A STUDY OF EPILEPTOGENIC LESIONS OF THE BRAIN

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I. INTRODUCTION

"Some understanding of neuropathology should be for a neurosurgeon more than an ornament; it should be the sine qua non of his entrance into the field of epilepsy."

Wilder Penfield.

Since it was found that a large percentage of patients afflicted with posttraumatic epilepsy were either attack-free or markedly improved following excision of the meningocerebral cicatrix, the study of the excised lesions has been a fascinating one. This has been true not because it was thought that the pathological study would reveal the etiology of epilepsy but because we have learned that various alterations observed stimulate the formation of hypotheses which frequently have led to the final understanding of a disease process. Each alteration observed and interpreted forms another link in a long chain of observations - physiological, chemical and pathological - the completion of which would explain the yet unanswered problem.

A further study of epileptogenic foci was undertaken at the suggestion of Doctor Wilder Penfield, who has contributed numerous worthy investigations and observations in the study of epilepsy which have greatly increased our understanding of the disease process.

It was originally planned to compare epileptogenic with non-epileptogenic lesions particularly in reference to the presence or absence of evidence of progressive tissue destruction. In the course of this study, however, new observations were made in epileptogenic foci, and these are submitted as further pathological alterations in epileptogenic lesions. A comparative study of epileptogenic with non-epileptogenic cicatrices referable to the presence of progressive tissue destruction comprises the remaining thesis.

A review of the literature on the pathology of epilepsy has been made and the reports considered noteworthy are presented.

An attempt has been made to limit this review to reports concerning only the pathology of epilepsy. However, such a limitation has been found to be difficult in view of the close relationship existing between the pathology and physiology involved in epilepsy.

It is hoped that the findings presented in this thesis will stimulate further work in regard to the long-concealed mechanism of the production of seizures.

II. REVIEW OF THE LITERATURE

"If I wished to show a student the difficulties of getting at the truth from medical experience, I would give him the history of epilepsy to read."

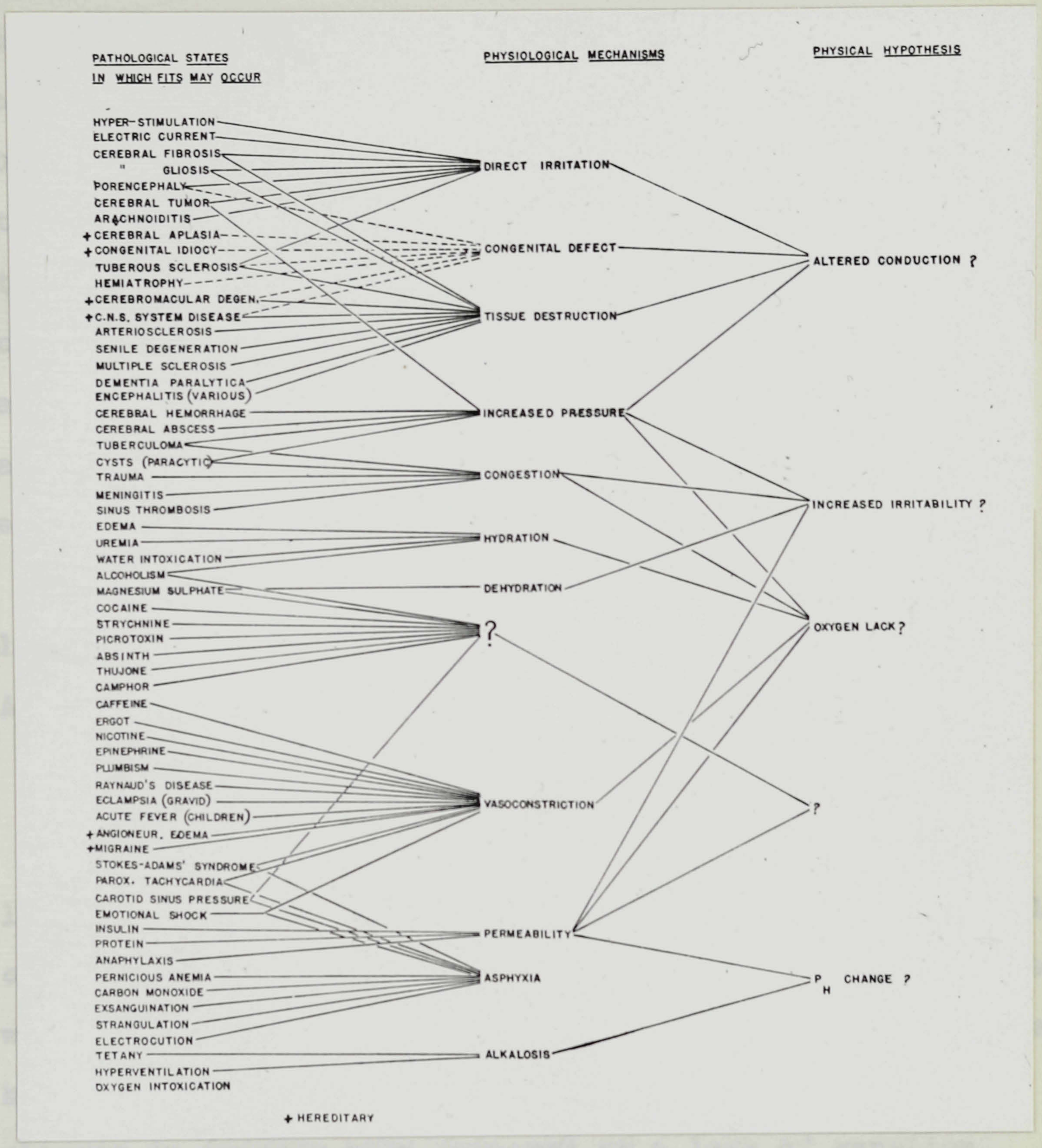
Oliver Wendell Holmes.

The above quotation can well be applied to the pathology of epilepsy. A complete classification of the pathology of epilepsy would include practically all cerebral lesions in that most of them have been observed to be accompanied by seizures at one time or another. Stanley Cobb (1936) has listed "sixty conditions associated with convulsions in man, some rare, some common" (Fig. 1). Not until the etiological factors of seizures are found can one accurately classify the pathology of epilepsy. This is obvious when one considers the possible co-existing changes in morbid anatomy found in some epileptic brains. Lennox and Cobb (1928) illustrated this in the three factors they described as being of etiological importance in the production of seizures, namely: (a) organic abnormalities in the structure of the brain or its coverings, (b) functional abnormalities in the cells of the brain that increase their "convulsive reactibility", and (c) abnormalities in the body outside of the brain tissue. They mention the intimate inter-relationship of these factors.

Fig. 1.

Sixty conditions associated
with convulsions in man.

(Cobb, 1936)


PATHOLOGICAL STATES IN WHICH FITS MAY OCCUR
PHYSIOLOGICAL MECHANISMS
PHYSICAL HYPOTHESIS
HYPER-STIMULATION
ELECTRIC CURRENT
CEREBRAL FIBROSIS
" GLIOSIS
PORENCEPHALY
CEREBRAL TUMOR
ARACHNOIDITIS
+CEREBRAL APLASIA
+CONGENITAL IDIOCY
TUBEROUS SCLEROSIS
HEMIATROPHY
+CEREBROMACULAR DEGEN.
+C.N.S. SYSTEM DISEASE
ARTERIOSCLEROSIS
SENILE DEGENERATION
MULTIPLE SCLEROSIS
DEMENTIA PARALYTICA
ENCEPHALITIS (VARIOUS)
CEREBRAL HEMORRHAGE
CEREBRAL ABSCESS
TUBERCULOMA
CYSTS (PARACYTIC)
TRAUMA
MENINGITIS
SINUS THROMBOSIS
EDEMA
UREMIA
WATER INTOXICATION
ALCOHOLISM
MAGNESIUM SULPHATE
COCAINE
STRYCHNINE
PICROTOXIN
ABSINTH
THUJONE
CAMPHOR
CAFFEINE
ERGOT
NICOTINE
EPINEPHRINE
PLUMBISM
RAYNAUD'S DISEASE
ECLAMPSIA (GRAVID)
ACUTE FEVER (CHILDREN)
+ANGIONEUR. EDEMA
+MIGRAINE
STOKES-ADAMS' SYNDROME
PAROX. TACHYCARDIA
CAROTID SINUS PRESSURE
EMOTIONAL SHOCK
INSULIN
PROTEIN
ANAPHYLAXIS
PERNICIOUS ANEMIA
CARBON MONOXIDE
EXSANGUINATION
STRANGULATION
ELECTROCUTION
TETANY
HYPERVENTILATION
OXYGEN INTOXICATION
DIRECT IRRITATION
CONGENITAL DEFECT
TISSUE DESTRUCTION
INCREASED PRESSURE
CONGESTION
HYDRATION
DEHYDRATION
?
VASOCONSTRICTION
PERMEABILITY
ASPHYXIA
ALKALOSIS
ALTERED CONDUCTION ?
INCREASED IRRITABILITY ?
OXYGEN LACK ?
?
P H CHANGE ?

+ HEREDITARY

The brains of epileptics have been described both grossly and histologically for well over a century in the hopes of determining the causative factors of seizures. Most of this study has been made with the brains of so-called idiopathic or genuine epileptics. During the past fifty years it has gradually been shown that many epileptics thought to be idiopathic were proved to be associated with intracerebral lesions, the removal of which was followed by relief from seizures. This afforded an excellent opportunity to study the physiology at operation as well as the histopathology after surgical excision.

The more contributory earlier reports in the literature on the pathology stressed, 1) sclerosis of Ammon's horn, and 2) marginal sclerosis.

Foci of Neuronal Destruction.

Spielmeyer (1924, 1927, 1928) reported focal lesions in 80% of 126 epileptic brains consisting of small, circumscribed areas of thick glial proliferation associated with a loss of ganglion cells usually occurring in Ammon's horn (Fig. 2) and the cerebellum. He stated that the changes in Ammon's horn appeared as a loss of ganglion cells in definite areas, these defects in the nerve-cell picture corresponding to an increase of the glial fibers forming a thick glial proliferation. He considered this usual observation to be an end-state and felt that the histological analysis of such a sclerotic atrophy could

Fig. 2.

Loss of cells in Ammon's horn from case of symptomatic epilepsy.

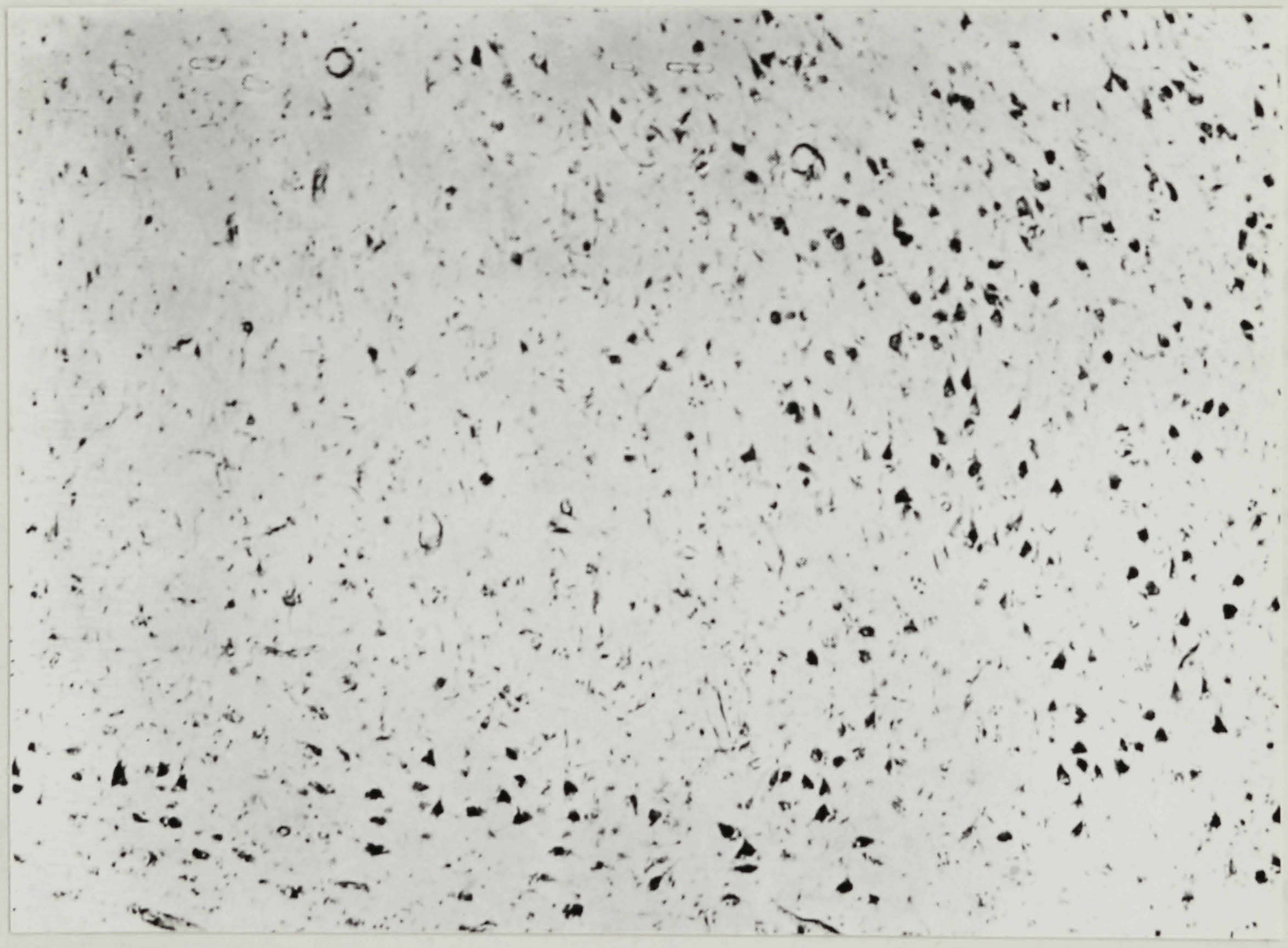
(Spielmeyer, 1930)

Fig. 3.

Loss of nerve cells on the border between the attacked foci in Ammon's horn and the normal adjacent tissue.

(Spielmeyer, 1930)





not give any explanation of the causative process. Later, however, (1930) he described the first changes in this process found in cases of "genuine" epilepsy, as well as in many different examples of symptomatic epilepsy due to trauma, intoxications, eclampsia, whooping cough and diffuse cerebral processes. These consisted of a "fresh loss of nerve cells on the border between the attacked foci and the normal contiguous tissue; most of the cells are gone, some are still recognizable as shadows. In the place of the ganglion cells, one sees proliferated glial cells of the rod form" (Fig. 3). The cerebellar changes also showed a sclerosis, the fibroglia in the molecular zone being proliferated, replacing the degenerated nervous tissue substratum. Further changes were a loss of Purkinje cells, shrinkage of the molecular zone and an increase in the number of Bergmann glial cells in a thick row. He felt that this change was the same histological picture that one sees in all the different symptomatic epilepsies with their different anatomical substrata.

He concluded from this that "in epilepsy, also, an impediment to the circulation must have been present; and since organic impediments are absent, the circulatory function must at some time have been disturbed." He pointed out the similarity of this focal, ischemic destruction to that seen in arteriosclerosis and endarteritis (Fig. 4) and suggested a functional circulatory change - an angiospasm causing vasoconstriction with

Fig. 4.

Loss of cells in Ammon's horn in case of endarteritis tuberculosa.
(Compare with Fig. 2).

(Spielmeyer, 1930)



destruction first where the vascular blood supply was relatively unsatisfactory.

This latter fact is confirmed somewhat by Scharrer (1940) who explains the vulnerability of the cornu ammonis in the opossum by a simple hydrodynamic effect of the drop in blood pressure and the dilatation of the blood vessels on the velocity of blood flow under the influence of carbon monoxide, the rake-like pattern of the vascular system of the cornu ammonis allowing the blood pressure to drop locally below a critical level before this condition occurs in the rest of the brain. He suggested that the results obtained in his experiments with the opossum may lend themselves to a satisfactory explanation of the selective vulnerability of Sommer's sector of the cornu ammonis in man, which has a rake-like vascular pattern of the type seen in the opossum.

On the other hand Heiman (1938), after studying the cerebral vessels by means of preparations of the brain rendered transparent by the method of Spalteholz, concluded that although the area of distribution of the lateral secondary hippocampal vessel corresponded roughly to Sommer's sector, there was so much individual variation in the territory supplied by the different vessels that morphological units could not be said to have a constant source of blood supply. As the vessel in question differed from the others only in its somewhat longer course, Heiman thought Spielmeyer's assumption of a

vascular basis for the peculiar vulnerability of Sommer's sector in cases of sclerosis of the cornu ammonis was hardly justified anatomically.(Spielmeyer did not limit his findings to Sommer's sector entirely but also to other areas in Ammon's horn, - writer's note).

Alexander and Putnam (1937) think that the vulnerability of Sommer's sector of Ammon's horn to circulatory deficiency is due to an anatomical pecularity of this area consisting of a lack of vessels of the 5th order (anastomosing branches which spread over the outer meningeal surface of the brain).

Other authors describing sclerosis of Ammon's horn are as follows:

Jelgersma (1888) described a sclerosis of the cornu ammonis in the brains of so-called idiopathic epileptics; Bratz (1920) reported sclerosis in Ammon's horn in 50% of the brains of epileptics and 20% of the brains of general paralytics examined. No sclerosis, however, was found in 16 children who expired while having convulsions. He failed to find such sclerosis in various other types of mental disease such as "acute exhaustive psychoses, alcoholism, apoplexy, tumor cerebri, or mental states in diabetics." Turner (1907) observed a patchily distributed ischemic change in 50% of 115 cases of idiopathic epilepsy. The lesions described showed shrinkage and degeneration of nerve cells, lipoid formation and gliosis. Taft (1921) reported 50 cases of general paralysis of which 18 out of 19 associated

with seizures showed sclerosis of Ammon's horn. The pathology described consisted of "a loss of the large pyramidal cells of the cornu ammonis; mainly those within the corpus dentatum, but frequently extending in some degree into the presubiculum. The areas from which the nerve cells were absent were infiltrated with large ameboid glial cells or large astrocytes, indicating the presence of a degenerative process." Ellery (1930) reviewed a series of 259 epileptic brains which showed findings such as thickened dura, thickened pia, large ventricles, and so forth, and mentioned sclerosis of Ammon's horn being found in only 14%. Lind's report (1926) on the pathological findings in 259 epileptic brains included sclerosis of Ammon's horn in 37 or 14%.

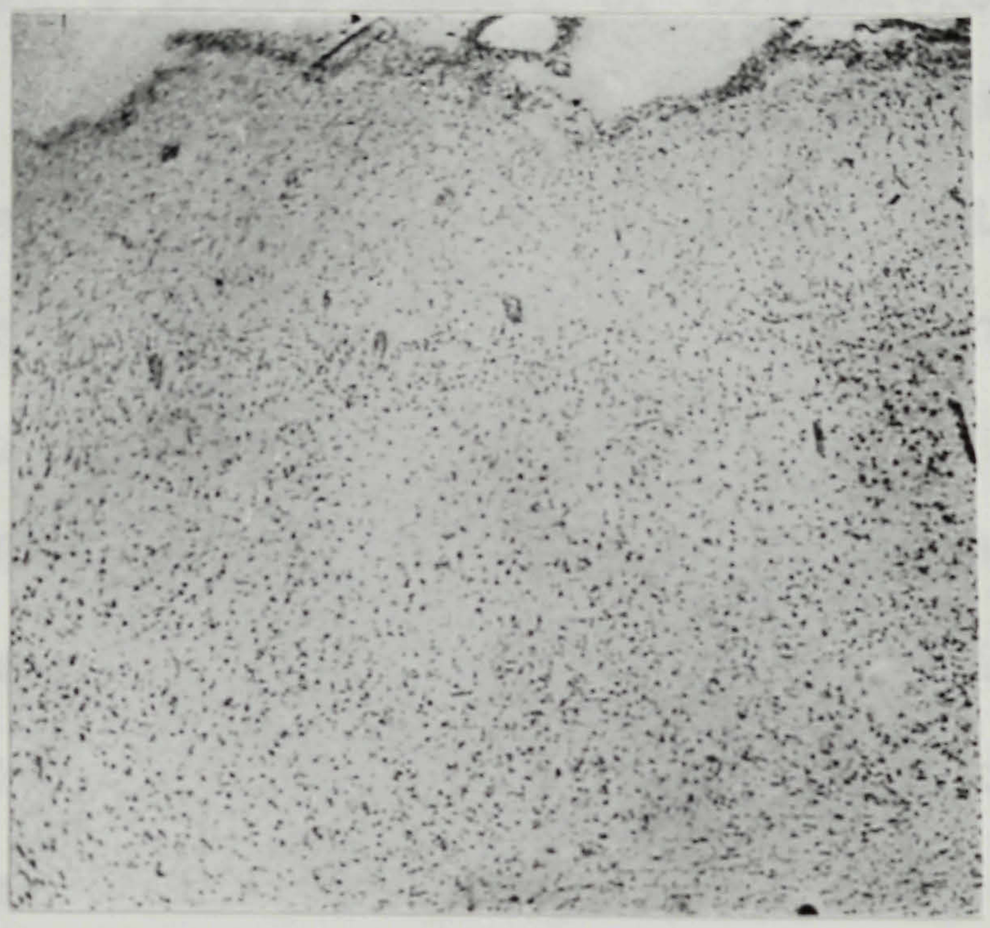
Similar changes to those described by Spielmeyer (1930) in Ammon's horn have also been found in other parts of the brain.

Zimmerman (1938) reported extensive necrobiotic changes of the ganglion cells found in the cerebral cortex, especially in Ammon's horn, the basal ganglia and the cerebellar cortex of the brains of a group of 16 children ranging in age from early infancy to 6½ years (Fig. 5). The lesions were similar to those described by Spielmeyer. None had inflammatory cerebral lesions. He concluded that cerebral anoxemia resulting from either the convulsions, the respiratory difficulty or the asphyxia was responsible for the central nervous system lesions.

Fig. 5.

Bleached appearance of the cerebral cortex due to necrobiosis of the ganglion cells. Nissl stain.

(Zimmerman, 1938)



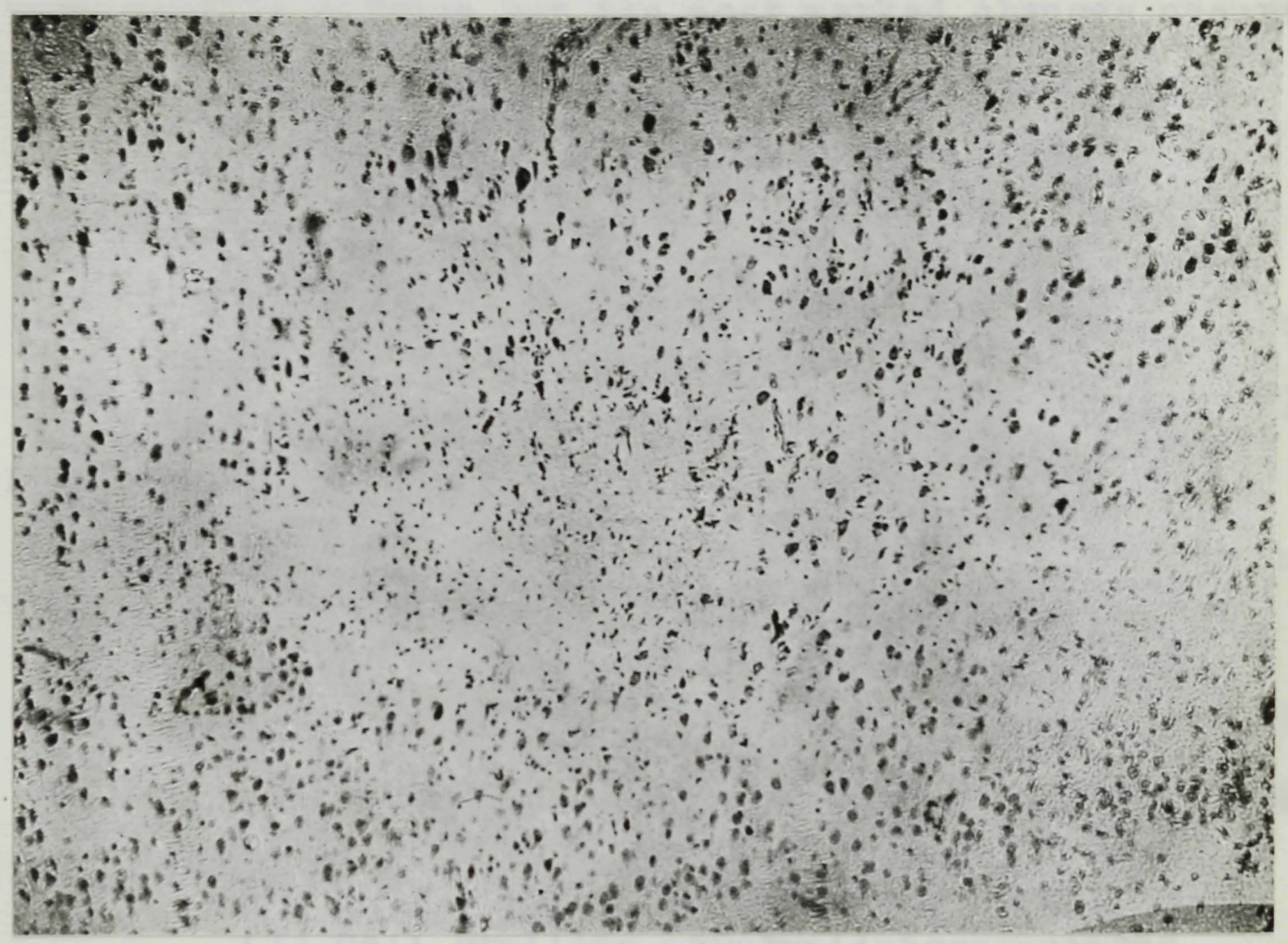
Scholz (1933) has found not only the known local changes in the cerebellum and Ammon's horn, but also focal areas of a falling-out of ganglion cells starting with a disappearance of single ganglion cell groups and going as far as destroying nerve cells in a large part of the cerebral cortex and other cerebral areas. He mentions that Doctor Malamud (New York) investigated a great number of traumatic epileptic brains and stated that the brains showed the same diffuse changes of the cortex and medulla at a distance from the scarred injury as did the brains of genuine epileptics.

