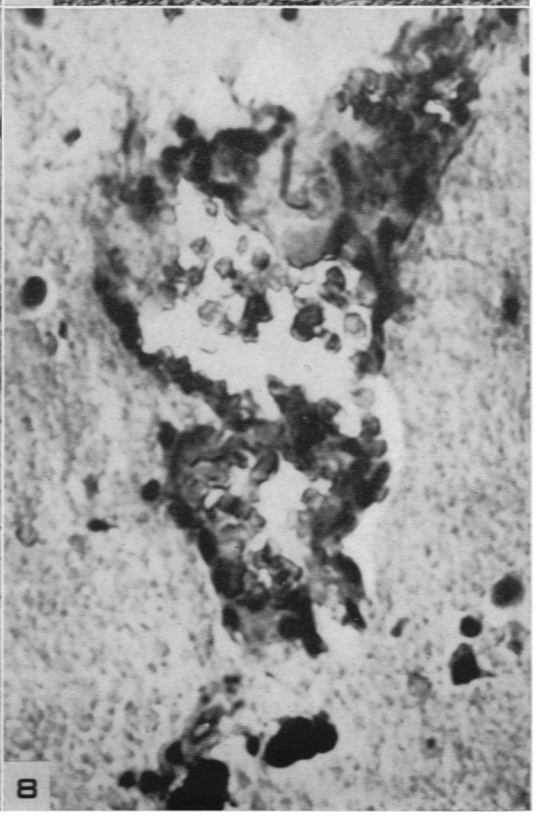
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