Gildea and Cobb (1930) produced cerebral anemia in cats and studied the brains microscopically. All cats that developed symptoms of marked cerebral anemia showed lesions in the cerebral cortex. Convulsions occurred in 65 of a series of 90 cats during the occlusion period. Areas of devastation corresponding to Spielmeyer's "Herde" were found interrupting the normal orderly laminations. Such areas showed absence of many neurons, the remaining nerve cells being shrunken and homogeneous, closely resembling Spielmeyer's ischemic nerve cell change (Fig. 6). Microglia were occasionally common along the small vessels. The neurons characteristically were shrunken, darkly stained and had an irregular nucleus. Fat in the perivascular spaces or in the endothelial cells of small vessels was an almost universal observation after cerebral anemia,

Fig. 6.

Area of devastation in the frontal cortex of a cat. Note loss of nerve cells and persistence of glia.

(Gildea and Cobb, 1930)



whereas control animals showed little fat in this location. They found that focal areas of necrosis required at least 24 hours to appear, but shrinkage, chromatolysis, and homogeneous staining of the cells appeared immediately after a period of cerebral anemia which was sufficiently complete and prolonged to cause death. The lesions were usually diffuse but the most marked changes occurred in laminae III and V.

Spielmeyer (1922, 1928) investigated the pathological changes in the brains of patients dying from various forms of vascular disease which were supposed to produce cerebral anemia (Fig. 7, 8, and 9 A, B and C). He described lesions in the cortex consisting of many shrunken, homogeneous, darkly-staining cells which he considered characteristic of cerebral ischemia. The main types of changes seen with Nissl's stain are included here for further reference as a classification of cellular changes in cerebral anemia.

(1) Cell swelling ("Schwellungsvorgänge", Nissl's "akute Schwellung").

The cells show rounded corners and plump processes; many of these staining blue and being visible for a long distance. The Nissl bodies show disintegration at least near the nucleus; the whole cell takes a diffuse blue stain, there being no unstained spaces.

(2) Cell shrinkage ("einfache Schrumpfungen", Nissl's "chronischen Zellerkrankung").

Fig. 7.

Types of ganglion cell change found in ischemic areas.

(Spielmeyer, 1922)

Fig. 8.

Three atrophic areas in cerebral cortex showing loss of neurons and absence of glial proliferation.

(Spielmeyer, 1922)

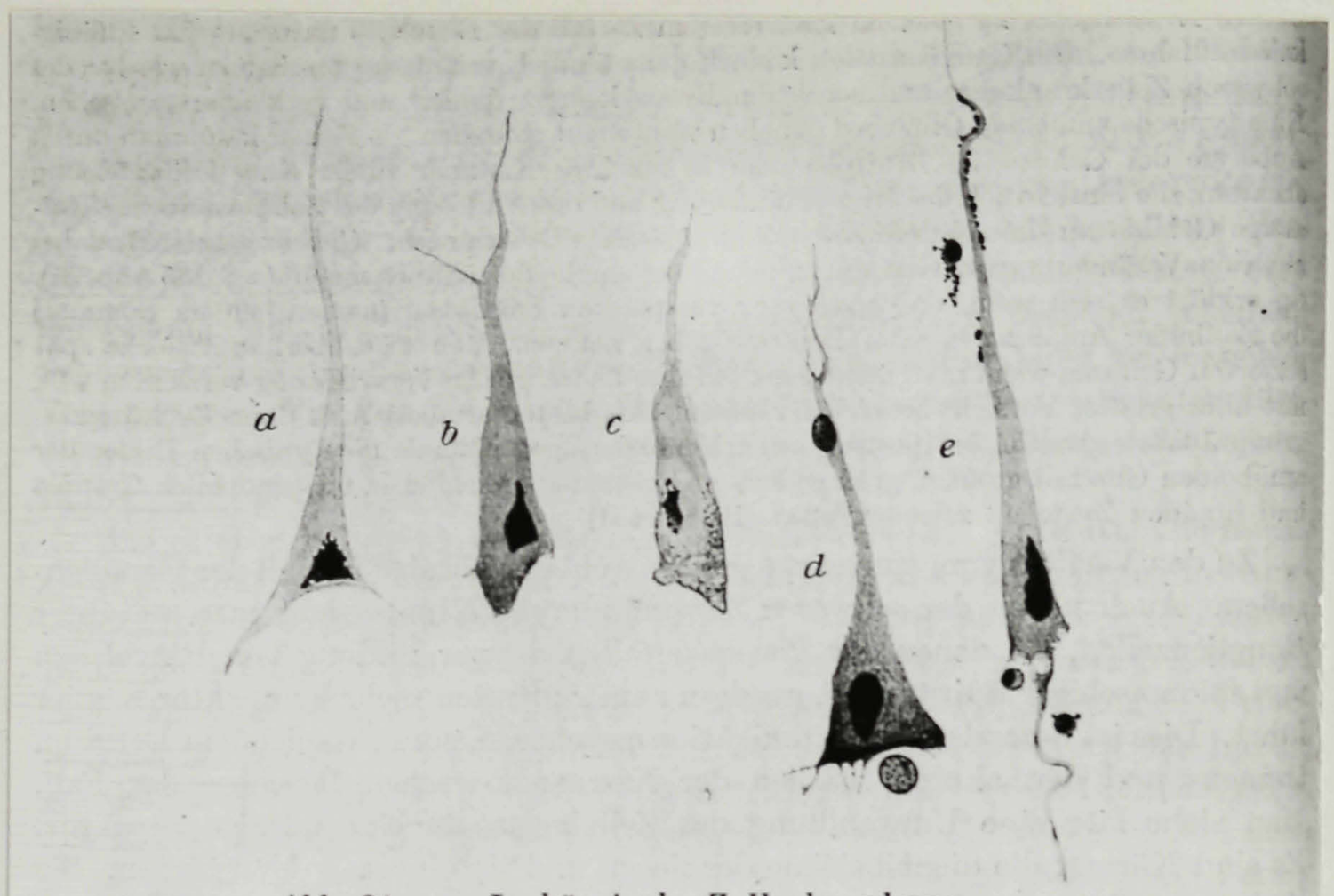


Abb. 34a—e. Ischämische Zellerkrankung.

a. Völlig entfärbte homogen erscheinende, sehr stark verschmälerte Ganglienzelle mit dreieckigem, dunkel gefärbtem Kern und großem Kernkörperchen.

b. Geringere Entfärbung und geringere Schrumpfung, aber ebenfalls ausgesprochene Homogenisierung des Zellinhaltes. Kern wieder dreizipfelig und dunkel.

c. Zerfall einer solchen Zelle und ihres Kernes. Schwinden der Zellkonturen und Auftreten leicht imprägnierter Zerfallstoffe.

d. Dreieckige, scharfumrandete Zellgestalt. Stummelartige Fortsätze in der Basis; hier Imprägnation.

e. Starke Verschmälerung, Entfärbung und Homogenisierung der Zelle mit dreieckigem, tiefdunklem Kern. Dabei Imprägnationen der sogenannten Golginetze in Kokkenschnürenform am Spitzenfortsatz. Kernpyknose an den Gliaelementen und Auftreten abnorm imprägnierbarer Stoffe auch an bzw. in ihren Zelleibern.



Fig. 9 A.

Two arteriosclerotic foci of neuronal destruction in adjacent gyri.

(Spielmeyer, 1922)

Fig. 9 B.

High power magnification of the rich vascular plexus seen in the focal area of neuronal destruction on the left in Fig. 9 A.

(Spielmeyer, 1922)

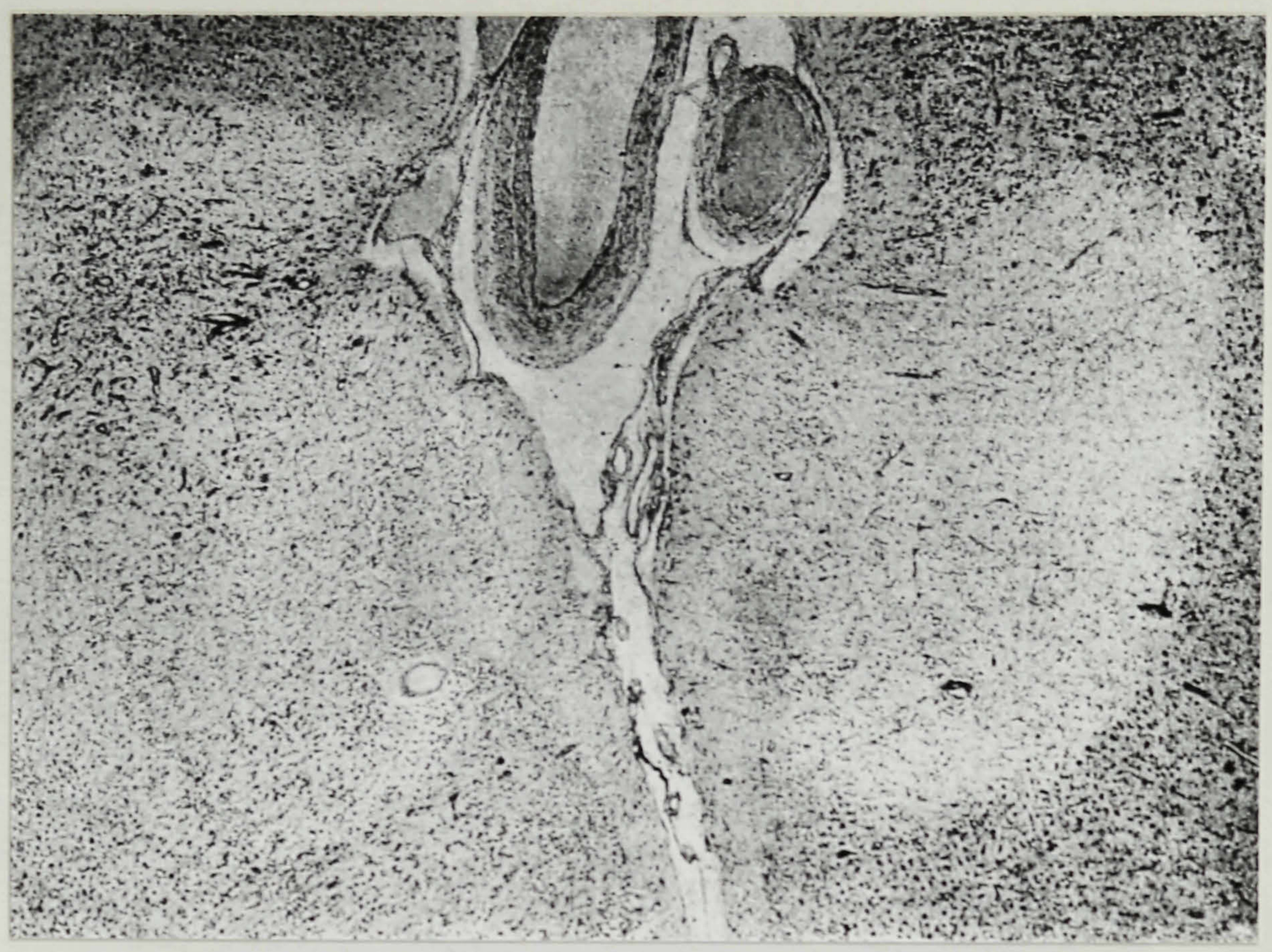
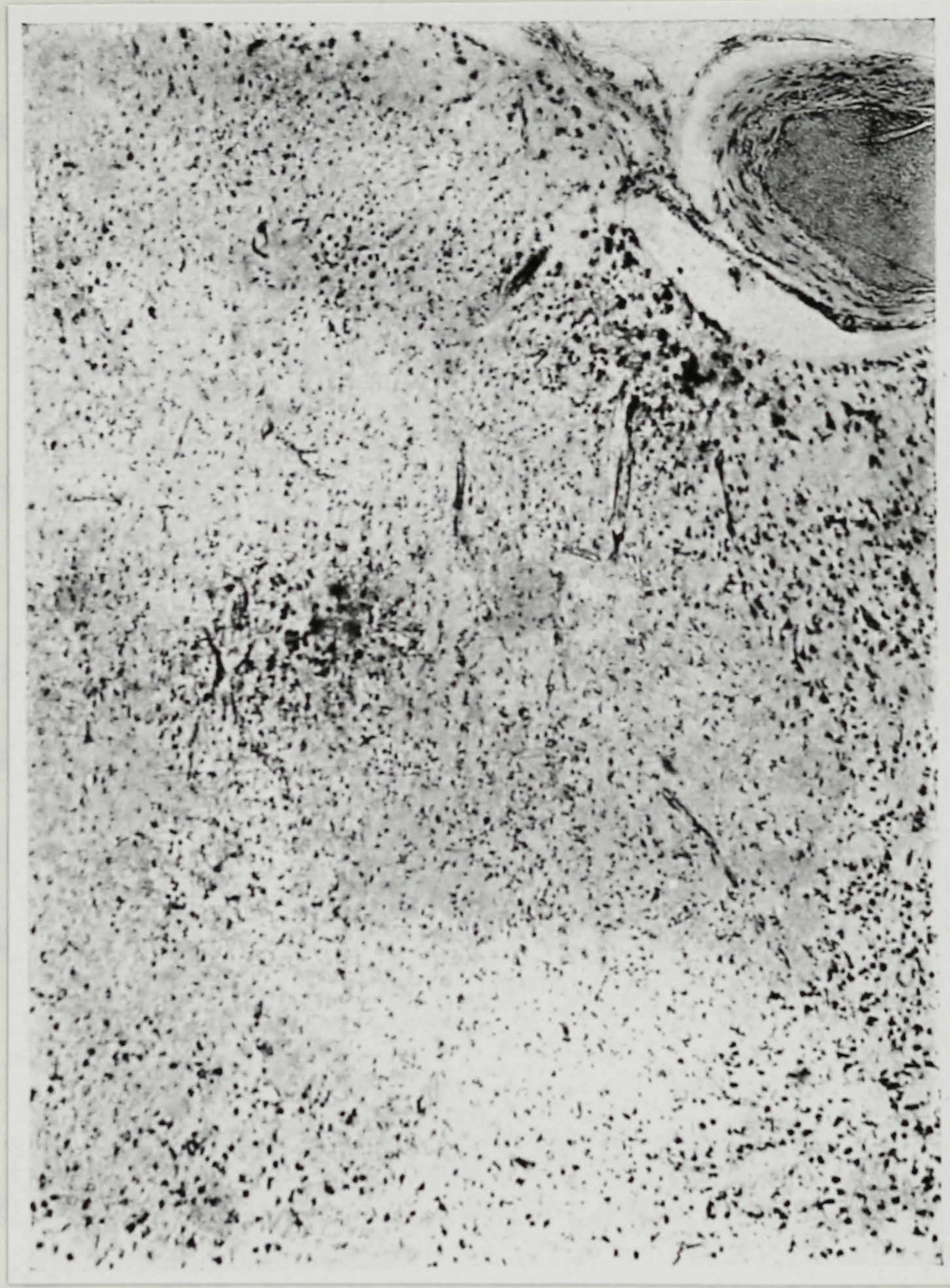




Fig. 9 C.

High power magnification of the focal area of neuronal destruction seen on the right in Fig. 9 A. No vascular plexus or glial proliferation is seen in the focus.

(Spielmeyer, 1922).



The whole cell is shrunken and often elongated, including the processes. Nissl bodies stain darkly, are less in amount and may be in clumps. The spaces normally unstained take on color and largely disappear. The cellular outline is angular, loses its round curves; and, when the processes come off, there are sharp angles. The nucleus also loses its roundness, is dark, and may take on something of the shape of the cell. The nucleolus may be larger than normal.

(3) Cell liquefaction ("Verflussigungsprozesse", Nissl's "schwere Zellveränderung").

The cells are pale and swollen with rounded outlines. Nissl bodies disappear and rings of detritus often remain in the cell body. Darkly staining gramules and globules are seen, most often in the processes. The nucleus is round, small and metachromatic; the nucleolus is large, dark, and near the edge.

(4) Cell coagulation ("Gerimmungs vorgange", Koagulationsneknose").

The cell body is pale, apparently discolorized, shrunken, angular and unusually elongated. The processes are lost or difficult to see and may be encrusted with degeneration globules. No Nissl bodies are seen and the cytoplasm is almost colorless, bluish and homogeneous. The nucleus loses its rotundity, may be triangular or irregular, very dark, and often metachromatic. The nucleolus is seen with difficulty, is usually enlarged and at the edge. This type of change is most frequently

found with vascular occlusion and is called "ischämische Zellveränderung" by Spielmeyer.

(5) Alzheimer's fibrillary degeneration.

The cells are swollen, irregular, and show a loss of chromidial substance. The Nissl picture is not entirely characteristic.

(6) Pigment and fat changes.

Special stains show fat clearly "but these elements are normal contents of certain cells."

Opper (1939) convulsed a series of cats and rabbits with monobromated camphor or with thujone. The resulting microscopic lesions were largely confined to the cerebral cortex. The cornu ammonis was spared and the cerebellum rarely affected. The pathological changes, consisting of necrobiosis, sclerosis of ganglion cells, petechial hemorrhages and chromatolysis of nerve cells, were much like those found in human epilepsy. The parietal, frontal and temporal lobes were mostly affected. A simple disappearance of nerve cells in focal zones throughout the cerebral cortex was most commonly found (Fig. 10). Almost as common as the necrobiotic lesions and involving larger cortical zones were sclerotic, hyperchromatic nerve cells generally acknowledged to represent a chronic type of injury. Ganglion cells were occasionally shrunken, darkly stained and had nuclei which could hardly be distinguished; cellular processes sometimes showed cork-screw configurations.

Fig. 10.

A "punched-out" zone of necrobiosis
in cortex of temporal lobe of rabbit.

(Opper, 1939)


A

Jansen, Környey and Saethre (1936) reported one case showing extensive cortical damage as well as alterations in other parts of the brain consisting of a degenerative process. In the cortex degenerative changes evidenced by areas of focal destruction of ganglion cells were found parallel to the cortical surface; in these areas glial proliferation, altered microglia and fatty degeneration were observed. Similar destructive areas were found in the thalamus, cerebellum and Ammon's horn.

Developmental Abnormalities.

Jakob (1914) reported the findings in the brains of 3 cases of so-called genuine epilepsy and discussed their significance. All of the cases showed a certain common factor "due to damage to an immature brain." The first case showed an "abortive tuberous sclerosis"; the second resembled tuberous sclerosis but differed from it by a more diffuse cortical gliosis (Jakob stressed the fact that the patient also had congenital webbing of the fingers); and the third case showed atrophic lobar sclerosis which Jakob believed was due to an exogenous process. He regarded the three as being cases of "organic" (secondary) epilepsy although they showed the features which one finds in genuine epilepsy. He stated he had found slight indistinct developmental abnormalities also in the cortex of genuine epileptic brains and that Turner (1907) found signs of

developmental abnormality of the cortex (such as preservation of ganglion cells in the white substance and immature embryonic types of pyramidal cells) in 70% of a series of 41 cases of genuine epilepsy.

Jakob concluded that genuine epilepsy was based on a developmental anlage failure of the cerebrum, differing from such obvious developmental anlage diseases such as Recklinghausen's disease, diffuse gliosis with cortical abnormality, and the formation of abnormal cell layers, only in time, intensity and localization.

Tuberous Sclerosis.

A malformation of the central nervous system having specific cellular changes and being most commonly associated with seizures is that referred to as tuberous sclerosis probably first recognized as a pathological entity by Bourneville (1880, 1897).

Comprehensive reviews have been reported by Critchley and Earl (1932) and Globus (1932).

Grossly the characteristic findings consist of varying numbers of firm nodules over the cortical surface of the cerebral hemispheres (Fig. 11) and in the ependymal lining. The latter are either in the form of small button-like nodules or as "candle-gutterings" described by Lind (1924). Such nodules occasionally form cysts in the center due to degeneration, and frequently small calcium deposits are found within these foci.

Fig. 11.

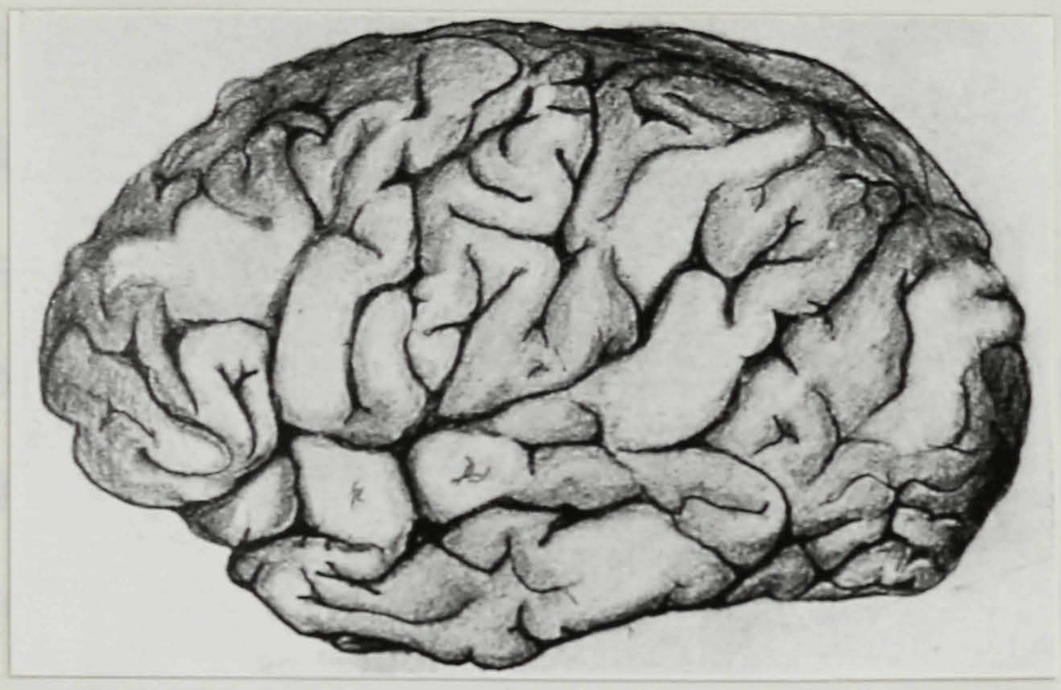
Gross appearance of brain surface in tuberous sclerosis. White areas are tuberous nodules.

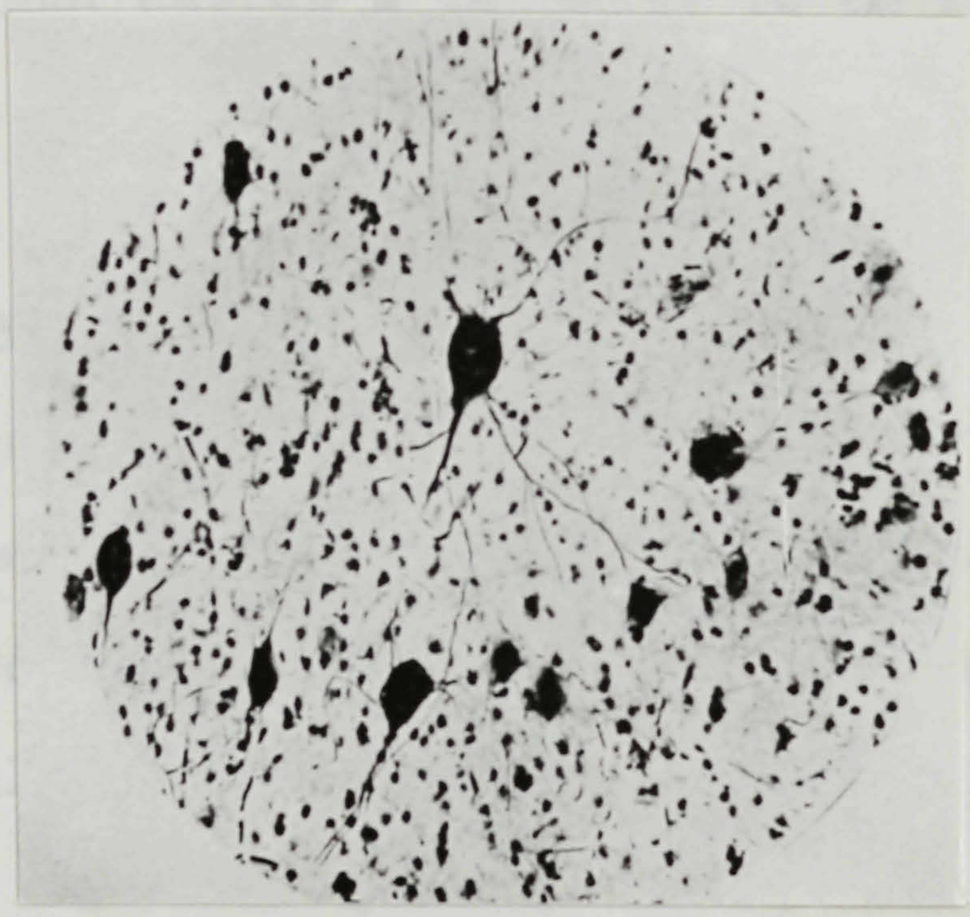
(Globus, 1932)

Fig. 12.

Tuberous nodules showing atypical ganglion and glia cell forms.

(Globus, 1932)





Microscopic examination shows abnormal findings not only in the region of the nodules but also in areas grossly appearing normal. The affected cerebral cortex shows a marked distortion of the cytoarchitecture and the border between gray and white matter is lost. Along with a decreased number of nerve cells there are accumulations of large, malformed nerve cells found both in the gray and the white matter (Figs. 12, 13 and 14). These nerve ganglion cells are frequently three to four times the size of Betz cells and occur in small groups or nests (Fig. 15), or occasionally as single units, surrounded by a dense gliosis. Another form of the large cell type appears in small groups surrounded by a zone of gliosis and having a tendency to be perivascular. These cells are considered by some to be glial forms rather than atypical forms of nerve cells.

The striking gliosis found is composed of small and large fibrous astrocytes, the former being most prominent around the large cell nests.

Perivascular gliosis and the presence of compound granular corpuscles about blood vessels in the nodules are not infrequently found, according to Globus (1932). Critchley and Earl (1932) state, however, that no perivascular gliosis is found.

The tumor-like lesions (Fig. 16) resemble either the picture of spongioblastoma multiforme, a neurofibroma or a combination of some of the features of both (Globus, 1932).

Fig. 13.

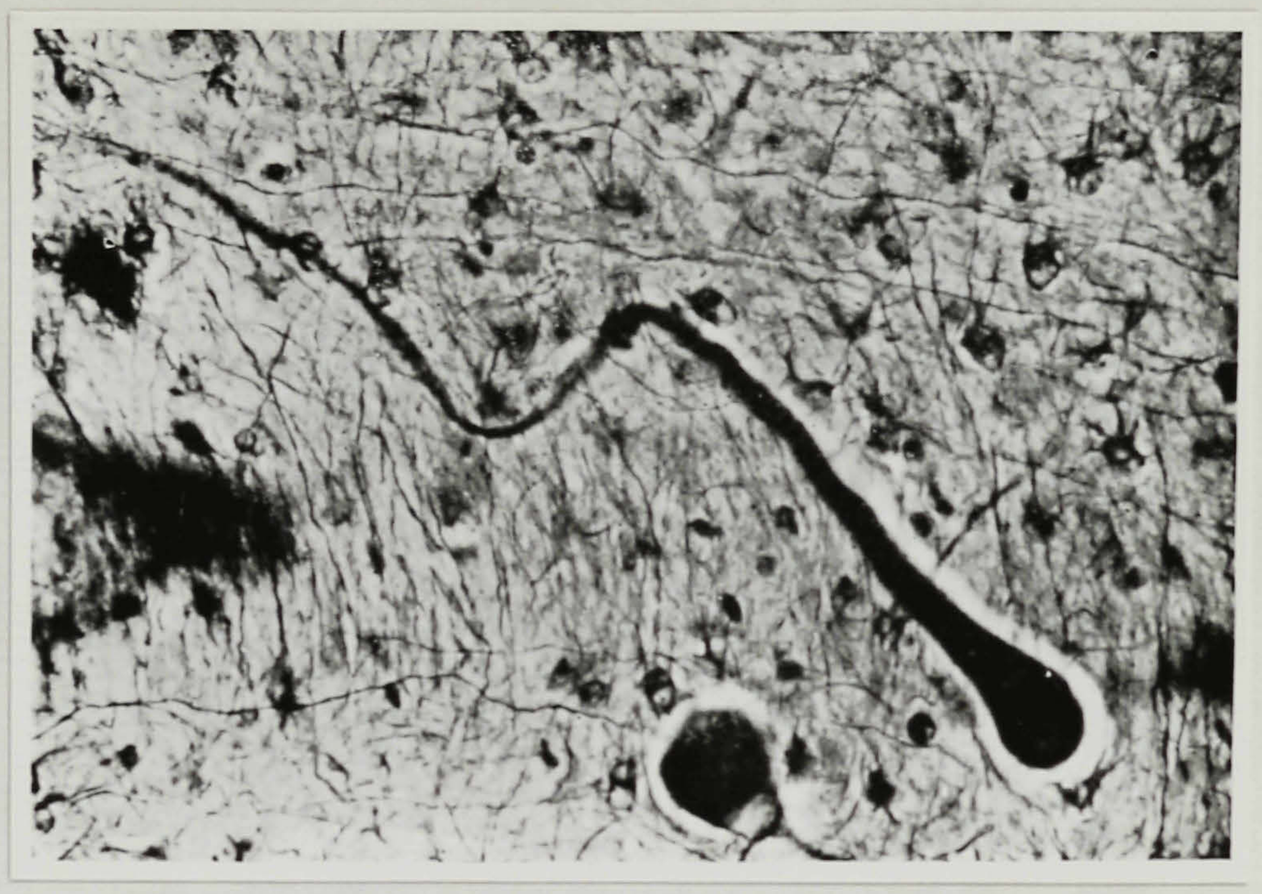
Monstrous cell in an area of dense gliosis in tuberous sclerosis.

(Globus, 1932)

Fig. 14.

Types of monstrous ganglion cells seen in tuberous sclerosis.

(Globus, 1932)



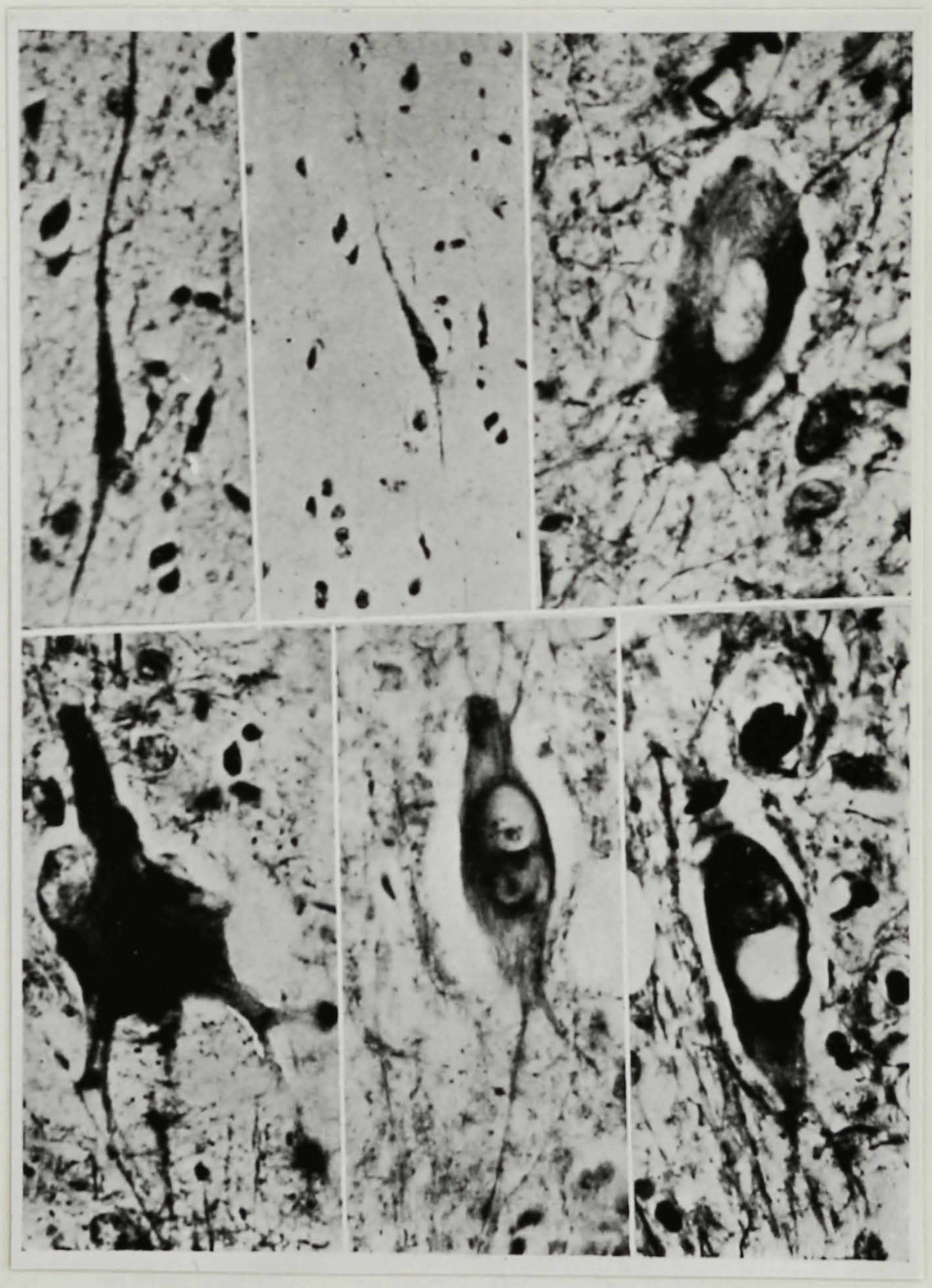


Fig. 15.

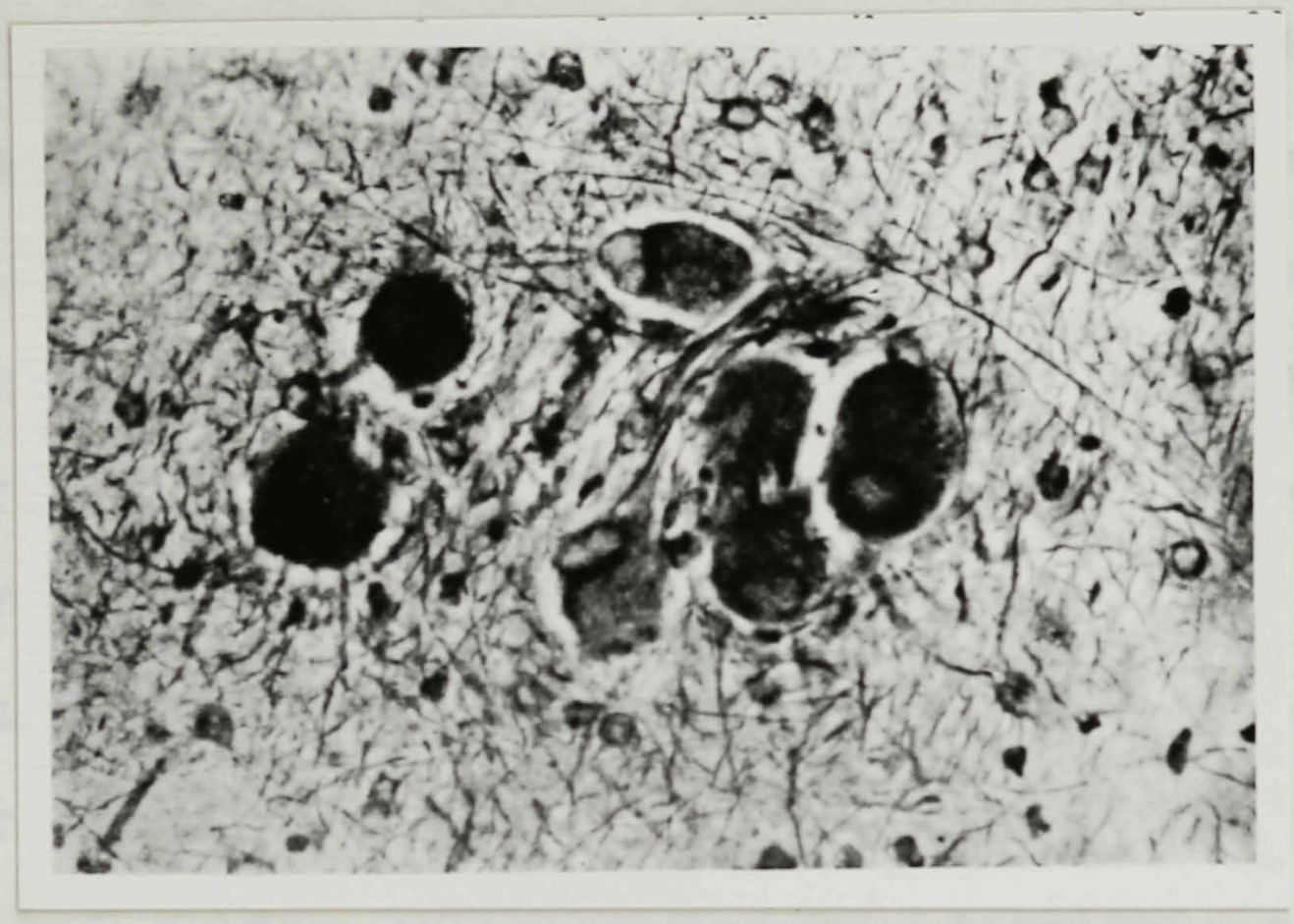
Nest of monstrous glia cells in tuberous sclerosis.

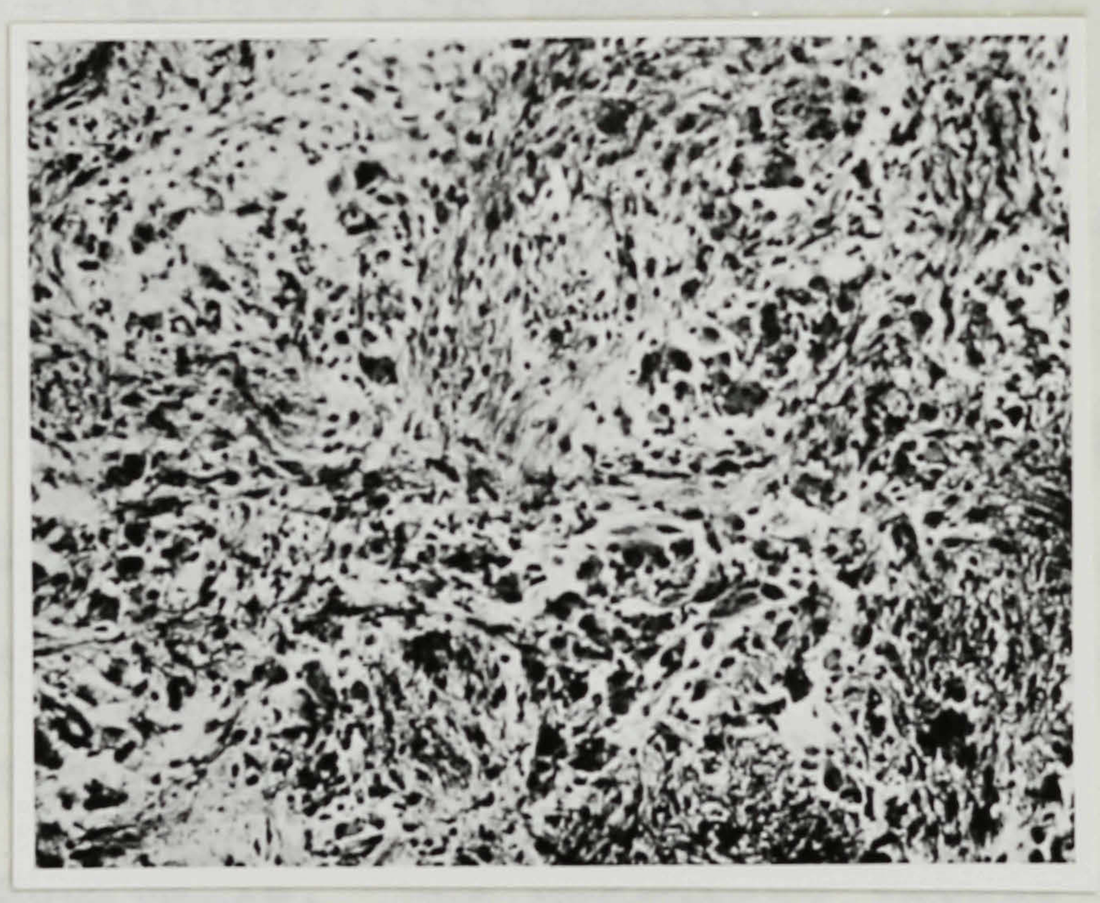
(Globus, 1932)

Fig. 16.

Cellular arrangement in a tumor associated with tuberous sclerosis.

(Globus, 1932)





Marginal Sclerosis.

Chaslin (1891), well known for his description of marginal gliosis ("faisceaux de fibrilles"), described this observation in 1891. He found neuroglial sclerosis in 4 of 5 epileptic brains. Microscopic examination of the fundamental lesion showed that the cerebral tissue, especially the gray cortex, had been invaded by a number of rough fibrillae of uncertain length. The author stated "In the normal state the first layer of the grey cortex contains certain so-called spider cells, whose prolongations are scarcely visible. In this condition, on the contrary, this first layer is formed by a bundle of fibrils arranged nearly parallel to the cerebrum, and it can be distinctly seen to originate from numerous cells with hypertrophied prolongations. This transformation can invade all the layers but leaves intact numerous nerve cells and vessels. In a certain space these fibrillae form in the depth of the cortex a network of nodal points in which lie the cells of the neuroglia" (Fig. 17). He pointed out that the fibrils and sheaves (bundles) were not connective tissue but developed at the expense of the neuroglia, "the sustained tissue of original ectoderm." Such an arrangement of piloid glia in stacks or sheaves along the cortical margin has been frequently observed in meningocerebral cicatrices by Penfield and Humphreys (1940) (Fig. 29). A description of this piloid gliosis will be found in a review of their paper given later in this chapter.

Fig. 17.

Neuroglial sheaves in the cortical gray matter.

(Chaslin, 1891)



Meningocerebral Alterations.

Probably the most progress in the study of the pathology of epilepsy is being made possible by close observations during operations on epileptics followed by a careful histological study of the removed specimen and close observation of the patient after operation.

Keen (1888) described a case of a simple depressed fracture of the skull, followed in four months by epilepsy. Thirteen months later a meningo-cerebral cicatrix including a spicule of bone was removed. The specimen on microscopic examination "showed extensive destruction of brain tissue, broken-down nervous tissue with pigment masses, and compound granule cells. Deeper down were perivascular hemorrhages, collections of lymphoid cells, fine granular pigment, compound granule cells and increased numbers of neuroglial cells." The patient recovered and for four months (up until the publication of the report) was free of seizures.

Collins (1896) reported a case of focal epilepsy beginning in the right hand. At operation a portion of the left cerebral cortex was removed which, when stimulated with a weak faradic current, produced flexion movements of the right hand. Microscopic examination of the excised cortex showed a thickened pia composed of much connective tissue

formation which was intimately attached to the underlying diseased cortex. In some areas there was "an actual growth of connective tissue from the pia into the cortex", causing a marked alteration of the cytoarchitecture. Many of the neurons showed evidences of degeneration and it was the author's opinion that the cell degeneration was "that of a slow, degenerative process, combined with a more or less acute one." He mentioned the softened areas being closely associated with neuroglial tissue in such a way that the former were surrounded by an "advancing zone of neuroglial tissue." Collins, in reference to this case, pointed out the careful clinical study, the exact location of the lesion, and the early operation with removal of the diseased area followed by careful histological study with the most approved technique.

The reports of Keen (1888) and Collins (1896) are included in this review because, to the writer's knowledge, they represent the first pathological studies made on epileptogenic scars removed at operation. Krause (1912) has mentioned a few pathological findings in excised cortical lesions which he removed from the brains of patients having seizures. He mentions the presence of connective tissue proliferation in the arachnoid and increased glial cells in the underlying cortex. Few details of the pathology in the excised lesions were given.

Dandy (1927) described dilated subarachnoid spaces forming pools of cerebrospinal fluid overlying small convolutions which were soft on palpation. He stated that the soft areas beneath the arachnoid were due to atrophy of cerebral tissue following emboli, thrombi, and traumatic destruction of the brain. He thought that the pools of fluid collected in the overlying subarachnoid space and the adjacent ventricles dilated, both as a compensatory measure.

Ney (1940) reviewed a series of 272 patients with "idiopathic epilepsy" in which "definite lesions" were found at operation. Two hundred and twenty-two of these cases showed what he described as being "cortico-dural fixations at the cerebral vertex, at or near the cortical motor areas." He mentioned "arachnoidal defects or fistulae through which cerebrospinal fluid leaked into the subdural space." He thought these were probably due as a result of tears in the arachnoid which failed to heal.

Foerster and Penfield (1930) reported 12 posttraumatic cases of epilepsy, each of which showed a displacement of one or all of the ventricles towards the side of the lesion. The lesions were excised after electrical exploration, and histological examination showed a dense connective tissue cicatrix which contained a rich vascular plexus and extended down into the brain substance. The fibers of the astrocytes were in general arranged in parallel and extended upward

toward the cicatrix. Deeper down a vaso-astral framework was present. Nerve fibers were rare and nerve cells rarer in the areas of gliosis. Occasionally localized areas were found which showed groups of phagocytes containing pigment. Such areas were thought to be in the vicinity of blood vessels which had been shut off and indicated a process of long continued destruction, recalling the focal perivascular destruction described in genuine epilepsy by Spielmeyer (1927). They postulated that the cicatricial contraction was responsible for the displacement of the ventricles described by Foerster (1925). A progressive increase in the vascular elements of the scar and a progressive decrease in the nervous elements were thought to take place during the years following the infliction of a brain wound.

They stated that at operation the focal epileptic attacks might often be produced in two ways, "either by electrical stimulation of the brain in the neighborhood of the wound, or by gently pulling upon the adherent dura." It was felt that traction upon the vessels was inevitable, suggesting a hypothesis that a vasomotor reflex secondary to this traction was responsible for the initiation of the convulsive seizures.

The mechanism of this cicatricial contraction was discussed in an experimental study by Penfield (1927) in which he found that the vaso-astral framework, being

caught in the mesh of contracting connective tissue scar, was drawn toward the scar, exerting traction upon and causing distortion of the surrounding brain. The presence of macerated cerebral tissue in a brain wound being a predisposing cause of much scarring was stressed.

This was further pointed out by Penfield and Buckley (1928) when punctures of the brain in dogs were made by a blunt needle in one series compared with those made by an open cannula in another. When the blunt needle was used, all the damaged tissue remained behind and a closed tract containing a connective tissue core firmly attached to the overlying dura resulted. Stab wounds made with an open cannula, removing a core of cerebral tissue, left a gaping tract containing little if any connective tissue. Clean removal of brain tissue resulting in little or no cicatrization was emphasized.

Further studies of the reparative process in brain wounds have been reported by Rio-Hortega and Penfield (1927), Wilson (1926) and Linell (1929).

Foerster and Penfield (1930) in a further report on the pathology of traumatic epilepsy observed that in the center of such scars ganglion cells were absent and nerve fibers rare; and also, that there were occasional altered microglia and compound granular corpuscles about individual vessels, giving evidence of progressive tissue destruction, even 10 to 13 years

after the injury. It was suggested that such vessels might be closed periodically by the progressive cicatricial contraction, resulting in local necrosis. It was pointed out that these vessels anastomosed with the blood vessels of the surrounding brain, this anastomosis being suggested as a possible element in the production of seizures.

Penfield and Humphreys (1940) reported a histological study of 95 focal cerebral lesions removed at operation from epileptic patients. The evidence indicated that the tissue excised was the starting point for the production of seizures; the lesions resulted from traumatic injury, healed abscess of the brain, arterial occlusion and focal ischemia.

A central scar was described which contained no ganglion cells and few if any nerve fibers; it being composed of a network of piloid astrocytes penetrated by connective tissue and blood vessels. An intermediate zone lying between the scar and the adjacent cortex was described as being composed of either thinned-out gray matter or isolated islands of ganglion cells. These islands were found to be usually supplied with a central artery (Fig. 18). A study of the blood vessels in the intermediate zone showed the small branches to be much reduced in number. Perivascular nerve plexuses were found to contain more fibers on the vessels in the scar than on those in the normal convolutions. It was concluded that the arteries of an aganglionic scar undergo

Fig. 18.

Islands of gray matter in epileptogenic lesion. Note the central artery.

(Penfield and Humphreys, 1940)



periodic positive constriction causing local irritability of the arteries of the central scar and producing the continuing destructive atrophy found to be the histological characteristic of epileptogenic lesions.

Alexander and Putnam (1937), who have given a classification of the cerebral vessels comprising seven categories according to branching and calibre, have shown that a destruction of vessels of the 1st and 2nd order (capillaries and precapillaries) follow cerebral scars from traumatic laceration.

Little (1861) reported brief observations of 63 children from 9 weeks to 18 years of age who had spastic rigidity and occasionally convulsions. He maintained that this paralysis was almost wholly due to asphyxia of the brain resulting from an accident at birth. He postulated "It is certain that, if examined after death, after having living many years, an anatomical condition very different from that present at or soon after birth would be found. We may conclude that although the effused blood particles may be absorbed, permanent lesion - atrophy of nervous tissue - results."

Ford (1926) stated that 5 of 17 cases of congenital hemiplegias from the Harriet Lane Home were subject to convulsions, and that there was no doubt but that one-third of all children with spastic paralysis due to birth injury develop focal, or less frequently, generalized convulsions. He felt it was probable that approximately 2 or 3% of all epilepsies were

related to birth injury.

Penfield and Keith (1940) reported the clinical and pathological findings in a series of 8 epileptics in whom the cerebral lesion dated from birth or infancy. Four types of changes resulting from cerebrovascular damage were discussed, namely: (a) focal microgyria resulting from ischemia produced by cranial pressure during birth, (b) large vascular occlusions occurring during febrile illnesses and causing an area of complete destruction bordered by narrow shrivelled gyri--a result of partial loss of blood supply, (c) meningocerebral cicatrix resulting from local laceration of brain tissue and consisting of a dense cicatrix of connective tissue, blood vessels and glia, (d) infantile meningitis causing dense, vascularized adhesions between the pia and the dura, irregular thickened leptomeninges and destruction of underlying brain, evidently by means of an interference with the circulation of blood through the leptomeningeal vessels. Areas of complete destruction were noted to alternate with areas of atrophy and partial destruction.

Evans and McEachern (1937) have pointed out that the late histological lesions following vascular occlusion, intracerebral hemorrhage and cerebral contusion and laceration are the results of an interference with normal cerebral circulation. They suggested that there were two main factors involved in the mechanism of cerebral cicatrix formation: (a) the relative

degree of anemia in the affected zone, and (b) the absence or presence of free blood in the cerebral tissues.

Cerebrovascular Changes.

No attempt is made here to summarize the literature regarding the relationship between the cerebral circulation and epileptic seizures. However, several reports referable to cerebrovascular spasm are included in this review.

Cobb (1934) reported a case having Jacksonian seizures which later resulted in status epilepticus. Postmortem examination showed no gross lesions; however, histologically, pale areas in the cortex showed early anemic necrosis of the nerve cells. He argued that partial anemia is more likely to cause seizures than complete anemia and also suggested that a small focal area of anemia was more prone to produce status epilepticus.

Penfield (1933) gave evidence for a cerebrovascular mechanism in epilepsy when he reported observations made of 26 epileptic cases which,when stimulated electrically, caused seizures and showed striking vascular changes; the almost invariably associated phenomenon found was the arrest of visible pulsation in the arteries of the brain.

Following the seizure, 9 cases showed focal areas of cortical anemia and 6 cases showed spasmodic closure of large pial arteries. Penfield concluded that

the vasomotor spasms and changes seen in the cerebral cortex of epileptics were due to vasomotor reflexes probably by a local vascular nerve plexus and not by the autonomic neurons outside of the cranial cavity.

In a later paper Penfield (1934) described a progressive degeneration of an occipital pole in an epileptic who suffered a progressive loss of vision in the homonymous half fields with succeeding attacks and at operation was found to have an extensive degeneration of the occipital lobe. This degeneration was interpreted as being due to an anemia consequent to recurrent vasospasm.

Penfield (1937) further discussed the circulation of the epileptic brain citing circulatory changes observed at operation in a large group of epileptic cases. With the use of the Gibbs' thermocouple it was shown that there was a local increased blood flow through that portion of the cerebral cortex involved in the convulsive discharge during an epileptiform seizure. No vasoconstriction or shrinkage of the brain was noticed during any seizure. Various vascular phenomena observed included cessation of visible pulsation in cerebral arteries during a seizure, postconvulsive hyperemia, flushing of the pia mater, blanching of the pia mater, post-convulsive arterial spasm and cyanosis of the brain; the latter was interpreted as being due to respiratory embarrassment. It was concluded that the evidences of vascular instability, as well as the hyperemia

occasionally seen in the cerebral scars, may have an important bearing upon the etiological phenomena that lead up to spontaneous discharges within the epileptic brain.

Observations of the capillary circulation in the cortex of cats immediately before, during and after convulsions produced with cardiazol have been reported by Dreszer and Scholz (1938-39). The animals were decapitated at various intervals and the cortex studied by means of Pickworth's benzidine stain (1934). They noted two components comprising the disturbance of the capillary circulation during the preconvulsive stage, namely:

(1) a generalized anemia of all capillaries varying in degree in each animal, and,

(2) numerous sharply circumscribed, ischemic foci scattered throughout the generalized anemic brain (Fig. 19). They stated that the time when the foci appeared was not clear.

The convulsive stage (during the actual convulsion) showed an increase of blood in the capillaries; however, the small circumscribed ischemic foci persisted (Fig. 20).

The postconvulsive stage showed a similar picture of hyperemia as that seen in the convulsive stage (Fig. 21).

Fig. 19.

Preconvulsive stage showing ischemic foci.

(Dreszer and Scholz 1938-39)

Fig. 20.

Convulsive stage showing an increase of blood in the capillaries. The ischemic foci persist.

(Dreszer and Scholz 1938-39)

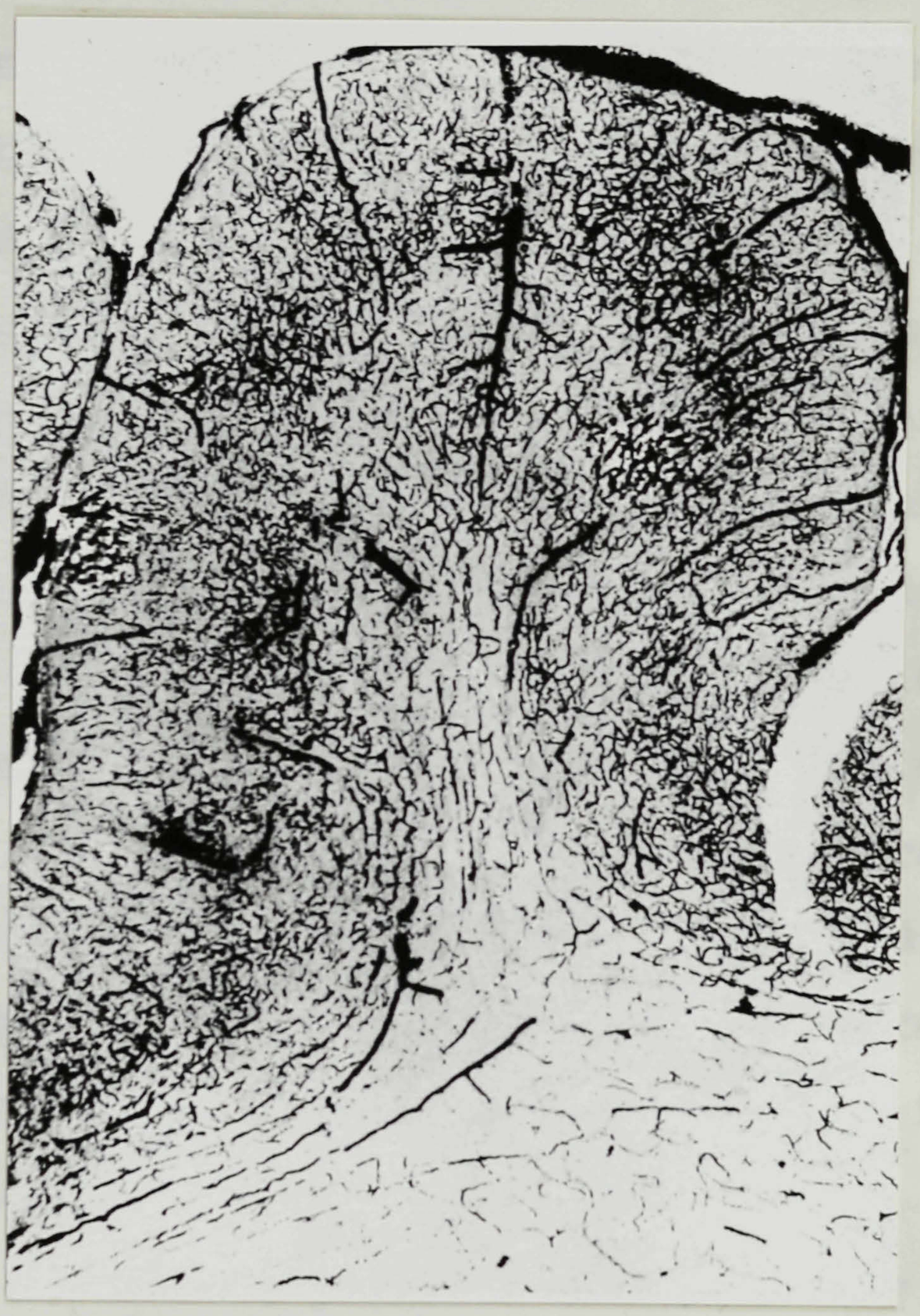




Fig. 21.

Postconvulsive stage showing similar picture as that seen in the convulsive stage. (Note Fig. 20).

(Dreszer and Scholz, 1938-39)



Meyer (1939) mentioned in a review of the histology of epilepsy that he had used Pickworth's method but had not seen generalized or circumscribed anemia as described by Dreszer and Scholz (1938-39). He found marked vasodilatation and an irregularity of the vascular pattern in the later clonic stage of the fit, which observation he stated was very constant in the preparations he examined.

Gibbs (1933) reported an experimental study of the cerebral blood flow preceding and accompanying experimental convulsions produced by oil of absinthium, camphorated oil, picrotoxin, caffein and induction shock and concluded that these convulsants did not cause a general diminution in the cerebral blood flow.

Further evidence of spasm of cerebral vessels occurring in man has been given by Cobb (1938) and Kennedy, Wortis and Wortis (1938). Other references to cerebrovascular spasm will be given later in their proper place.

The summary presented has purposely been limited to the pathology of epilepsy found within the cranial vault.

Numerous pathological alterations found in the body other than those in the brain have been reviewed; however, their significance relative to the production of seizures is questionable, particularly because of conflicting reports and the lack of convincing data.

Lennox and Cobb (1928) have made a thorough critical review of such extracranial findings.

As far as other intracranial pathological alterations accompanying seizures are concerned (tumor, abscess, meningitis, arteriosclerosis, hemorrhage, tuberculoma, etc.), no reports concerning their resultant epileptogenic role have been found in the literature.

In concluding this review of the literature on the pathology of epilepsy it is obvious that no constant anatomical lesion has been demonstrated in the brains of epileptic patients. The most frequently reported finding in the brains of so-called genuine epileptics is that of focal areas of neuronal destruction identical with those resulting from cerebral ischemia. Such foci, however, have been found frequently in the brains of non-epileptic patients. That the removal of pathological lesions of the brain, such as meningocerebral cicatrix, tumor, cysts, and so forth, is frequently followed by relief from seizures, suggests that an irritative focus plays a prominent role in the production of seizures. Whether there exists a difference in the pathological picture between lesions accompanied by seizures and similar lesions not accompanied by seizures remains to be demonstrated.

The significance of observations which have appeared to be characteristic of epileptogenic lesions (such as evidence of progressive tissue destruction in meningocerebral cicatrix) must depend upon a similar study on control (non-epileptogenic) lesions.

The need for a more thorough microscopic study of the brains of patients with both genuine and acquired epilepsy is essential before further knowledge of the pathology of epilepsy can be obtained.

III. NEURONAL CHANGES IN EPILEPSY

"The question in pathology is not 'What causes epilepsy?' but 'What pathological processes lead to local 'discharging lesions'?'"

John Hughlings Jackson.

Since the work of Spielmeyer (1930) describing the small circumscribed foci of glial proliferation associated with a loss of ganglion cells in Ammon's horn (Fig. 2) and the cerebellum in the brains of both genuine and symptomatic epileptics, much thought has been given to these ischemic foci relative to the pathology of genuine epilepsy. Spielmeyer stated, however, that this focal ischemic destruction was the same as that seen in arteriosclerosis, endarteritis tuberculosa, thrombosis and embolism (Fig. 4). He suggested an angiospasm causing vasoconstriction and a consequent impediment to the circulation as being the etiology of these ischemic foci.

Such focal areas of destruction have been described not only in Ammon's horn and the cerebellum but also in the cerebral cortex by Scholz (1933), Zimmerman (1938), and Jansen, Kornyey and Saethre (1936).

The writer wishes to illustrate the presence of such focal areas of ischemia in traumatic epileptogenic lesions removed as epileptogenic foci at operation.

Scholz (1933) mentioned Malamud as having "investigated a great number of traumatic epileptic brains

and stated that the brains showed the same diffuse changes of the cortex and medulla at a distance from the scarred injury as did the brains of genuine epileptics." The writer has been unable to find other references to this work in the literature.

In studying traumatic epileptogenic lesions removed at operation the writer was impressed with the similarity of the Nissl preparation to the sclerotic atrophy described by Spielmeyer in Ammon's horn and the cerebellum (Fig. 2).

In view of this a study of excised traumatic epileptcgenic lesions was made, using Nissl's stain, in an attempt to demonstrate focal neuronal destruction.

Method of Study.

Various epileptogenic lesions were removed at operation by Doctor Wilder Penfield after thorough localization of the focus by using the thyratron stimulator. The focus or firing point was considered found, if when stimulated electrically, a seizure resulted which resembled in pattern the attacks which the patient usually experienced. (No sudden diffuse anemia or obvious constriction of the vessels has been observed by the members of the operating team).

Following excision of the cerebral cicatrix or area of focal atrophy, the specimen was placed either in (1) 10% formalin for 24 hours, or, (2) 80% alcohol for 24 hours.

After fixation and washing (unless alcohol fixed), the blocks were dehydrated in 95% alcohol, absolute alcohol and toluol followed by embedding in paraffin and hydration of the cut paraffin sections. The staining technique was as follows:

(1) Cresyl violet (0.5% cresyl violet in 20% absolute alcohol) for 20 minutes.

(2) Differentiation in 95% alcohol using microscopic control.

(3) Absolute alcohol 3 to 5 minutes.

(4) Toluol (3 changes) for 5 to 15 minutes.

(5) Mount in neutral balsam.

A series of 23 excised epileptogenic lesions was studied, mainly comprising the following types of epileptogenic foci, namely, meningocerebral cicatrix, cerebral cicatrix and microgyri.

In this group there were 11 examples of meningocerebral cicatrix, 7 of cerebral cicatrix and 4 of microgyri. One case consisted of gliosis surrounding a cyst thought to be due to a vascular occlusion at birth.

Observations.

A search was made for focal areas of destruction of neurons in the cerebral cortex, not in the immediate scarred area, which usually showed complete disorganization and sclerosis caused by the original injury, but in the adjacent cortex distant to the intermediate zone described by Penfield and Humphreys (1940).

Of the 23 cases studied, all but 3 showed focal areas of neuronal destruction in the cerebral cortex. The presence of these foci was repeatedly checked by other laboratory workers.

Of the 20 epileptogenic foci showing focal areas of destruction, 12 were selected as representing circumscribed areas not directly involved in the scar per se, that is, they were outside of the intermediate zone of the scar, in the surrounding cortex.

The remaining 8 were discarded as not being representative of such ischemic foci due to surrounding hemorrhages or close association of the foci to the actual scar (frequently due to the small amount of specimen received for study).

These foci occasionally contained no neurons whatsoever (Fig. 24 A) and appeared to represent what Spielmeyer called terminal stages of neuronal destruction due to the initial injury to the cortex (Stern, 1941). Spielmeyer (1922) described and illustrated such foci in the vicinity of old gunshot wounds of the cortex. Similar areas were described by Rand and Courville (1936) in the cortex of a brain removed from a patient having had a head injury of a little over 6 hours' duration.

The focal areas studied in the 12 cases selected, were most frequently found to consist of shrunken, elongated, darkly stained neurons having an irregular nucleus and either no processes or ones hardly discernable (Figs. 22, 23, and 24 B and C). This type

Fig. 22.

Focal area of neuronal destruction in cerebral cortex. Nissl stain.



Fig. 23.

Focus of neuronal destruction in cerebral cortex near epileptogenic lesion.
Nissl stain.

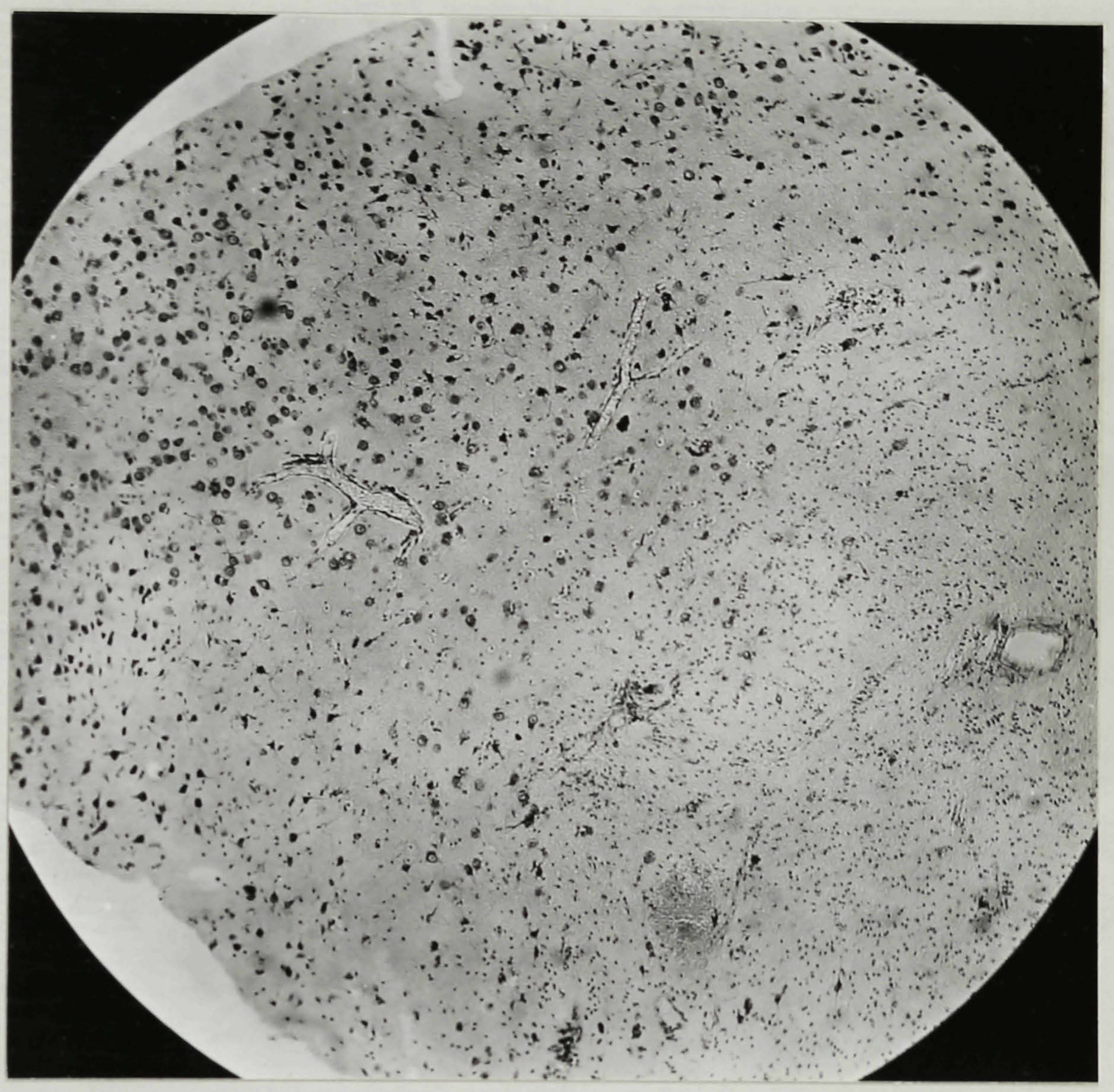


Fig. 24 A.

Focus of neuronal destruction
containing only glia cells.
No neurons remain.
Nissl stain.

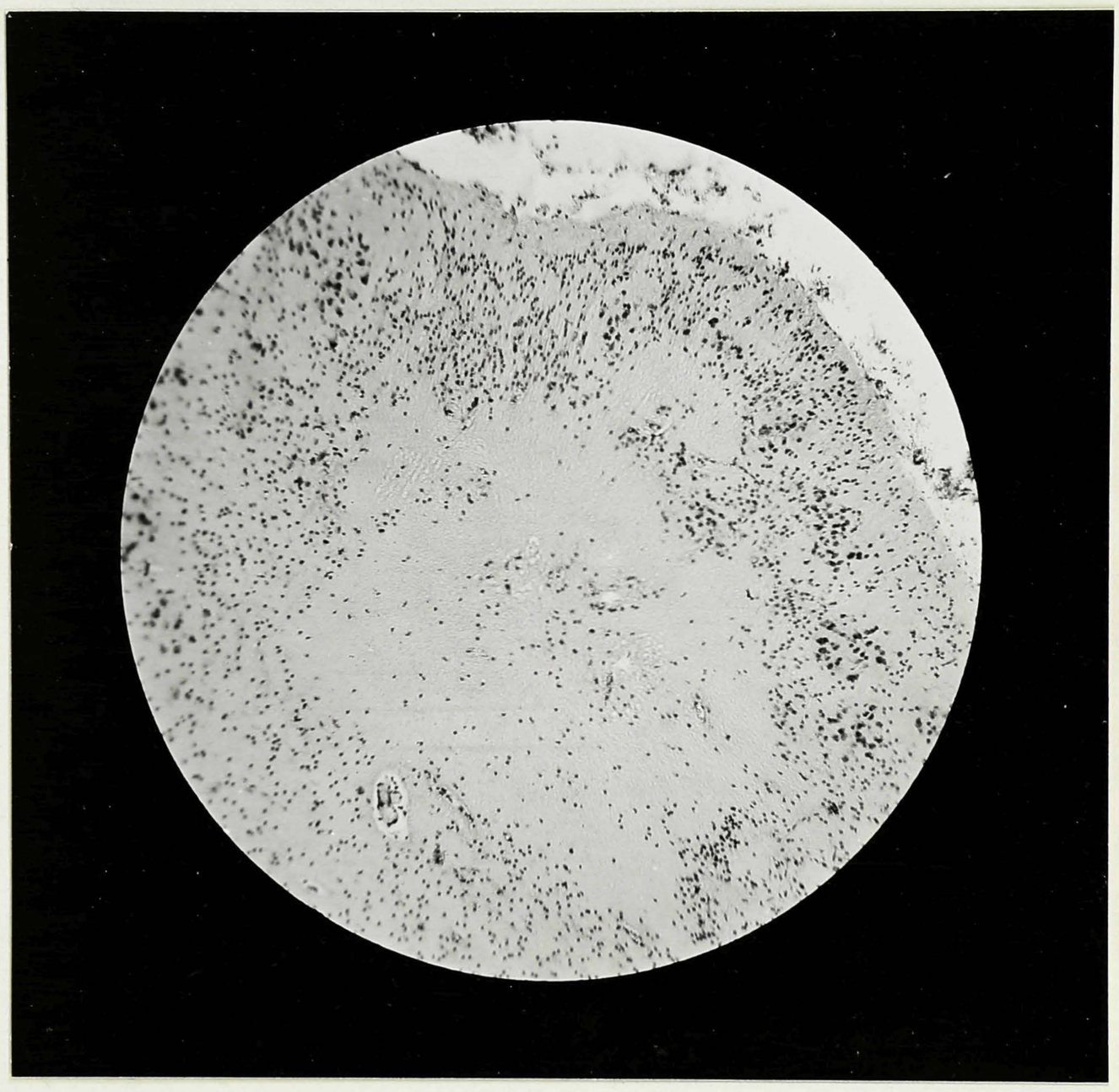


Fig. 24 B.

Foci of neuronal destruction in cerebral cortex near epileptogenic lesion.
Nissl stain.

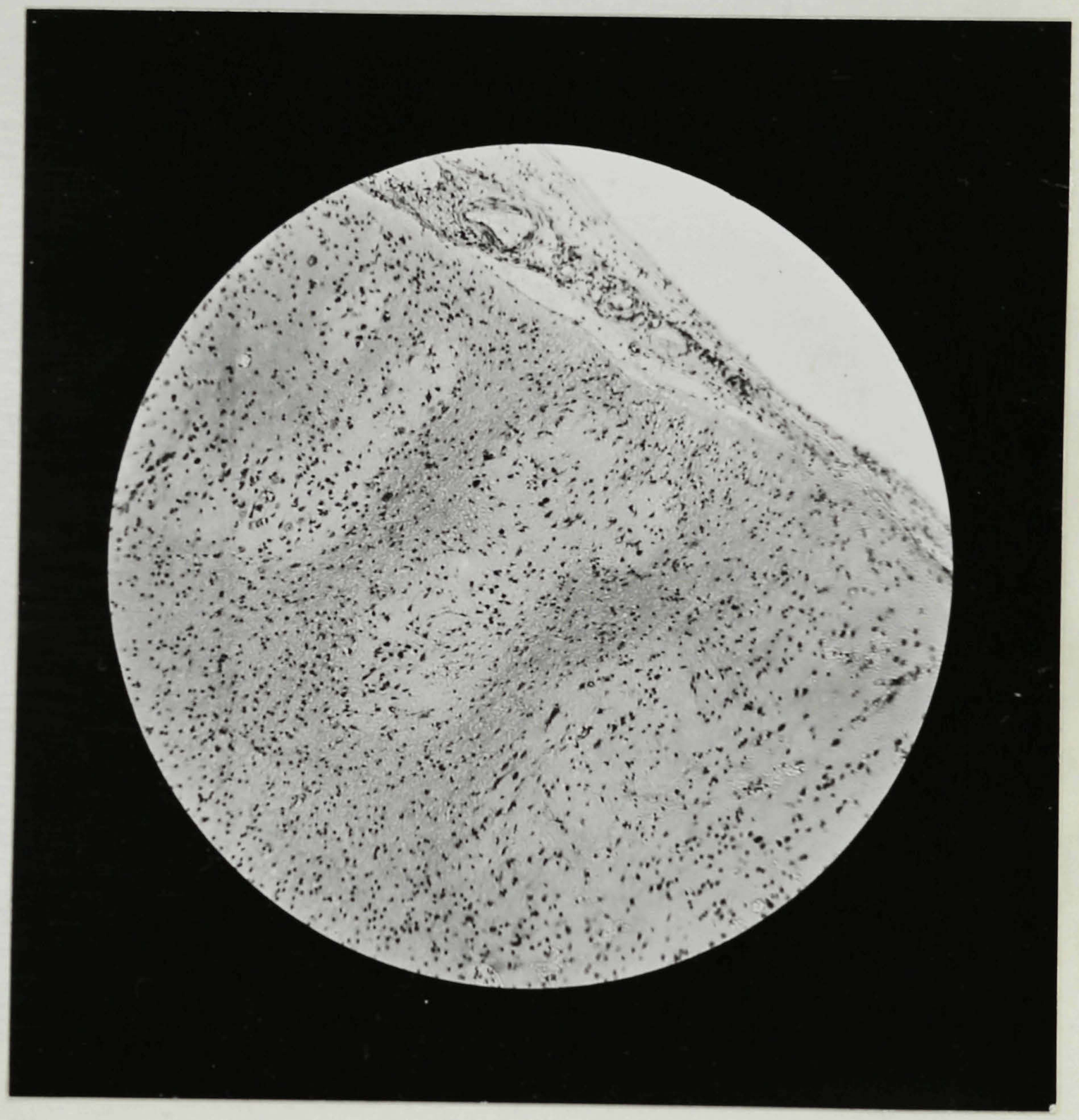
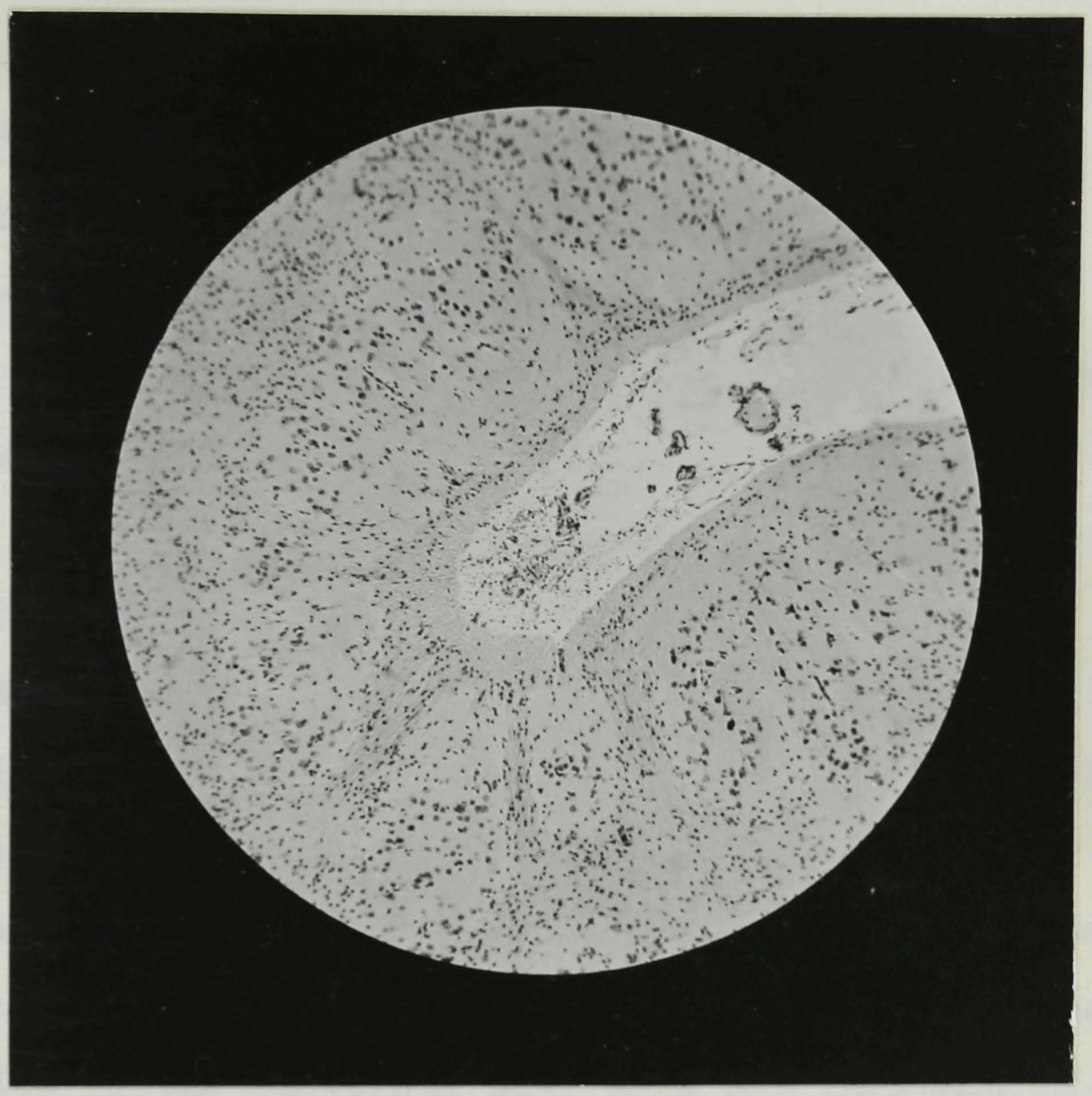


Fig. 24 C.

Intracortical islands of gray matter showing neuronal destruction. Note piloid glia extending from pial margin. Nissl stain.



of neuron simulated one of the types described by Spielmeyer (1928) as a characteristic change found in cerebral ischemia.

Usually accompanying these foci were glial nuclei which were increased in number compared to those in the surrounding cortex. Around such areas the surrounding neurons frequently showed a marked contrast, being either normal or slightly altered (Figs. 27 and 28).

Occasionally when there appeared a diffuse neuronal change in the cortex, the foci of destruction were striking because of an absence of neurons or the presence of remaining neuronal debris. These foci had the appearance of the punched-out areas described by Gildea and Cobb in experimentally produced cerebral anemia and designated by them (1930) "areas of devastation." Sections of cortex showing focal or patchy areas of neuronal destruction in areas of hemorrhage outside of the immediate scar were not included in the 12 cases.

The circumscribed focal areas of destruction found in a few cases proved to be intracortical islands of gray matter (Penfield and Humphreys) surrounded by piloid glia as demonstrated by P.T.A. and G.C.S. stains (Fig. 40). The Nissl picture showed primarily glial nuclei, few if any neurons being present (Figs. 25 and 26 A and B). Such foci, found in the intracortical islands, were usually smaller and more

Fig. 25.

Focus of neuronal destruction
showing increased number of glia.
Nissl stain.

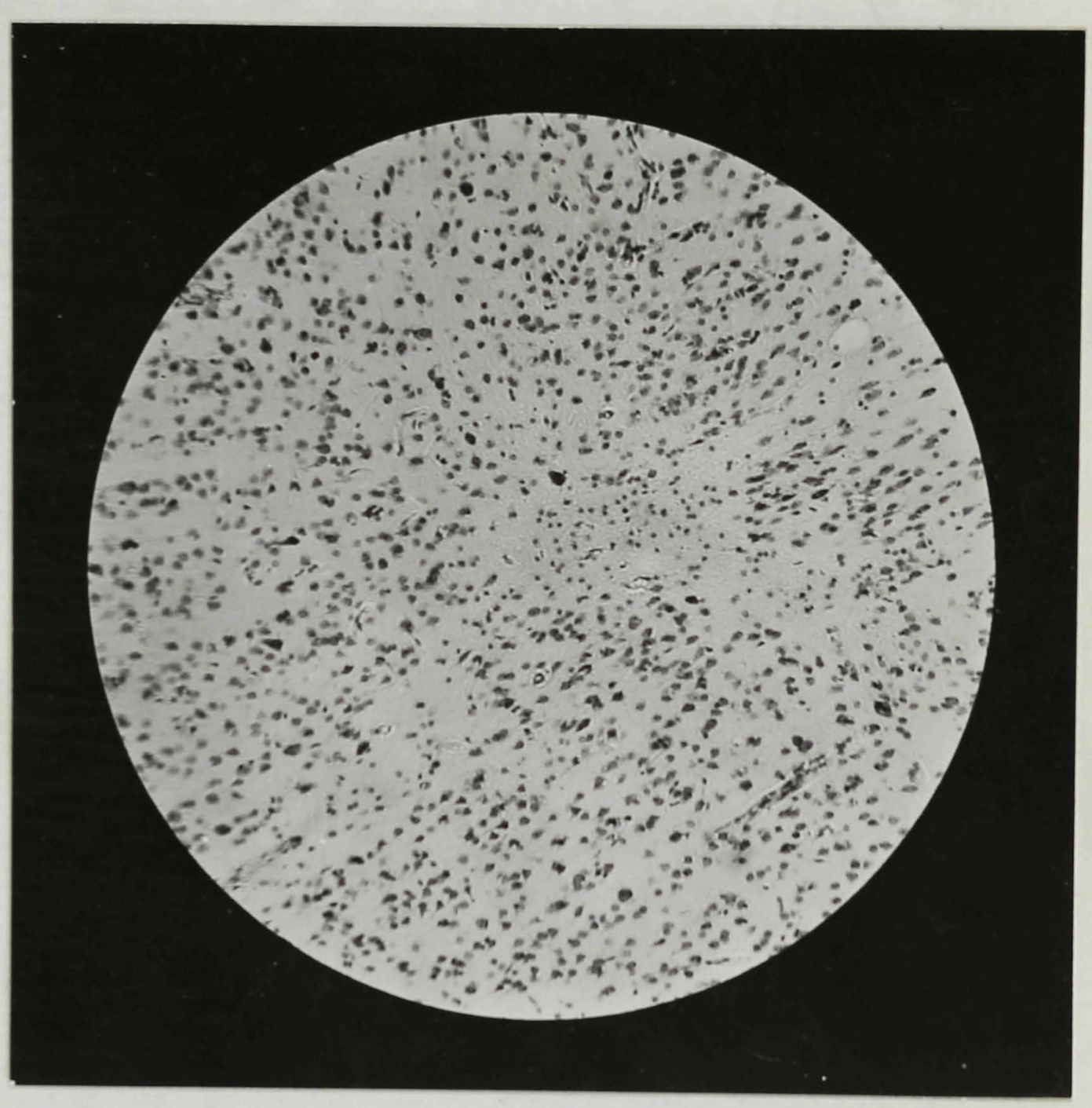
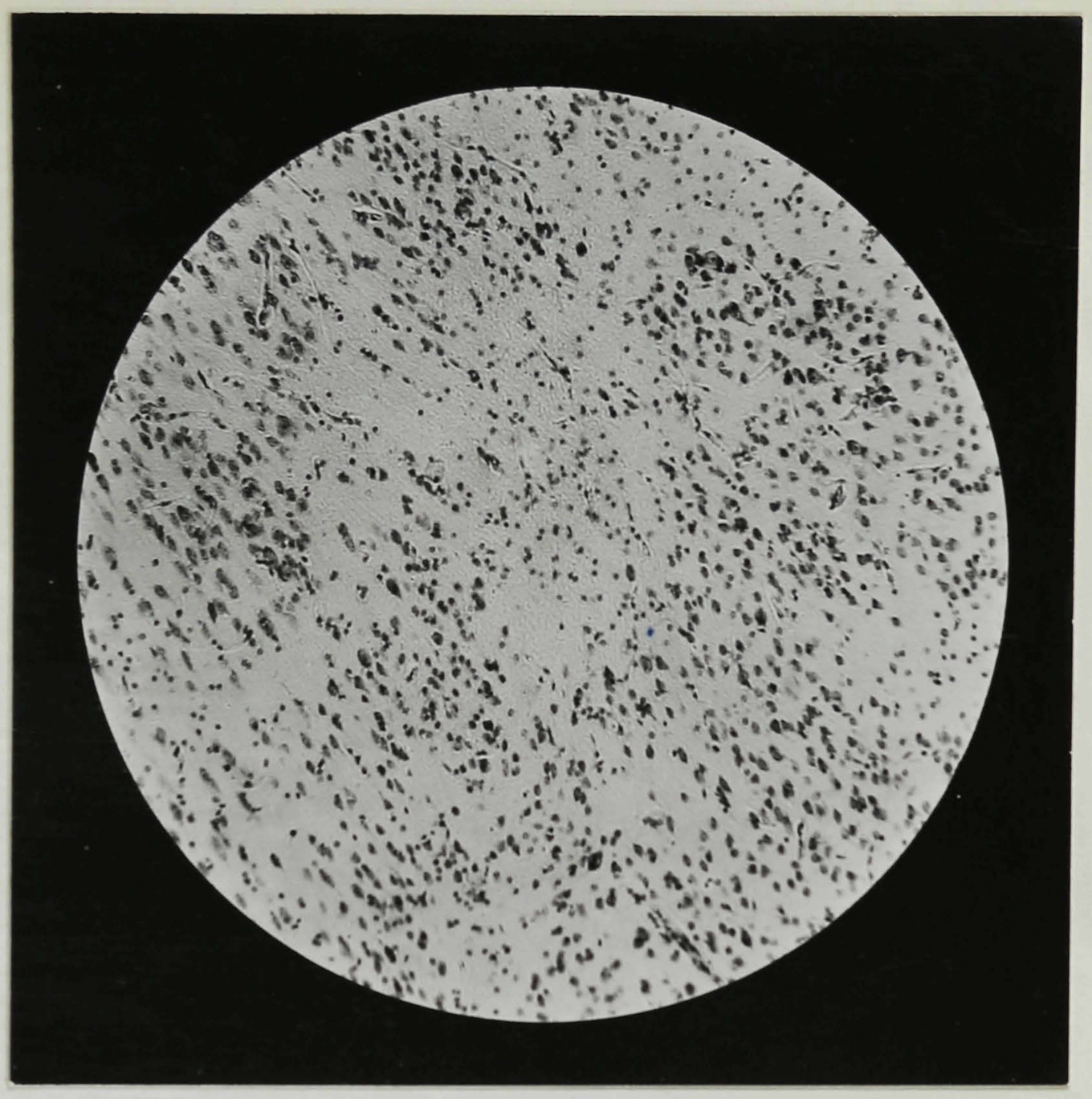


Fig. 26 A.

Area of neuronal destruction containing increased number of glia cells.

Fig. 26 B.

Area of neuronal destruction showing increased number of glia cells.
(Higher magnification of Fig. 26 A).
Nissl stain.



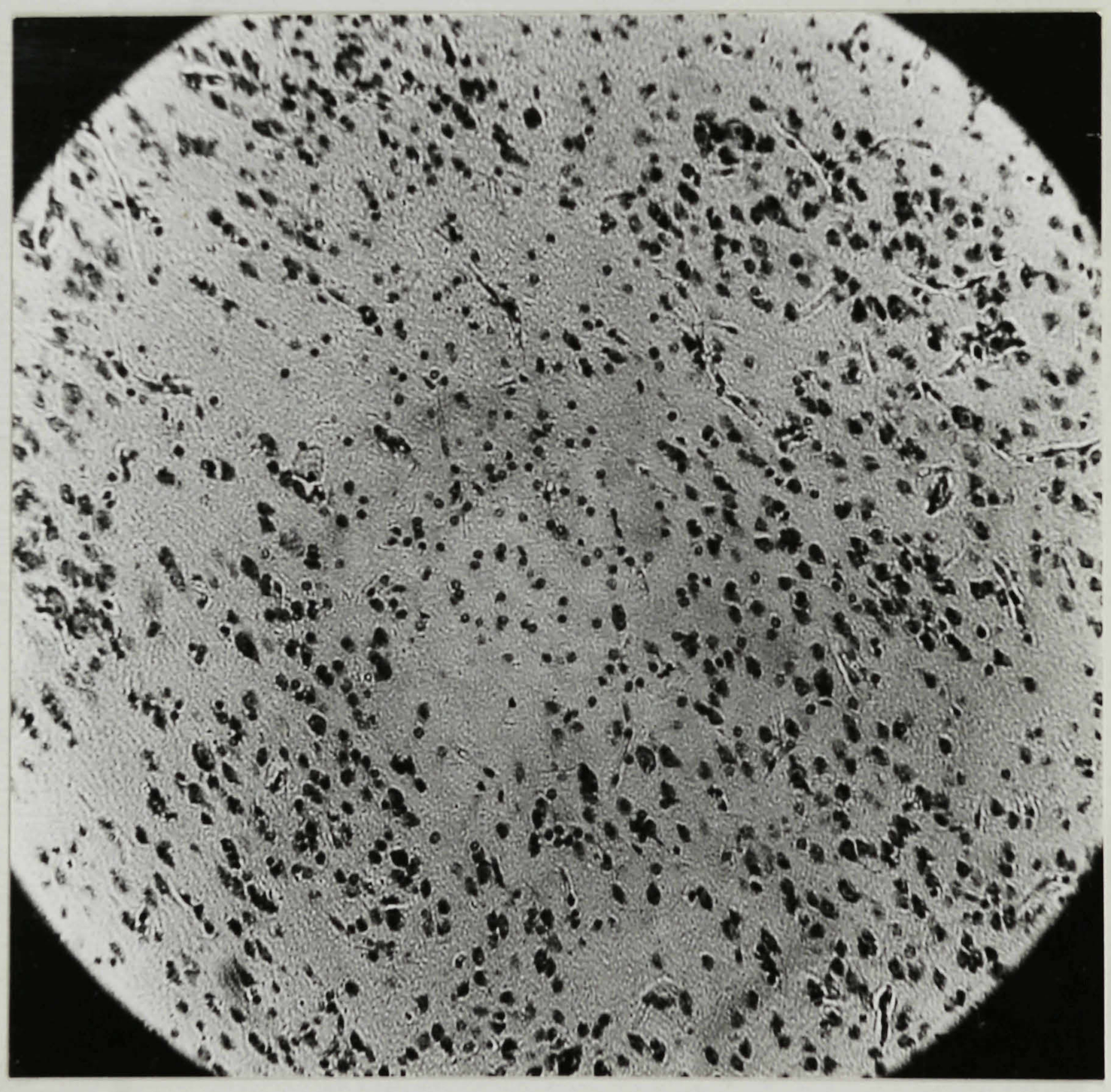


Fig. 27.

Focal area of neuronal destruction. Note large ganglion cells in adjacent region. Nissl stain.



circumscribed than those found in the cortex, unrelated to islands.

The altered neurons which still remained in focal areas of destruction usually showed various stages of destruction, most of which were like those described in Spielmeyer's classification of types of cell change in cerebral anemia (Spielmeyer, 1922).

The most frequent type of neuronal change consisted of a shrunken, elongated, angular cell body with darkly stained chromidial substance, the latter occasionally being in clumps. The processes had frequently disappeared or, if present, were thread-like and formed sharp angles as they extended from the cell body. The nucleus was usually dark and had assumed somewhat the shape of the cell. The nucleolus was eccentrically placed, enlarged and deeply stained. This type of cell change resembled Spielmeyer's cell shrinkage or "Einfache Schrumpfungen" and Nissl's "chronischen Zellerkrankung."

The next most frequent type found showed a pale cell body which was elongated, angular and shrunken having either remnants of processes or none. The nucleus was frequently irregular and darkly stained, often making the nucleolus invisible. If the nucleolus were seen, if would be enlarged, eccentrically placed and deeply stained.

As a rule the circumscribed foci showed representative cells of both of the above types.

One variation occasionally found consisted of a pale, rounded nucleus surrounded by a fuzzy rim of what appeared to be the remaining cellular cytoplasm. The nucleolus was found at the edge of the nucleus and was frequently difficult to find. One case showed a large circumscribed cortical focus, the center of which was composed of cells representing all of the three types described (Fig. 27). Around this area were many less sclerotic neurons among which could be seen several very large neurons having a granular, globule-like cytoplasm, a fairly darkly stained nucleus either irregularly round or oblong, containing a centrally placed, dark nucleolus. The processes were either absent or pale and thread-like. These cells were not only encountered in this focus but also were occasionally found in layers III and IV along the cortex, suggesting a congenital abnormality of the cytoarchitectonics of the cortex and simulating the signs of developmental abnormalities found in the cortex of genuine epileptic brains described by Turner (1907), Yakovlev (1939) and Jakob (1914).

Similar abnormal neurons have also been described by Schob (1930) who found such cells scattered throughout the cortex of a brain having a porencephalic defect of long duration. He pointed out that these abnormally large, deeply stained cells resembled at superficial glance the picture seen in the cortex

showing tuberous sclerosis.

Discussion.

The foci of neuronal destruction found in Ammon's horn and the cerebellum in the brains of genuine epileptics by Spielmeyer are very likely due to a disturbance in the blood supply as he has suggested. Such foci were found by Spielmeyer in several different pathological states such as endarteritis tuberculosa, arteriosclerosis, thrombosis and embolism. He later stated (1930) that the same foci were present in traumatic lesions, carbon monoxide intoxication, morphine intoxication, chloroform necrosis, hypertension, pseudo-uremia and other spasmodic conditions. Other authors have shown these circumscribed areas of destruction not only in Ammon's horn and the cerebellum, but also in the cerebral cortex and basal ganglia. That such foci can be found near posttraumatic epileptogenic lesions has been shown in this chapter.

Granted that such changes occur anatomically, it is of interest to speculate what type of physiological process causes such foci.

Spielmeyer has suggested the old theory which is still probably the most plausible, that of a vasomotor spasm.

In accepting this view, which one is inclined to do in the absence of any anatomical evidence of cerebral obstruction, one is reminded of the

observations of Penfield (1933) who noted striking vascular changes in 26 of 30 epileptic cases when electrical stimulation at operation produced a seizure. Cessation of arterial pulsation in the brain during an epileptic seizure was a constant observation.

This latter finding may well account for small circumscribed foci of neuronal destruction due to a temporary decrease in blood supply.

Evans and McEachern (1937) have stressed the fact that moderate grades of anemia will cause neuronal destruction but at the same time will cause hypertrophy of glial and connective tissue elements.

It is probable that these foci of neuronal destruction represent a pathological result rather than a cause, which fact impresses one with the importance of the physiology involved in the production of pathological changes as was so frequently stressed by Hughlings Jackson in his investigations of epilepsies.

Various observations have been reported which indicate vasoconstriction of cerebral vessels in human beings (Osler, 1896; Kennedy et al., 1938; Penfield, 1936; Cobb, 1934; Elvidge, 1938).

Whether periodic constriction of arteries in a cerebral scar takes place because of an increased perivascular plexus of such arteries or the lack of side branches causing abnormal stretch stimuli (Penfield and Humphreys, 1940; Echlin, 1939) is at

the present time not conclusive. The foci of destruction of neurons found in the vicinity of such lesions certainly suggest a process resulting from vasoconstriction.

The presence of such foci of neuronal destruction in the vicinity of epileptogenic cicatrices strongly suggests circulatory deficiency in small focal areas. The absence of demonstrable obstruction to vessels seems to further indicate a localized vascular spasm causing a transient ischemia with resultant focal neuronal change.

The writer has observed no foci of neuronal destruction in the vicinity of non-epileptogenic scars reported in Chapter V; few such scars, however, were available for study.

Summary.

(1) 23 epileptogenic lesions excised at operation were examined for the presence of circumscribed areas of neuronal destruction in the vicinity of the actual scar.

(2) 20 of these lesions showed such areas represented by foci of neurons undergoing changes characteristic of cerebral ischemia.

(3) 12 cases were selected as being representative of focal areas of neuronal destruction occurring in the vicinity of the scar and not directly involved in the scar itself.

(4) A description of such foci is given.

(5) It is suggested that such foci give further evidence of a vascular spasm occurring at the border of cerebral scars.

IV. ISLANDS OF GRAY MATTER IN CEREBRAL CICATRIX

"One of the most striking features in the pathological histology of the nervous system is the trifling and always passive share taken by the proper nervous elements in all those changes which affect the brain, spinal cord, or peripheral nerves. As every effort has been made to refer the diseases of the nervous system ..... to morbid changes in the ganglion cells and nerve fibers, we may with perfect confidence, supported by the negative result of all such investigations, maintain the thesis, that the causes, perhaps of all (?) diseases of the nervous system, are to be sought in anatomical lesions of the non-nervous elements."

Rindfleisch (Morbid Anatomy
of the Nervous System).

The study of cerebral cicatrix has been a fascinating one for many years, particularly with the advent of the gold and silver methods of the Spanish school. The clinical importance of such a study is obvious when one considers that such a pathological process is frequently accompanied by epilepsy.

The fact that a rapid and extensive connective tissue response followed trauma to the cerebral cortex has been known since the experimental report of DaFano (1939) who showed the presence of connective tissue in brain wounds followed by an enmeshment with the neuroglia. Bériel (1916) showed that following

superficial brain wounds a dense connective tissue scar formed adhering the meninges to the underlying cortex and also extending down into the cortex. Trotter (1926) pointed out that a tear in the arachnoid provokes a vigorous connective tissue response.

A complete review of the further studies on cerebral healing will not be given here since some of the most important reports have been reviewed in the first part of this paper (Foerster and Penfield, 1930; Penfield and Buckley, 1928; Penfield, 1927, 1928; and Penfield and Humphreys, 1940). Humphreys (1940) has described in detail the several types of epileptogenic foci classified by Doctor Wilder Penfield from his observations.

(1) The first type is the posttraumatic meningocerebral cicatrix containing a vigorous connective tissue reaction characterized by either penetrating the cerebral cortex as a mass or dipping into the cortex as strands of collagenous fibers, both types emerging with piloid astrocytes in a mesh-like arrangement (Fig. 67). Astrocyte processes were described which extended up through the former pial limits into the connective tissue, their vascular feet still remaining attached to the blood vessels and occasionally foot plates were found attached to collagen strands. Vascular studies showed many large, thick-wall vessels entering the cortex along with the connective tissue; however, first and second order vessels were missing in such

regions.

Islands of gray matter were described as follows:

"Within the collagen-glial network are often noted islands of cells. These islands may vary markedly in size from very tiny ones, with but few cells, to very large ones containing many cells. In these islands may be seen normal nerve cells and normal astrocytes, some of the protoplasmic order. As the borders of the zone are approached the astrocytes shade off into the piloid type and the nerve cells disappear. In the larger islands one may see all evidences of both acute and chronic anoxia as shown by clasmatodendrosis, the presence of Nissl's plump cells, monsterzellen and macrophages full of fat. It is the smaller islands that one sees most often, the monsterzellen. Comparative vascular studies of these areas are most instructive. In these regions where the changes are most severe there are but few first and a diminished number of second order vessels. These groups of smaller vessels are surrounded by relatively avascular tissue containing only large vessels. These areas of large vessels correspond to the areas of gliosis."

He mentions condensations of glial fibers described by Penfield (1932) and appearing in the oldest part of the lesion in the form of either slender wisps or great masses ("sheaves") (Fig. 29). These bundles were made up of fibers thinner than the ordinary piloid

Fig. 29.

Piloid gliosis in a microgyrus.
Note condensation of fibrils
into faggots.

(Penfield and Humphreys,
1940)



fiber and apparently having no cell body associated with them. Piloid glia with their nuclei could be found in the same region.

(2) Atrophic gyri or microgyri comprised the second type described, being characterized by very small gyri resulting from an early interference with blood supply. The cortex was found to be markedly replaced by piloid gliosis and the "sheaf" formation was very prominent. Further "islands" or "patches" of nerve cells were described in this glial mesh, "apparently trapped in the reaction" (Fig. 18).

(3) The third type consisted of cicatrices resulting from brain abscesses. They showed marked connective tissue reaction with an increase in number of large blood vessels. Here also, islands of normal cells were found within the mesh of connective tissue and glia. Sheaves of glia were present in the "oldest areas." (Fig. 29).

(4) The cicatrix due to closure of a large artery represented the fourth type which was described as being a cyst occasionally bordered by microgyri. The wall of the cyst showed a dense gliosis, strands of connective tissue and an absence of nervous structure, the latter being replaced by piloid glia. The atrophic gyri showed the same findings as the microgyric type described under (2).

(5) The fifth type, headed as miscellaneous, consisted of cicatrices resulting from arteriovenous aneurysm, posthemorrhagic intracerebral cyst and pachymeningitis. Two cases representing this type showed features in common with the preceding types, namely, piloid gliosis in which could be seen small islands of cells and "evidences of progressive degeneration."

In review of the five types of cerebral cicatrix the following points were found represented in each, namely:

(A) Islands of gray matter within the collagen-glial network.

(B) Islands of gray matter within the glial reaction.

(C) Glial fibers forming "sheaves."

(D) Marked evidence of progressive tissue destruction in the border zone between the normal and abnormal tissue.

(E) Reduction in the number of first and second order vessels where the evidence of progressive tissue destruction was most marked.

Foerster and Penfield (1930) mentioned a further observation referable to the predominance of connective tissue in meningocerebral scars when they reported 12 cases of traumatic epilepsy giving the pathological findings of the excised lesion. In two cases of birth injury (19 years' duration) the most marked degree of scar formation was found consisting of "tubes and sheets of neuroglia" surrounded by

connective tissue sheaths. The authors stated that such tissue forming these strands could hardly be called cerebral tissue in that no nerve cells and no nerve fibers were present. The neuroglial tubes were coated over with collagen, "just as nerve fibers in other portions of the nervous system are invariably coated."

An illustration of the cross sections of such strands gave the appearance of many varied sized islands of neuroglial tissue surrounded by a dense band of collagen (Fig. 30).

In reference to the islands of gray matter described by Penfield and Humphreys and the tubes of neuroglia surrounded by connective tissue described by Foerster and Penfield, the writer is presenting a further study of both and a suggested correlation between the two in an attempt to explain the formation of such pathological alterations found in cerebral scars.

As the tubes of neuroglia (Foerster and Penfield) in cross section simulate islands as do the islands of gray matter (Penfield and Humphreys) the writer will henceforth refer to both as islands, differentiating them by designating the tubes of neuroglia as extra-cortical islands (Fig. 30) and islands of gray matter described by Penfield and Humphreys (Fig. 18) as intra-cortical islands. Explanation of such terminology will follow in the discussion of this chapter.

Fig. 30.

Strands of cicatrix in cross section. Collagen forms a dark line about each. The dots within are neuroglial nuclei.

(Foerster and Penfield, 1930)



In this work many epileptogenic lesions excised at operation were used for study. Seven cases were selected, the pathological findings of which well illustrate the purpose of this chapter.

It is thought advisable to present a short clinical summary of each of the cases in view of possible reference as well as clarification in regard to the pathology to be described.

Case 1 (S-55-39, N.H.)

A 12-year-old girl, with a history of questionable birth injury began to have right-sided seizures at the age of 3 years occurring approximately every 5 months and later every month. A left craniotomy was performed when the patient was 6 years of age and "a removal of adhesions and cystic growth over the left hemisphere" is said to have been done.

Objective findings on physical examination showed mental retardation (Binet - I.Q. 56, mental age of 6 years, 8 months); right 6th nerve weakness; bilateral optic atrophy; visual acuity - right 6/17, left 6/13; deviation of uvula to the left; a well healed old craniotomy scar, left frontoparietal region; weakness of right leg; and, a marked horizontal nystagmus.

Accessory findings showed the following: (1) Electroencephalography - "An epileptiform focus in the left occipital pole and a large area of delta waves extending from this point into the left

parietotemporal region."

(2) Encephalography - "Diffuse cerebral atrophy, much greater in the left hemisphere which showed marked destruction of the occipital and parietal lobes."

Operation: Left parieto-occipital osteoplastic craniotomy with removal of focal area of brain, including occipital lobectomy.

Operator: Doctor Arthur Elvidge.

Pathological Diagnosis: Cerebral cicatrix, parieto-occipital region, left, due to circulatory disturbance (porencephaly).

Case 2 (S-245-40, M.B.)

A 20-year-old male with a history of having had cyanosis at birth associated with respiratory difficulty began having seizures at the age of 7 years.

Objective findings on physical examination showed internal strabismus, right; constant nystagmus with quick component to the left on looking in any direction; and, decreased visual acuity, right - 6/66, left 6/13.

Accessory findings were as follows:

(1) Electroencephalography: "A very extensive lesion of the left posterotemporal and parieto-occipital regions giving rise to large paroxysmal sharp wave discharges."

(2) Encephalography: "Large cystic lesion in the left parieto-occipital region. Cortical atrophy in the frontoparietal regions on both sides."

Operation: Left occipital osteoplastic craniotomy with excision of cyst and areas of focal cortical atrophy.

Operator: Doctor Wilder Penfield.

Pathological Diagnosis: Meningocerebral cicatrix, microgyric type, occipital lobe, left.

Case 3 (S-17-41, R.C.)

A 15-year-old male was admitted with a history of having had a severe hemorrhage from the left occipital region the third day after birth followed by status epilepticus (about 50 convulsions) on the fifth day after birth. No further attacks were observed until the age of 11 years, after which time the patient had frequent right-sided seizures.

Objective findings on physical examination showed marked mental retardation; horizontal nystagmus, bilaterally, more marked on the left; slight ataxia of arms and legs; marked ataxia on walking, and a slight linear depression over the left frontal area of the skull.

Accessory findings were as follows:

(1) Electroencephalography: "An active epileptogenic focus in the left frontal region, the abnormality suggesting the possibility of a cyst bordered by a region of microgyria in the left frontal region."

(2) Encephalography: "A superficial, atrophic, parasagittal lesion of the left frontoparietal lobe."

Operation: Left frontal osteoplastic craniotomy with removal of a meningocerebral cicatrix.

Operator: Doctor Wilder Penfield.

Pathological Diagnosis: Meningocerebral cicatrix with cyst, frontal, left.

Case 4 (S-39-41, R.E.)

A 17-year-old female was admitted with a history of having had a head injury when 9½ years of age, being unconscious 5 days and having sustained a fractured skull and a laceration of the scalp in the right posteroparietal region. Drainage from this area followed in a few months. An operation was performed and several spicules of bone were removed. Approximately 7½ years later the patient, having had only frequent bifrontal headaches since the accident, had bed-wetting on three occasions. Seizures began 10 days prior to admission to the Montreal Neurological Institute.

Objective Findings on physical examination showed a small, well-healed scar in the right posterior parietal region with a palpable bony deformity; neurological examination was normal.

Accessory findings were as follows:

(1) X-ray of skull: "Old fracture of the right mid-parietal bone showing evidence of healed osteomyelitis with focal hyperostosis of the internal table."

(2) Electroencephalography: "Sharp waves and delta were recorded from deep in the right temporal region."

(3) Encephalography: "Focal atrophic lesion in the

midparietal region immediately beneath the old skull fracture."

Operation: Right osteoplastic craniotomy with removal of meningocerebral cicatrix.

Operator: Doctor Wilder Penfield.

Pathological Diagnosis: Meningocerebral cicatrix posterior parietal region, right.

Case 5 (S-100-41, H.F.)

An 11½-months-old baby boy presented with a history of birth trauma consisting of an intracranial hemorrhage observed 2 days following delivery and characterized by bloody spinal fluid and full fontanelles. Normal development followed until the age of 4½ months after which time mental retardation and left-sided convulsions were noted.

Objective findings on physical examination showed dissociation from surroundings and fixed facial expression; use of left arm much less than the right; pallor of the optic discs bilaterally; hyperactive deep tendon reflexes; and, absent abdominal reflexes.

Accessory findings were as follows:

(1) X-ray of skull: "Asymmetrical skull demonstrating a lesser volume of the right hemicranium than the left. Question of atrophic lesion on the right side."

(2) Electroencephalography: "Evidence of a focal lesion in the right parietal region near the temporal lobe."

(3) Encephalography: "Large, cystic, atrophic lesion

in the right frontoparietal region superiorly. Question of old subarachnoid hemorrhage."

Operation: Right frontal craniotomy with removal of subdural hematoma, and, at a later date, removal of a cerebral cicatrix including a cyst bordered by a narrow gyrus.

Operator: Doctor Wilder Penfield.

Pathological Diagnosis: (1) Subdural hematoma. (2) Meningocerebral cicatrix and cyst, frontal lobe, right.

Case 6 (S-121-41, H.S.)

An 8-year-old boy was admitted with a history of having been in an automobile accident at 4 years of age in which he sustained a fractured skull. At operation, performed shortly after the accident, a subdural hematoma, extradural hemorrhage and depressed fractures were found; the latter were removed and a subtemporal decompression was done. For 2 weeks the patient had a paralysis of the right arm and leg and for 3 weeks was unable to speak. A weakness of the right arm and leg persisted. Right-sided seizures began approximately 2 years after the accident.

Objective findings on physical examination showed the skull to be smaller on the left side with a defect in the left parietal region where pulsations were visible and palpable; slight horizontal nystagmus on lateral gaze; right partial homonymous hemianopia;

palsy of the right facial nerve; weakness of the right hand grip; slight ataxia of right arm and leg; and, increased deep reflexes of the right arm.

Accessory examinations were as follows:

(1) X-ray of skull: "Large cranial defect, left lower parietal and upper temporal areas; thickening of the left parietal bone; question of cerebral atrophy or agenesis secondary to injury.".

(2) Electroencephalography: "Two foci of maximum epileptiform discharge, the more active being in the frontal region and a less active focus being posteriorly in the parietal region. In addition there was abnormal sensitivity to hyperventilation with bilaterally synchronous discharges."

(3) Encephalography: "Left-sided cerebral hypoplasia or atrophy apparently secondary to an old injury; large cranial defect."

Operation: Left parietal craniotomy with removal of meningocerebral cicatrix.

Operator: Doctor Wilder Penfield.

Pathological Diagnosis: Meningocerebral cicatrix, temporal region, left.

Case 7 (S-137-41, C.V.)

A 26-year-old male was admitted with a history of having been shot in the head at close range, when 12 years of age, a .22 bullet entering the right frontal bone, driving in fragments of bone and lodging

in the occiput. The bullet was removed from the parieto-occipital region one week after the accident. One month later an abscess in the right parietal region was drained, followed by a meningitis, a left-sided paralysis and a left homonymous hemianopia.

One year later the patient was struck over the head and following this blow had three convulsions. After this many focal epileptic attacks were observed.

Objective findings on physical examination showed a scar in the right frontal region; large scar and bony protuberance in the right parietal region; scarring of the occipitoparietal region transmitting an impulse with the patient coughing; left homonymous hemianopia; slight deviation of uvula to the left; slight diminution of vibratory sense over left ankle; and, mild astereognosis of left hand.

Accessory findings were as follows:

(1) X-ray of skull: "Numerous metallic fragments lying within the brain substance on the right side, extending from a small opening adjacent to the coronal suture to a large opening in the occipital bone; a smooth round defect in the right parietal bone.

(2) Electroencephalography: "A slight disorganization and tendency for low amplitude paroxysmal spike activity from the right frontal region."

(3) Encephalography: "Fairly large atrophic lesion in the right occipital lobe. A small focal atrophic lesion at the frontal pole of the right temporal lobe."

Operation: Right frontoparietal craniotomy with removal of meningocerebral cicatrix; temporal lobectomy.

Operator: Doctor Wilder Penfield.

Pathological Diagnosis: Meningocerebral cicatrix, temporal lobe, right.

In each of the epileptogenic lesions removed from the beforementioned patients islands of neuroglia were found being quite separate from the adjacent cortex and encircled by collagenous bands (Figs. 31, 32, 33, 34, 64 and 65). Such islands were identical with those described and illustrated by Foerster and Penfield (1930) (Fig. 30). These authors found no nerve cells in such "neuroglial tubes"; consequently they did not regard them as being cerebral tissue.

The writer was impressed by the marked similarity in the appearance of such islands to the adjacent cortex; therefore a careful search for evidence of neuronal structure was made.

In each of the 7 cases, definite neurons were found in many of the isolated islands indicating that such islands were definitely cerebral tissue (Figs. 35, 36 and 37). The existence of such small, well-circumscribed areas of cerebral tissue would naturally cause one to wonder how these isolated areas were formed. In view of this a further description of the various forms encountered will be given.

Fig. 31.

Numerous extracortical islands of gray matter. Note rim of connective tissue around each island.

Hematoxylin and van Gieson stain.



Fig. 32.

Intracortical islands in the process of being extruded from the cortex to form extracortical islands. Several completely extruded islands can be seen.

Hematoxylin and van Gieson stain.

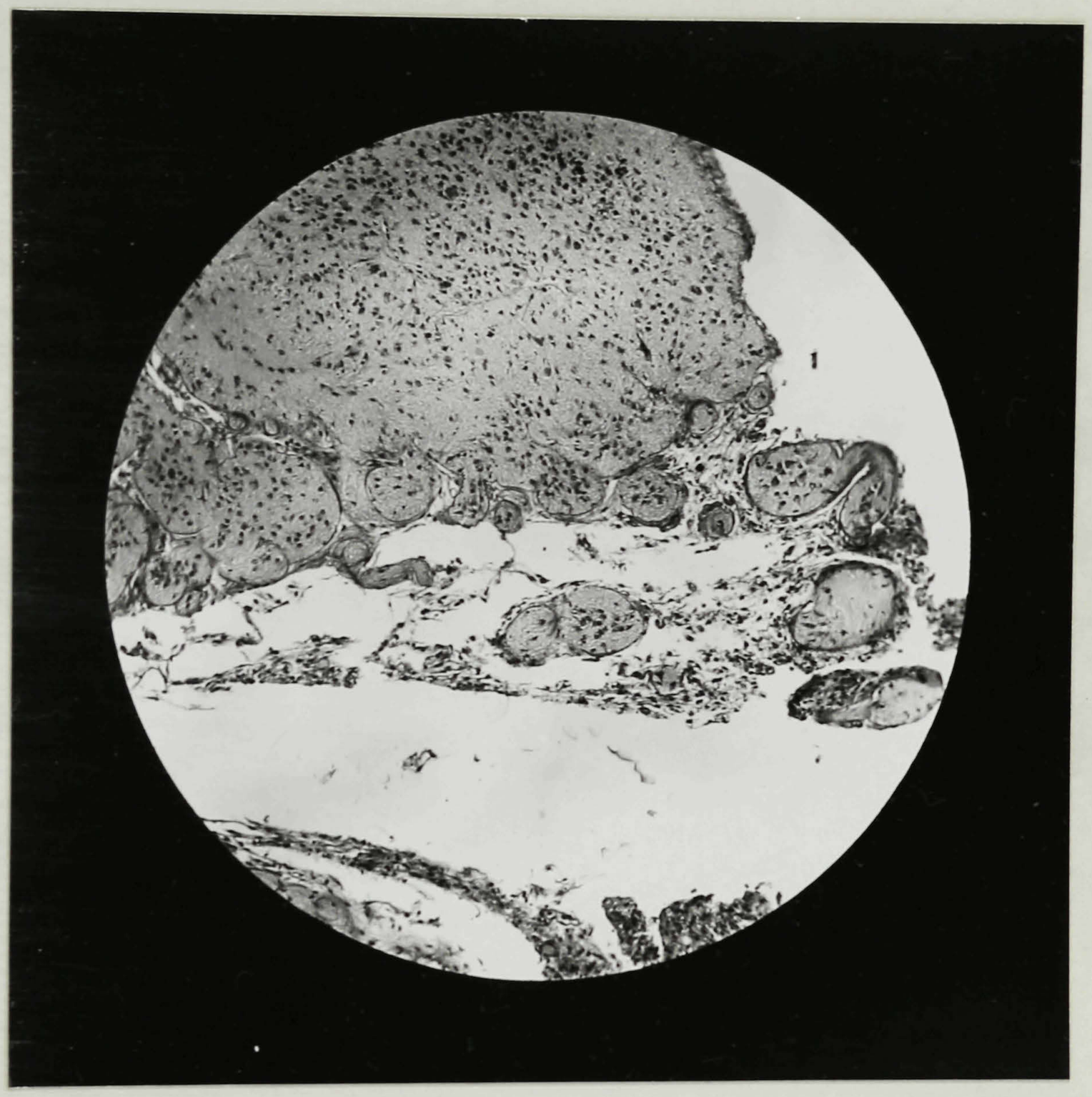

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Fig. 33.

Extracortical islands of gray matter rimmed with a connective tissue layer. Note three small islands being extruded.
Hematoxylin and van Gieson stain.

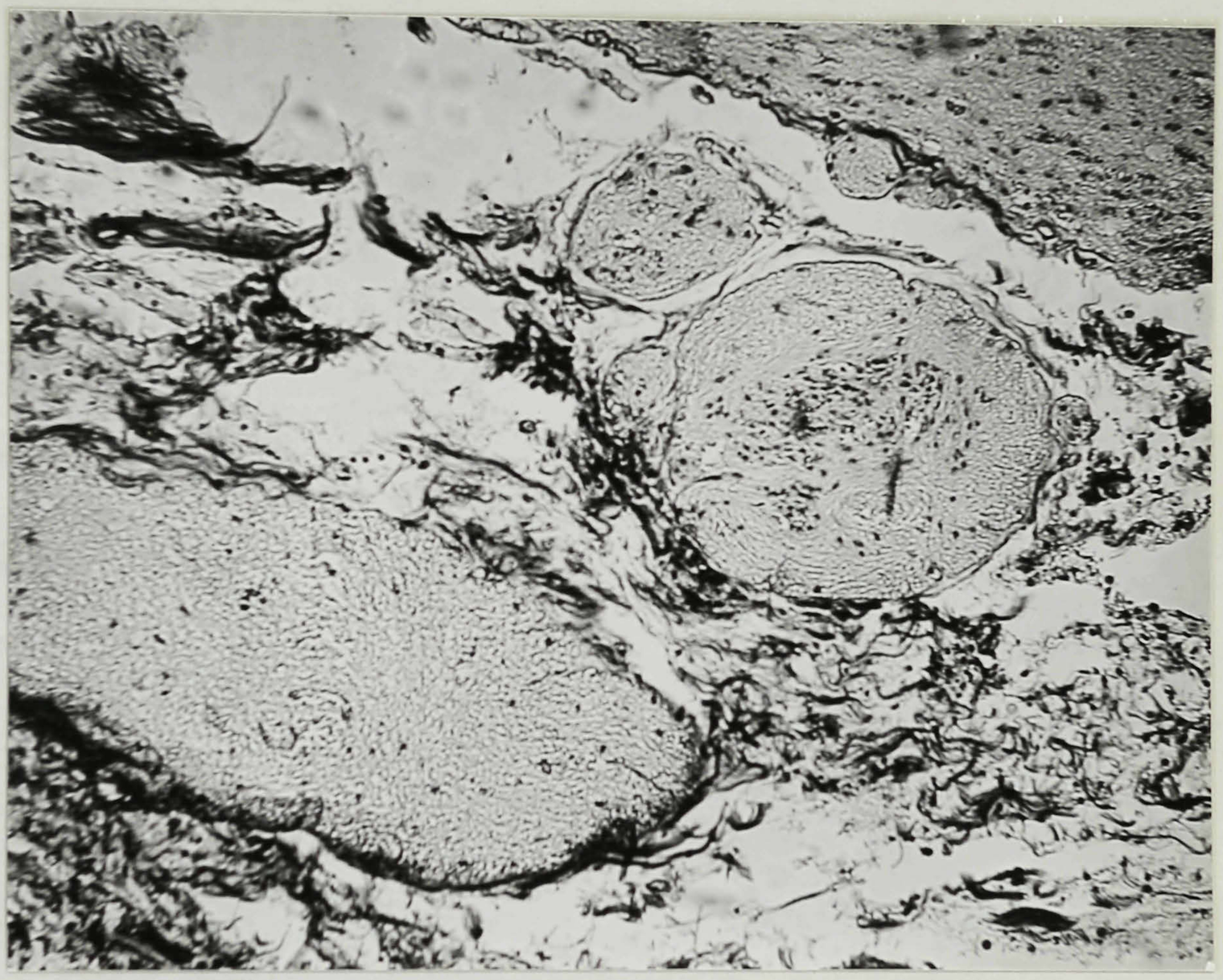


Fig. 34.

Extracortical islands of gray matter. Note partial division of trabecula into three islands. Mallory's Phosphotungstic Acid Hematoxylin stain.

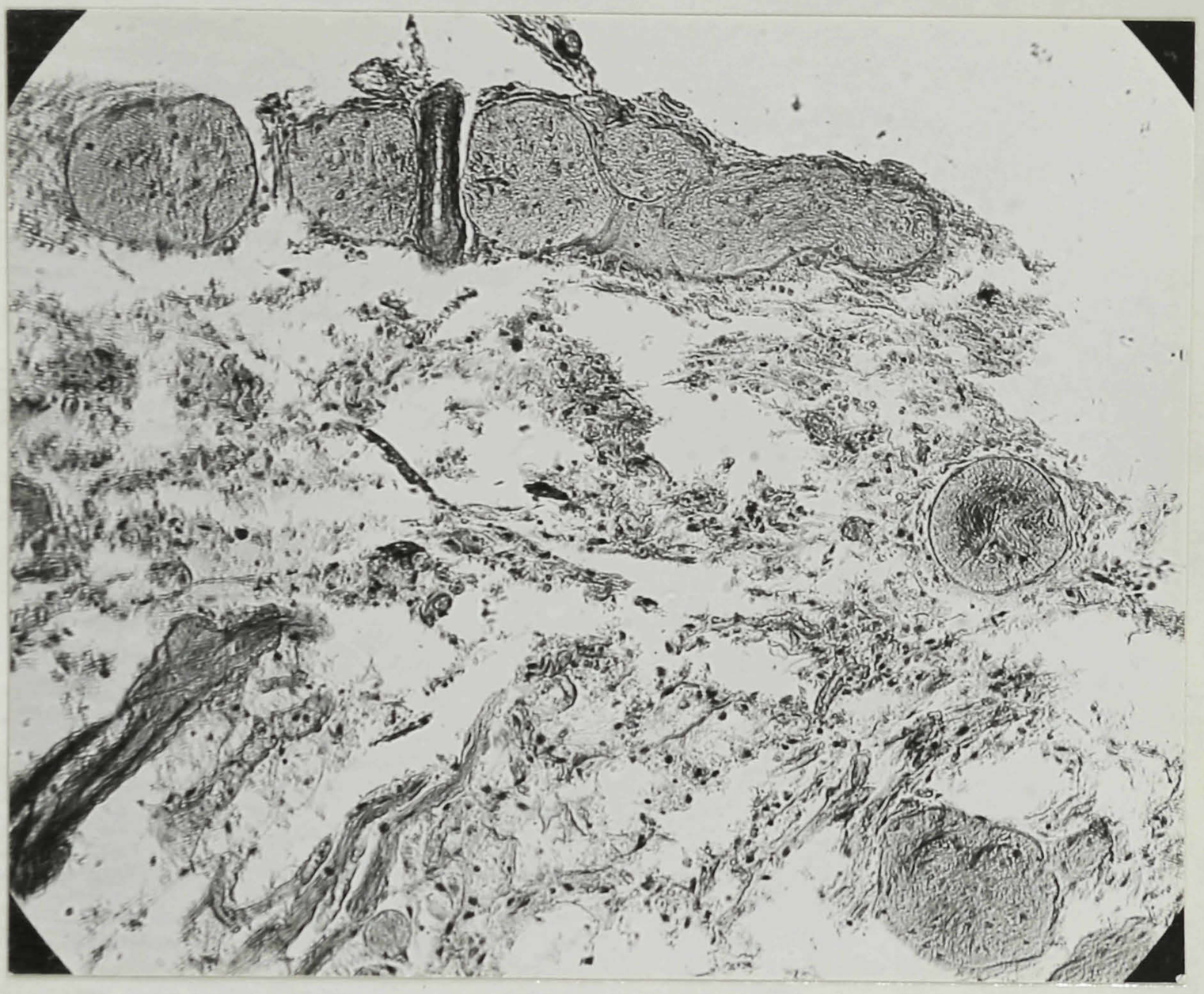


Fig. 35.

Extracortical island of gray matter containing neurons.

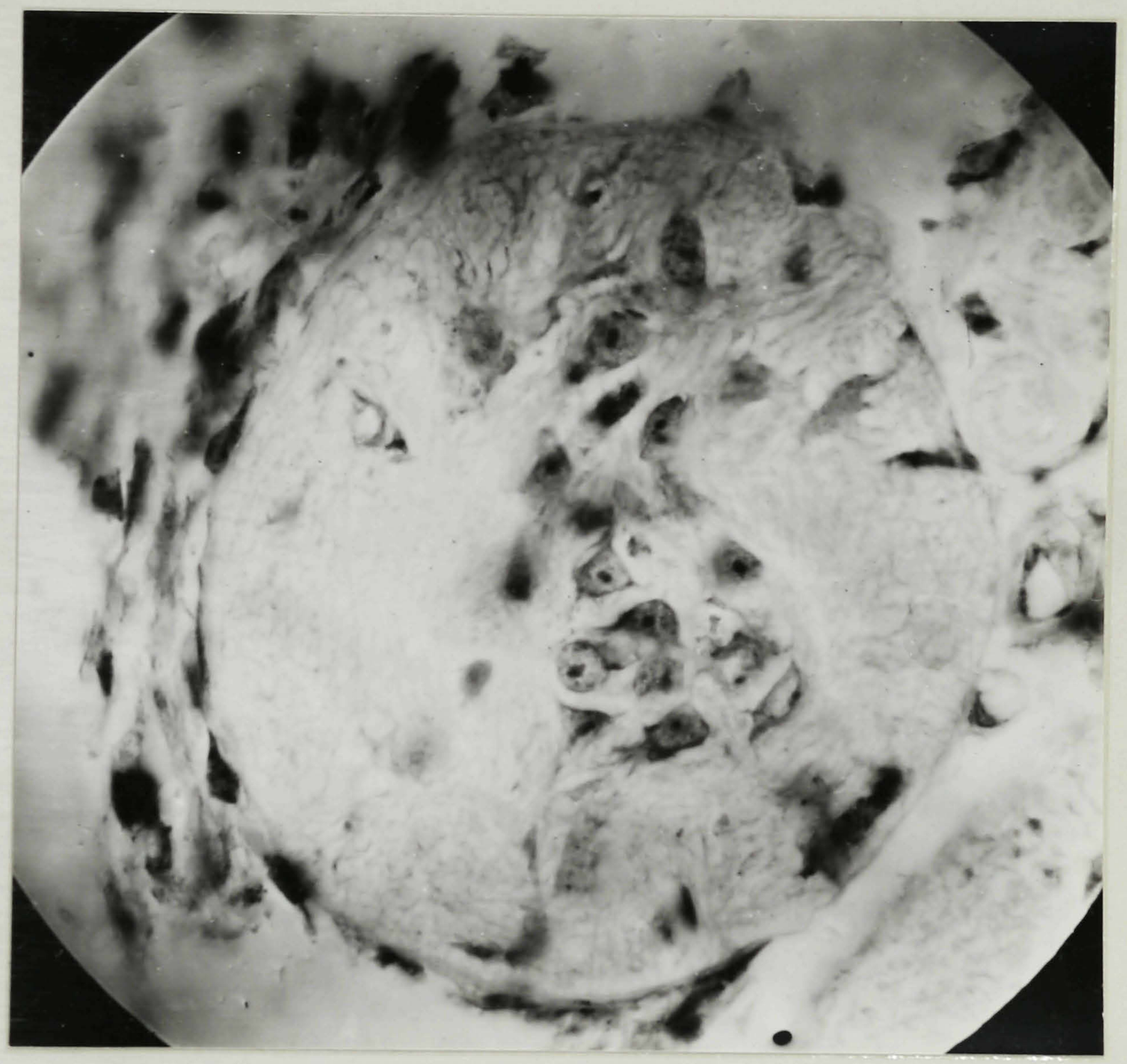


Fig. 36.

Extracortical island containing neurons. Nissl stain.

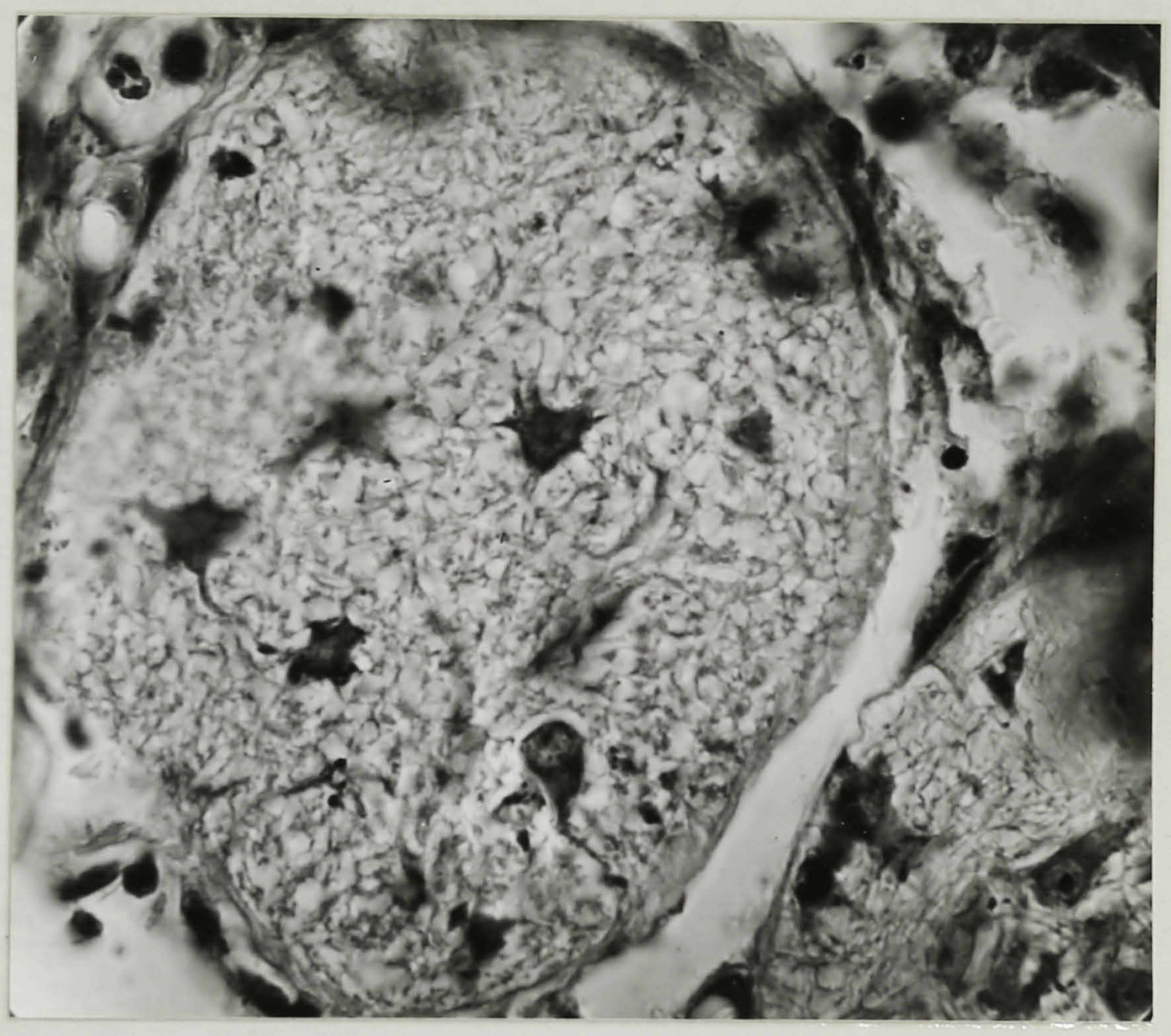


Fig. 37.

Extracortical islands of gray matter containing neurons. Nissl stain.



The usual picture found consists of a markedly distorted cortex associated with a rather severe amount of atrophy. The cortex in such areas is thinned-out and frequently indented at intervals along the pial margin, often having a beaded appearance, each bead representing a partially or completely isolated area of cortical tissue (Figs. 38, 39 and 40). In the more advanced areas of atrophy can be found many trabeculae of cortical tissue projecting out from the gyrus as finger-like processes (Figs. 41, 42 and 66). In such areas one finds small, completely isolated islands of gray matter most often containing neuroglia but frequently containing neurons. Many such islands have been minute, containing only two or three nuclei and even here occasionally there are one or more neurons present (Figs. 31 and 62). The trabeculae of cortical tissue, frequently in folds, most often show neurons where they begin to thin out from the cortex. However, even though the neuroglia become more prominent as the distance from the cortex increases, neurons can often be found at a distance from the more normal-appearing gyrus (Fig. 64).

The connective tissue stroma in between such islands and trabeculae is almost invariably very vascular having many large vessels (Figs. 34 and 63). In one instance (Case 4) several fairly large vessels were thrombosed (Fig. 43). Throughout many trabeculae, as well as the

Fig. 38.

Intracortical islands in the process of being extruded from the cortex to form extracortical islands of gray matter.

Mallory's Phosphotungstic acid Hematoxylin stain.

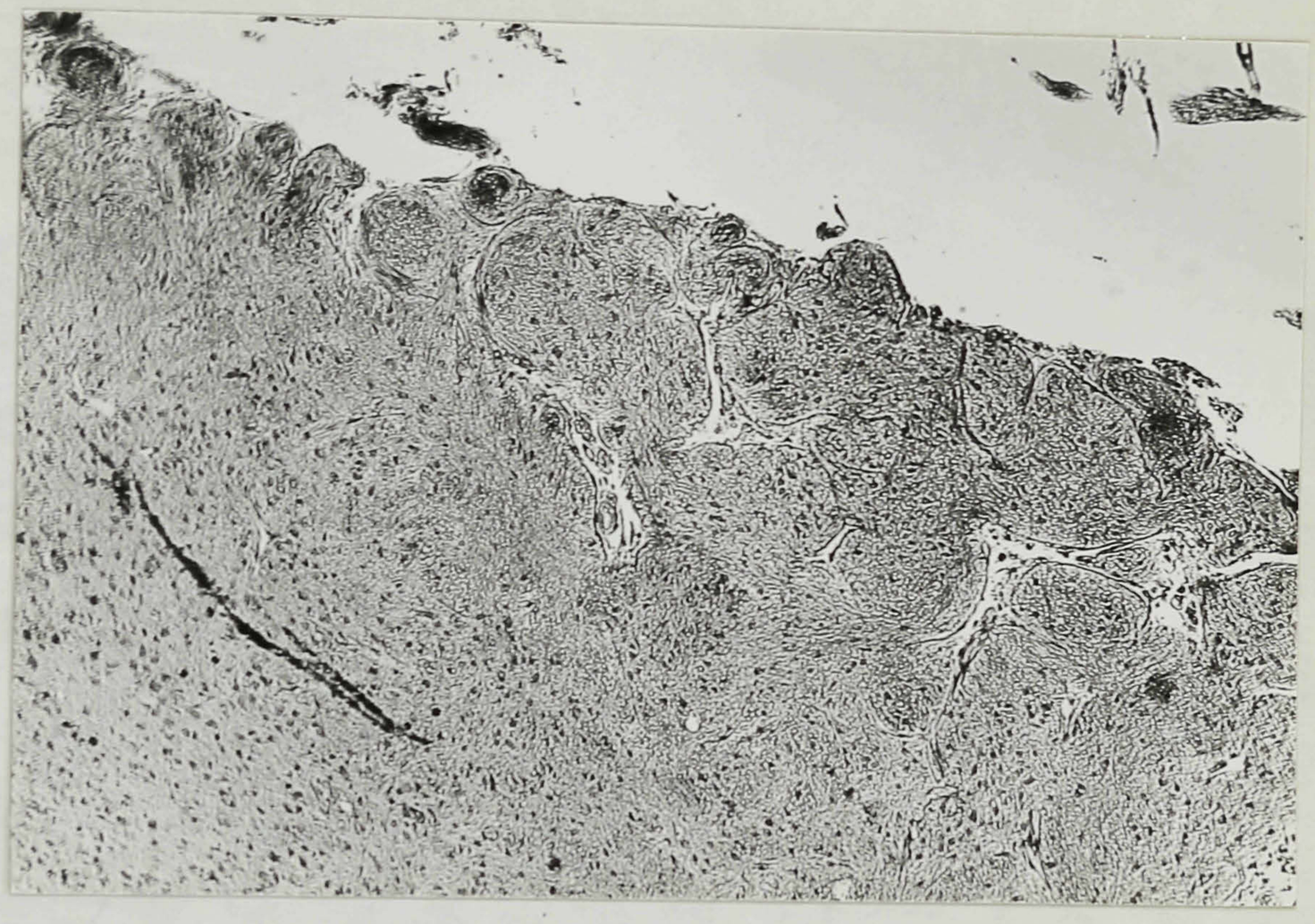


Fig. 39.

Bead-like appearance of intracortical islands formed by piloid glia. Note absence of nuclei in islands.

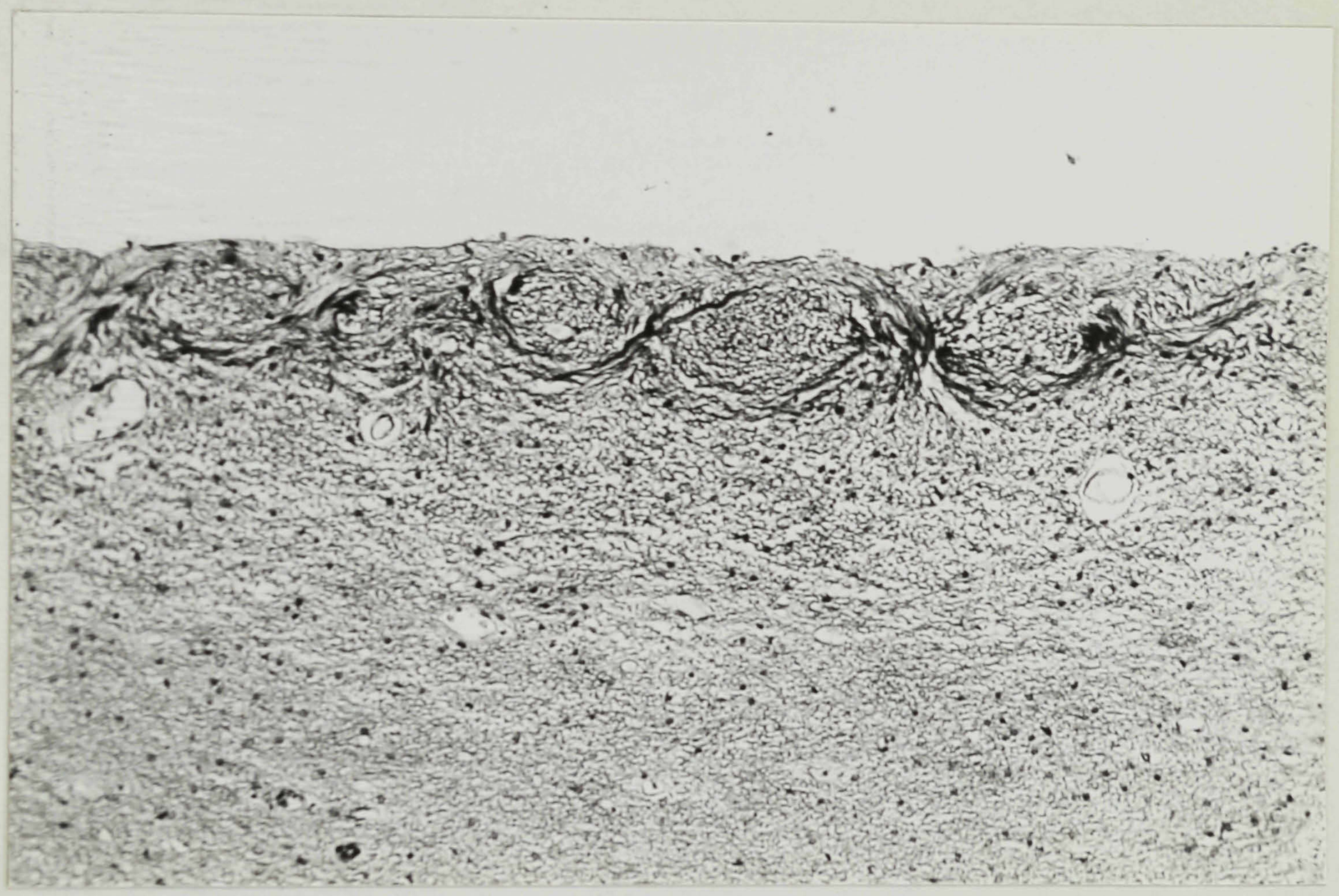


Fig. 40.

Intracortical islands of gray matter separated by streams of piloid glia.

Cajal's Gold Chloride Sublimate Stain.

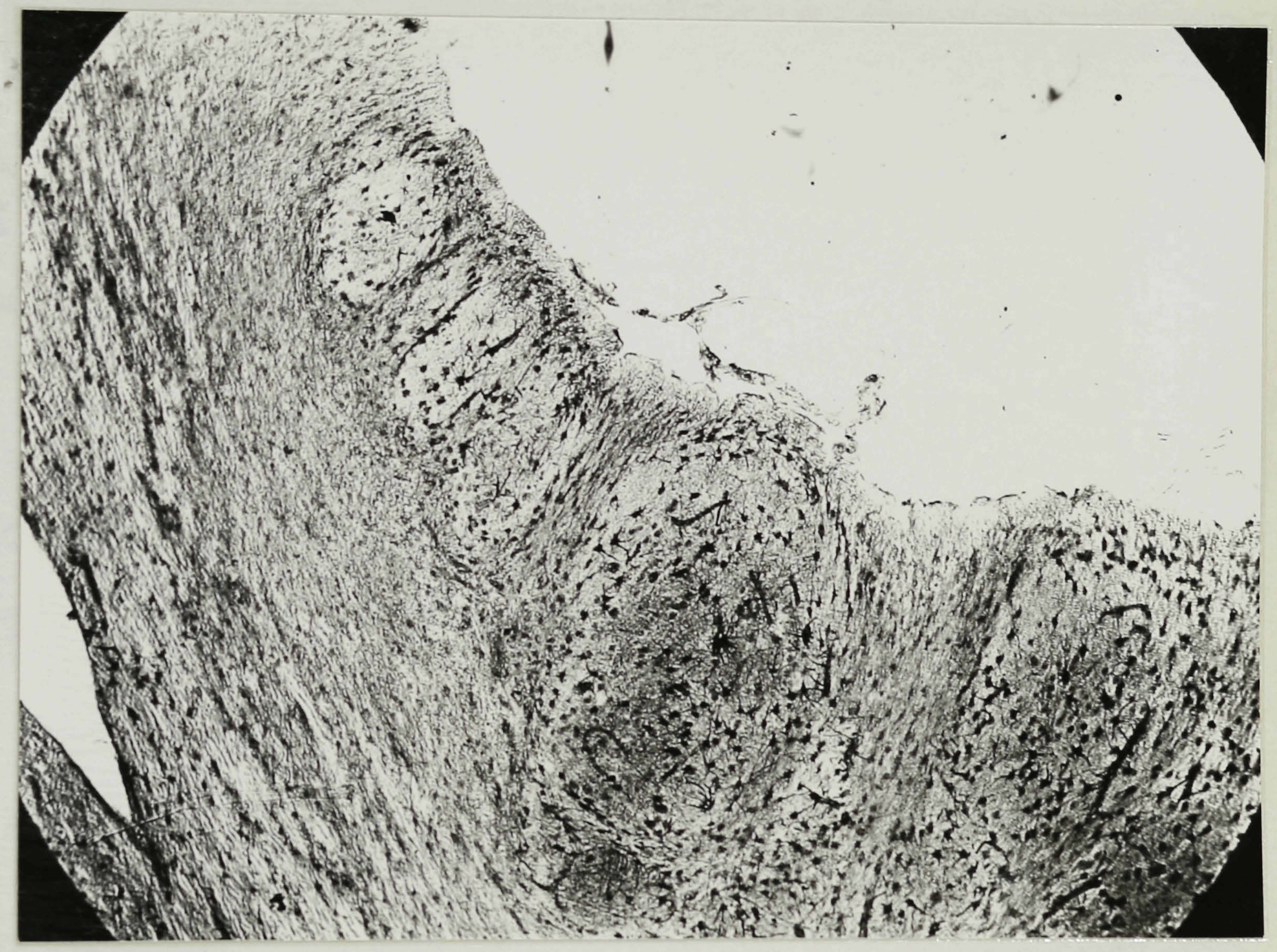


Fig. 41.

Piloid sheaves in trabecula of cortex. Note isolation of cortical area in center. Mallory's Phosphotungstic Acid - Hematoxylin stain.



Fig. 42.

Trabecula of cortex containing piloid sheaves. Note isolation of concentric areas by piloid gliosis.

Mallory's Phosphotungstic Acid Hematoxylin stain.



large islands, ribbon-like strands of connective tissue are found.

The study of the piloid glia in such areas is of extreme interest. That they play an important part in the process of island formation is evidenced by the fact that almost each section studied showed beginning piloid glial proliferation around an area of cortex, frequently in the form of a wedge (Fig. 44). Some sections show what seems to be a later stage where the piloid gliosis has completely encircled such a trapped cortical area (Figs. 39, 41 and 42). Further progress is indicated by a gradual increase in connective tissue in this piloid gliosis, until few glial fibers remain. Here one finds an isolated area of cortical tissue, still below the pial margin but completely encircled by collagenous fibers (Figs. 32, 38 and 45). Many islands were surrounded by a dense connective tissue wall and the island itself was raised above the pial margin, giving one the impression that the increasing connective tissue scar was extruding the island out into the subarachnoid space (Figs. 32, 46, 64 and 66). Islands have been seen which varied in location from intracortical to extracortical (Fig. 32).

In two of the cases studied, sections stained by Cajal's gold chloride sublimate method showed several intracortical islands identical with those described by Penfield and Humphreys (1940). These isolated areas were surrounded by piloid glia (Fig. 40). The relationship

Fig. 43.

Trabeculae of gray matter bordered by numerous vessels, two of which are thrombosed.

Hematoxylin and van Gieson stain.

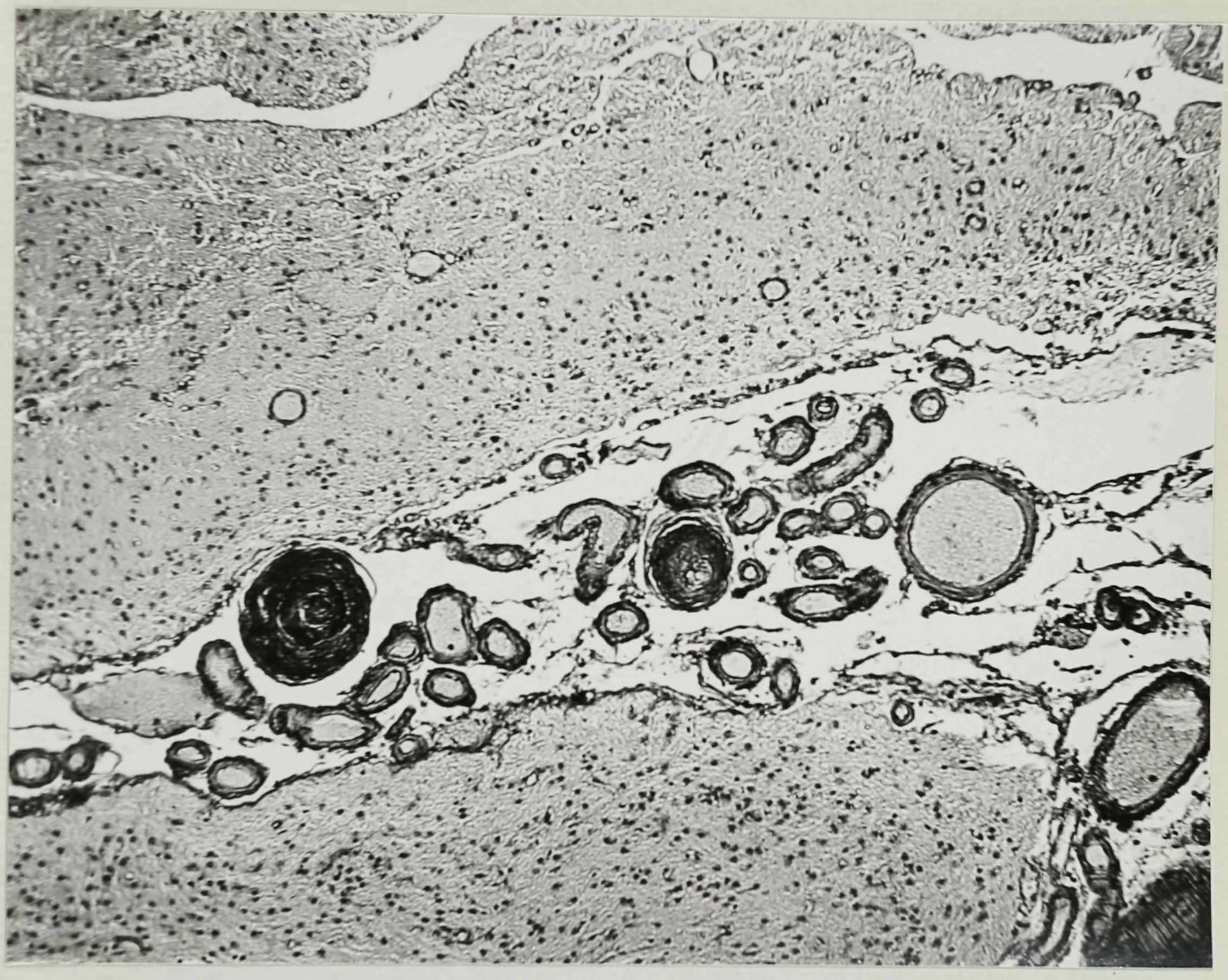


Fig. 44.

Piloid glia in streams extending from the pial margin and separating areas of gray matter.
Mallory's Phosphotungstic Acid Hematoxylin stain.

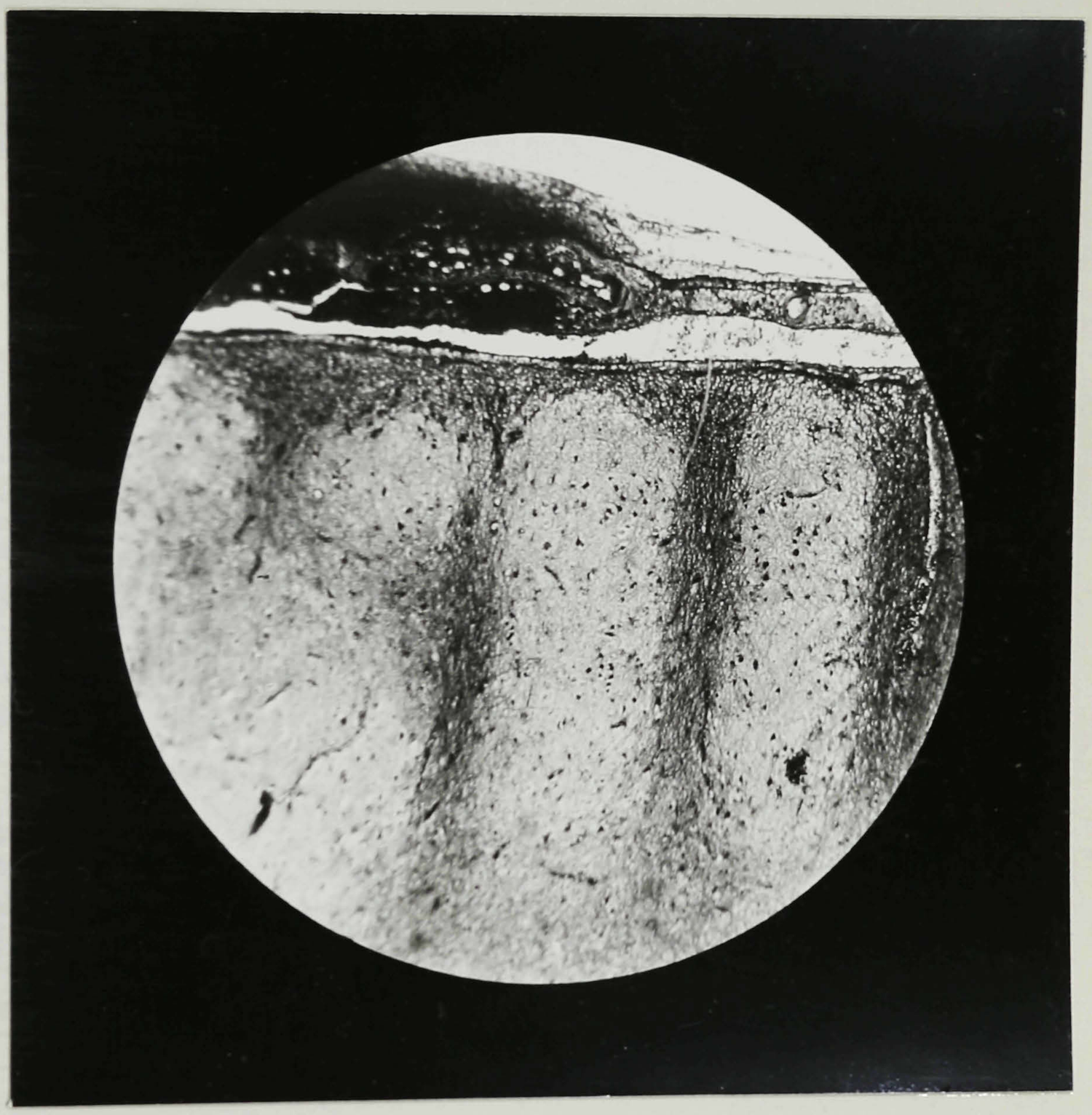


Fig. 45.

Intracortical islands surrounded by connective tissue. A few extracortical islands can be seen after having been extruded.

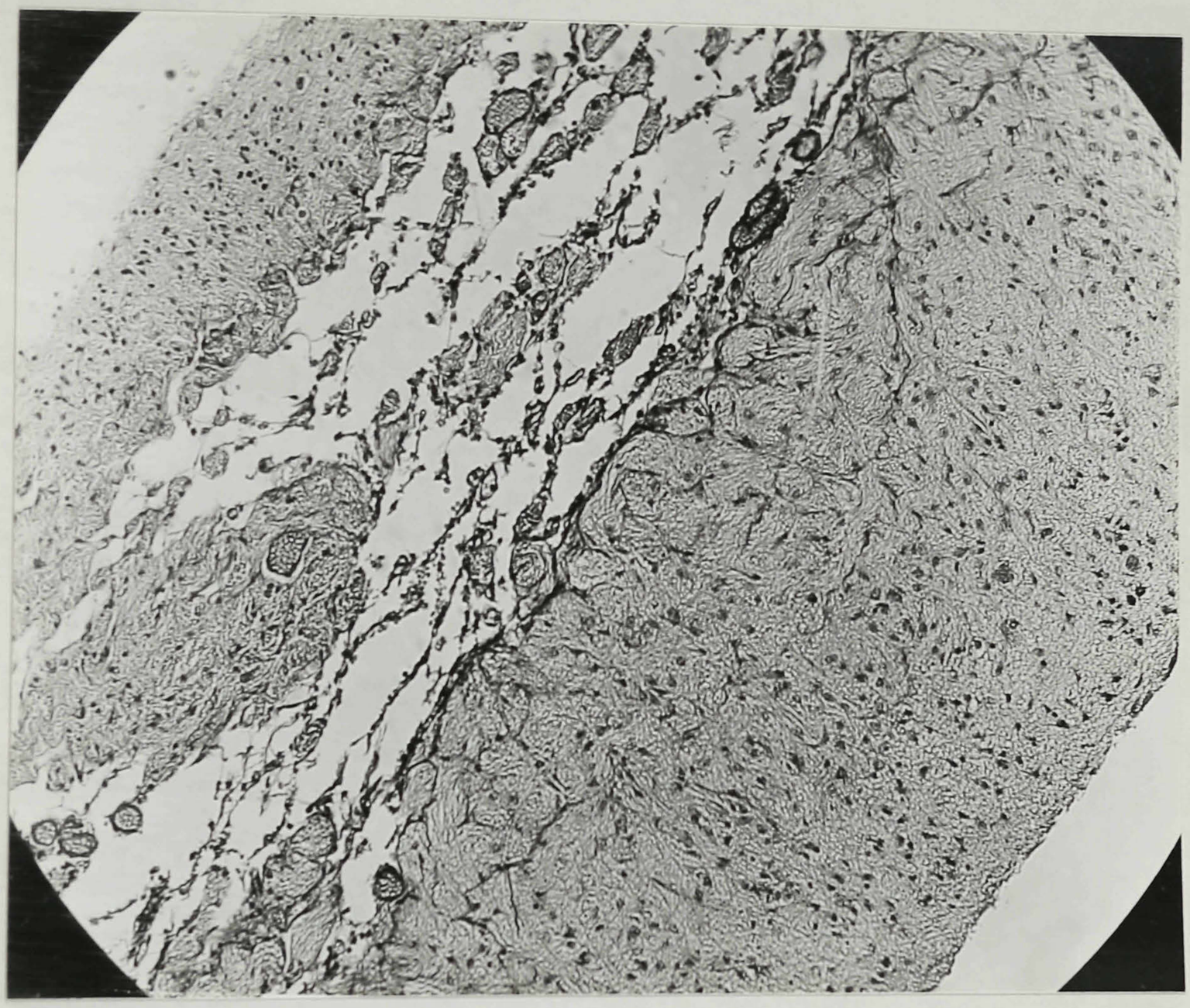


Fig. 46.

Intracortical islands being formed.
Note extruded islands of gray matter
in center.

Mallory's Phosphotungstic Acid
Hematoxylin stain.

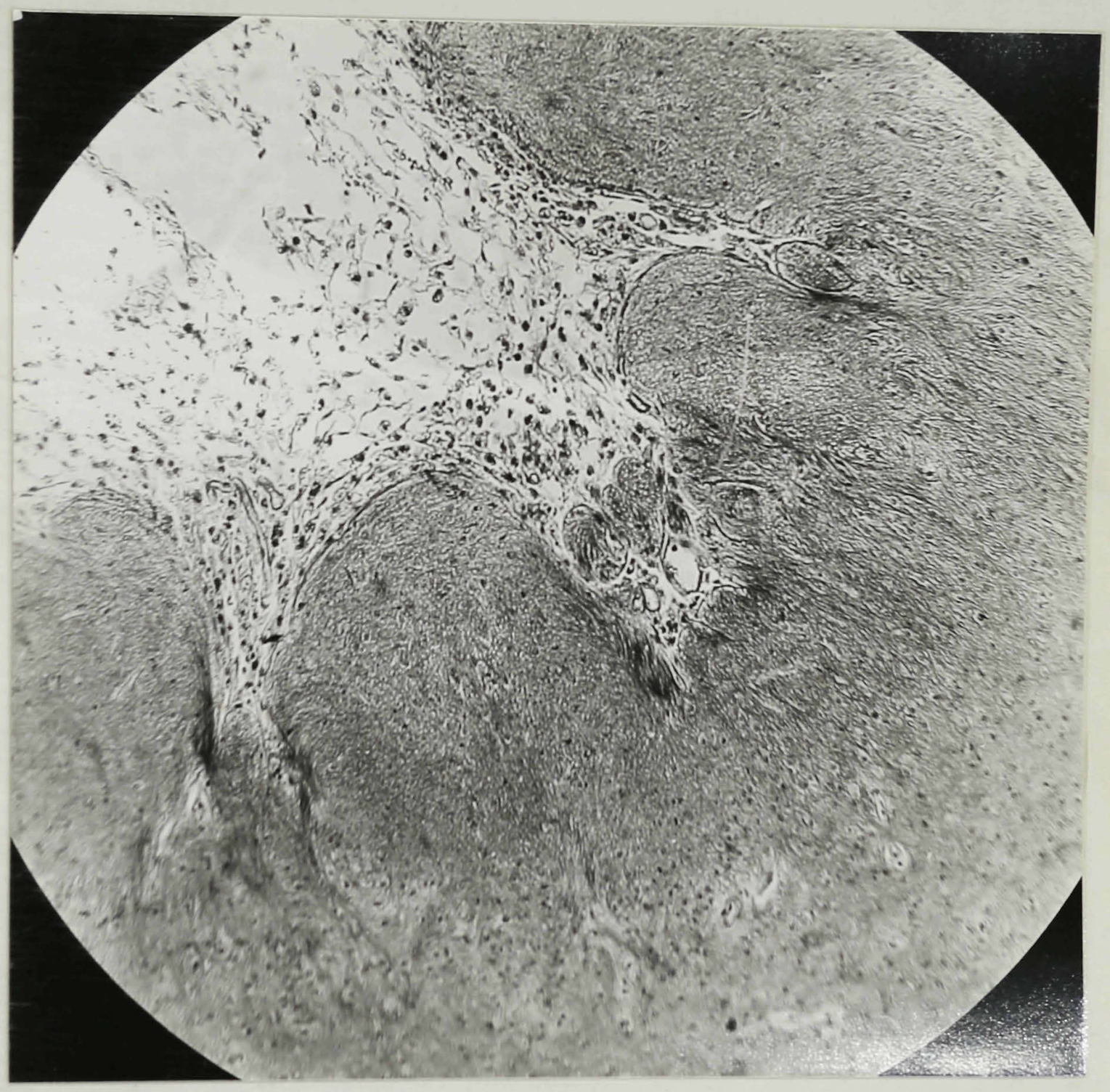


Fig. 47.

Fat-filled compound granular corpuscles in cyst bordered by intracortical and extracortical islands. Scharlach-R stain.

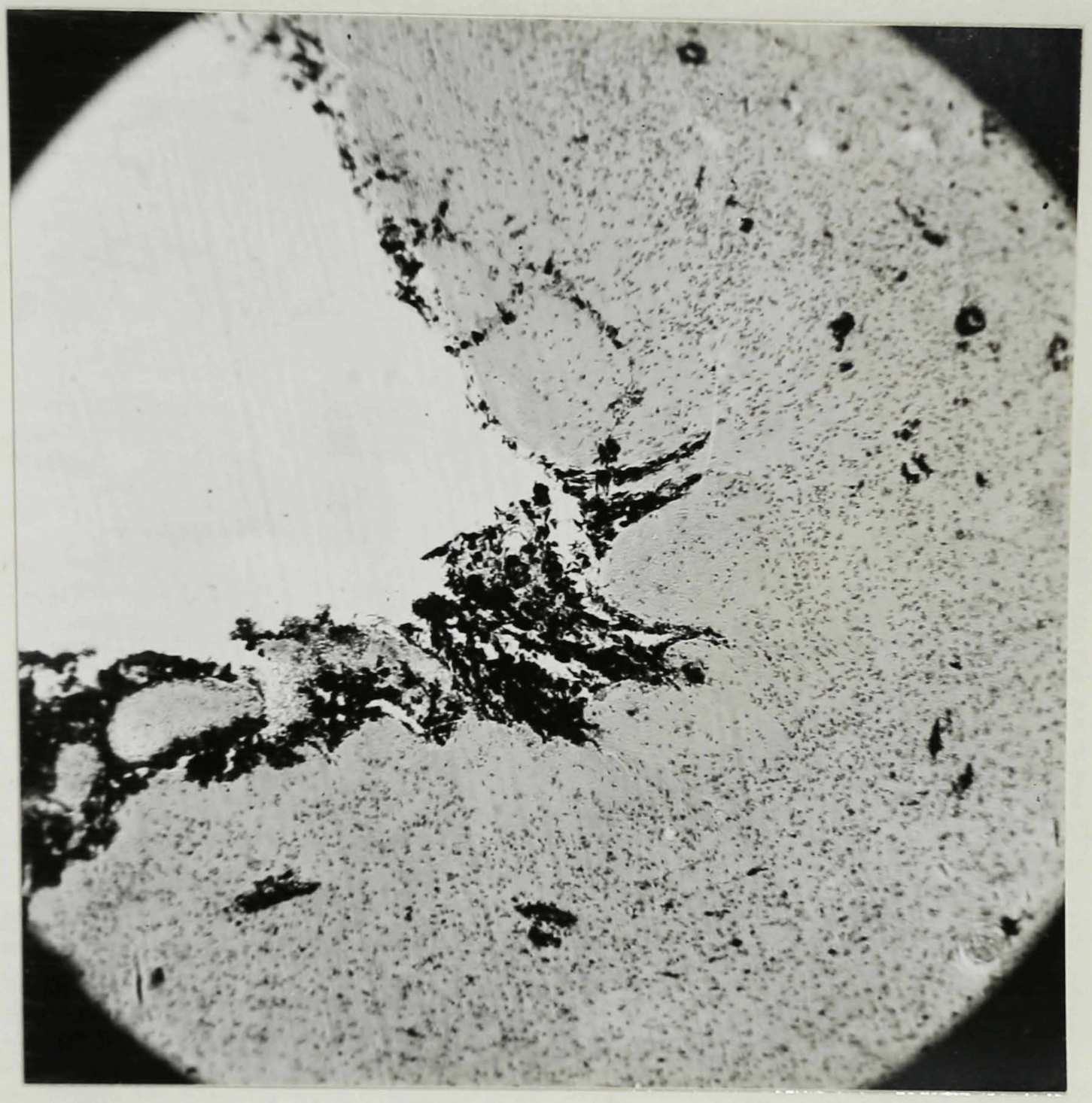
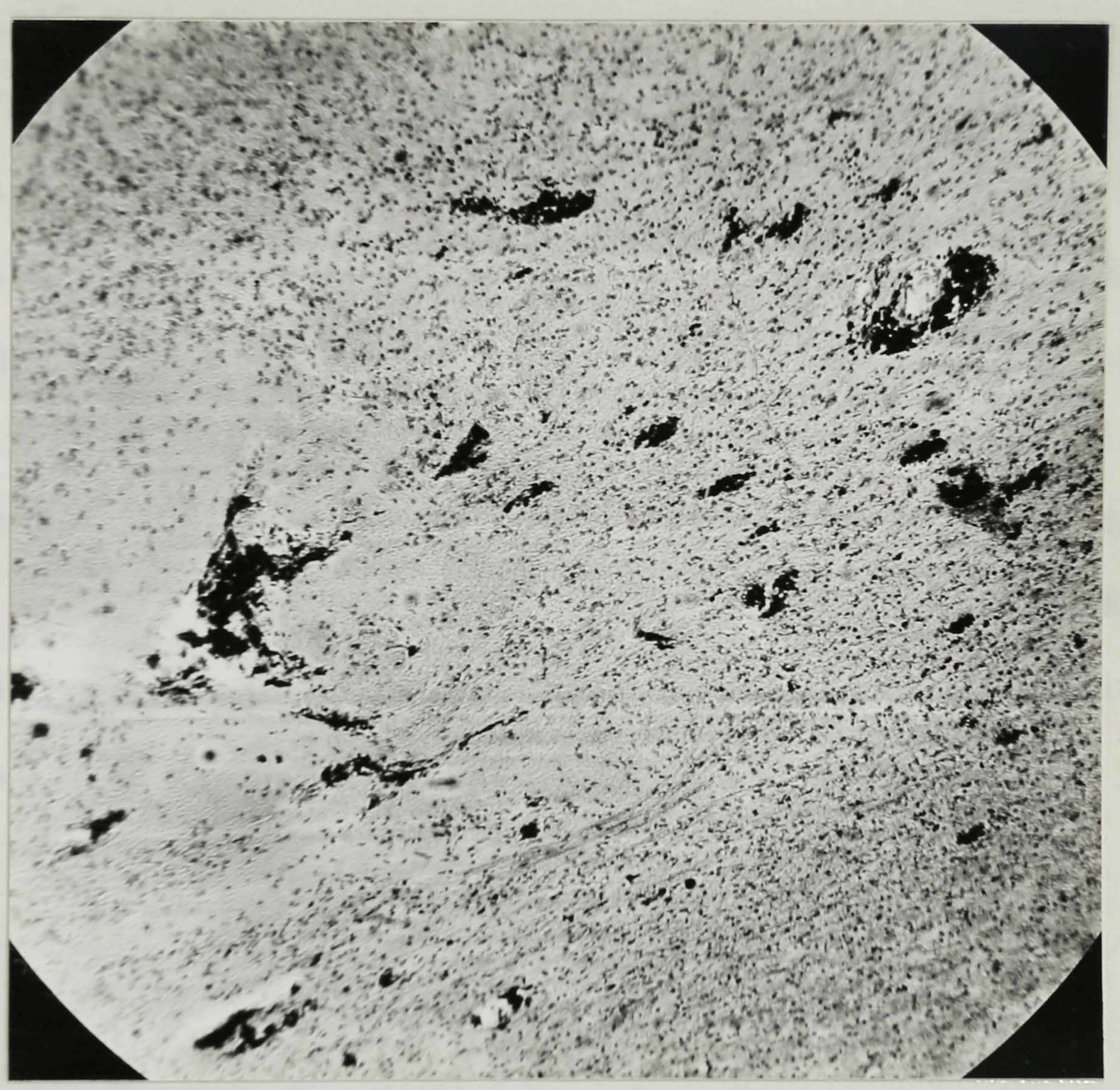


Fig. 48.

Compound granular corpuscles filled with fat in perivascular areas near island formation and also bordering islands.
Scharlach-R stain.



of these islands to the surrounding cortex was definite.

Fat stains of the described atrophic areas frequently showed many fat-filled compound granular corpuscles in the loose connective tissue meshwork surrounding the islands and also grouped in perivascular spaces (Figs. 47 and 48). Fat-filled compound granular corpuscles were very rarely found within an extracortical island, however; frequently such phagocytes were found around beginning island formation, that is, islands partially surrounded by streams of piloid glia (Fig. 47).

Iron stains showed large quantities of iron pigment in both intra- and extracortical islands as well as in the cortical trabeculae and connective tissue stroma. Most of this pigment seemed to be in compound granular corpuscles.

Discussion.

The presence of intracortical and extracortical islands of gray matter in cerebral scars is well borne out by the cases presented in this chapter. The fact that neurons were demonstrated in extracortical islands confirms the cerebral origin of these islands. The following formation of such isolated areas of gray matter is suggested by the varied stages of their development seen in the cases studied.

After the formation of thinned-out gray mantles due to atrophy following inadequate circulation, apparently the first step in the isolation of islands

is represented by an increase in piloid glia, particularly in the form of sheaves or stacks along the cortical margin (Figs. 41 and 42), as described by Chaslin (Fig. 17) and Penfield and Humphreys (Fig. 29).

Many cases showed the thinned-out gray mantles to contain piloid glia arranged in streams extending from the pial margin and partially separating a small area of cortex from the adjacent cortex (Fig. 44). Further examples show such a piloid gliosis completely encircling an area of gray matter forming an intracortical island (Fig. 40).

Later, this piloid gliosis is accompanied by fine connective tissue fibers which gradually replace the piloid fibers; thus an encircling band of connective tissue is formed about an intracortical island (Fig. 32). As the connective tissue becomes denser and collagenous, probable contraction results. This contraction gradually extrudes such an island out into the subarachnoid or cystic space forming an extracortical island (Figs. 32, 38, 45 and 65).

Further formation of isolated islands takes place in the finger-like trabeculae extending from atrophic gyri. The piloid gliosis frequently extends across such trabeculae and as the scarring continues finally separates small areas to form extracortical islands (Figs. 34, 41, 64 and 66).

Several sections studied showed piloid glia encircling an area of cortex in which no neurons

were found, they having been replaced by piloid glia (Fig. 39). This probably results from a circulation inadequate for neurons but sufficient for piloid neuroglia.

Even though the isolated areas of cortex are referred to as islands in cross section, it must be remembered that they are actually trabeculae of cortical tissue probably receiving their blood supply along the longitudinal axis. This is suggested by the presence of a central vessel frequently seen in the intracortical islands (Fig. 18). The presence of neurons in many of these islands and the absence in others can be explained on the basis of varying blood supply retained during the scarring process.

It is plausible that the blood supply to such extracortical islands gradually decreases as the scarring process continues, until finally all neurons in these islands disappear due to inadequate circulation. This was suggested when it was noted that scars of relatively short duration showed many more islands containing neurons. The greatest number of islands containing neurons was found in Case 5 where the original trauma apparently took place only 12 months prior to operation at which time the specimen was obtained for study, whereas in a cerebral scar of 40 years' duration (Case 3, Chapter V) extracortical islands showed no neurons.

Summary.

(1) 7 epileptogenic lesions showing "extracortical islands" are presented.

(2) Evidence that such islands are derived from the gray matter is given.

(3) A hypothesis as to the formation of extracortical islands is described.

(4) A correlation between intra- and extracortical islands of gray matter is suggested.

V. EVIDENCE OF TISSUE DESTRUCTION IN OLD CEREBRAL SCARS

"Explanation of unseen things there must be, but deduction must, if possible, be based on evidence."

Lennox and Cobb.

The suggestion that cerebral destruction in epileptogenic lesions continued over a long period of time was mentioned by Foerster and Penfield (1930) when they described occasional localized areas in which groups of phagocytes containing pigment were found. They stated that "such patches are evidently in the vicinity of blood vessels which have been shut off and they seem to indicate the process of cerebral destruction is a long-continued one as they were present twelve to fourteen years after the initial wound."

Penfield and Humphreys (1940) mentioned the presence of occasional fat-filled compound granular phagocytes and altered microglia in patches as being testimonial of recent destruction having taken place in epileptogenic lesions. Such areas were said to occur in small patches rather than being diffuse.

A normal-appearing vessel was often found in the center of such a patch, the latter containing acutely swollen oligodendrocytes and clasmatodendrosis of astrocytes. They stated that such perivascular patches of degenerative change were constant in all of 95 focal cerebral lesions removed at operation from

epileptic patients and indicated progressive tissue destruction.

In the discussion of this paper Doctor Penfield stated that in the epileptogenic lesions studied there existed a zone in which tiny areas of progressive destruction were occurring, a zone which lay between the inert, the dead lesion (for example, a scar), and the active brain. He hypothecated that the vessels in the center of such areas close long enough to cause focal destruction but added that he could not say anything more than that these focal constrictions occurred in the zone of advancing atrophy.

Doctor William Lennox mentioned that "if it were just the lesion itself that was important, one would ask the authors to demonstrate in what way histologically the lesions obtained from patients having seizures differ from lesions obtained from patients not subject to seizures."

With this statement in mind the writer undertook to compare non-epileptogenic with epileptogenic lesions in so far as progressive tissue destruction was concerned.

Since the problem at hand consisted of comparing epileptogenic with non-epileptogenic lesions, first a study of 17 epileptogenic lesions excised at operation was made. The routine stains used for the selected blocks of tissue after proper fixation

consisted of the following:

(1) Non-metallic:

a. Weigert's iron hematoxylin and van Gieson method (H.V.G.).

b. Mallory's phosphotungstic acid and hematoxylin (P.T.A.).

c. Nissl's stain (cresyl violet modification).

d. Scharlach-R Sudan IV stain.

(2) Metallic:

a. Laidlaw's silver impregnation (L.C.T.).

b. Cajal's gold chloride sublimate (G.C.S.).

b. Hortega's silver carbonate (S.C.O.).

Other stains not routinely used were the following:

a. Rio-Hortega's double impregnation method for neurofibrils.

b. Mallory's modification of Turnbull's blue method for iron pigment.

c. Rio-Hortega's silver lithium carbonate method for astrocytes (S.C.A.).

d. Alexander's benzidine technique for blood vessels.

e. Penfield's second modification for oligodendroglia and microglia (S.C.O.M.).

(Technique of above stains obtained from "Manual of Technique", Laboratory of Neuropathology, Montreal Neurological Institute. Edited by Robert H. Pudenz , M.D.).

Observations.

For the most part the various epileptogenic lesions showed the pathological alterations described by Penfield and Humphreys (1940) which were reviewed

in Chapter IV.

A few elaborations of further findings in epileptogenic lesions are given at this time referable to the alterations found in non-epileptogenic lesions described later in this chapter.

Penfield and Humphreys (1940) mentioned that the progressive tissue destruction was not found to be diffuse but occurred in small patches, apparently being perivascular in distribution. In the epileptogenic lesions examined by the writer this was found almost invariably; however, associated with such a picture many lesions demonstrated diffuse changes as well.

In several excised lesions acute swelling of oligodendroglia was seen throughout the section being identical with that found in perivascular areas.

Fat-filled compound granular corpuscles were not only found grouped in perivascular areas, but also frequently scattered throughout the section of brain tissue at a distance from the markedly atrophic area and intracortical islands (Fig. 49). Several cases showed many fat-filled compound granular corpuscles in the subarachnoid space, particularly in regions of the extracortical islands of gray matter described in Chapter IV (Fig. 47).

Other cases showed diffusely scattered, fat-filled phagocytes in areas of marked degeneration, the latter having the appearance of a loose meshwork.

Fig. 49.

Fat-filled compound granular corpuscles in perivascular areas in region of epileptogenic meningocerebral cicatrix.
Scharlach-R stain.



The intracortical islands usually showed a nearby area or an adjacent area containing a few fat-filled compound granular corpuscles and altered microglia. Such phagocytes were occasionally not perivascular in location.

In one lesion (cerebral cicatrix, microgyric type) removed from a patient 39 years of age, most of the neurons contained fat granules.

With these findings in mind, together with the classical description of epileptogenic lesions described by Penfield and Humphreys, the writer collected and studied a group of cortical, non-epileptogenic lesions.

Method.

For the purpose of adequate controls for a histological comparison with the epileptogenic lesions described it was felt that the non-epileptogenic lesions studied should have the following qualifications:

(1) Lesions should be caused by trauma to the brain cortex.

(2) Such lesions should not be accompanied by epileptic manifestations.

(3) The lesions should be of long duration in view of the late appearance of posttraumatic epilepsy.

Non-epileptogenic Cicatrices in Human Brains.

1. Secondary to Depressed Fracture of Skull.

A review of the autopsied cases in the Neuropathology Department of the Montreal Neurological Institute revealed 2 human brains having non-epileptogenic scars resulting from depressed fractures of the skull received 2 years and 6 months, and 7 years and 4 months respectively prior to death.

The writer was granted permission to remove a brain from an autopsy case in the Pathology Department of the Royal Victoria Hospital, the brain having a non-epileptogenic cerebral scar resulting from a depressed fracture of the skull received 40 years prior to the death of the patient.

Brief summaries of each of the case histories follow.

Case 1 (N-2252, A.M.)

A 71-year-old male was said to have been struck on the head by a brick in October 1928. Unconsciousness followed and the patient was immediately admitted to the Royal Victoria Hospital.

Objective findings showed coma; hematoma about right eye; comminuted fracture in right fronto-parietal region with a marked depression; and, a lacerated dura exposing bulging lacerated brain.

Operation: A wide debridement was done, the depressed fragments of the skull removed, bleeding points controlled and softened brain removed by light suction and irrigation. The dura was closed tightly and the wound drained through a separate stab wound.

Operator: Doctor William Cone.

Postoperative Course: The patient improved following operation and was discharged, after which nothing was noticed during the ensuing several years except occasional irritability and nervousness. The patient's wife stated that no seizures were had by the patient. In February 1936 (7 years and 4 months after injury) the patient was admitted in a state of cardiac decompensation to the St. Luc's Hospital where he expired a few days later.

Description of the Brain: In the right frontal region there was a portion of the dura adherent to the underlying atrophic cerebral tissue over an area approximately 4.5 x 2.5 cm. in its greatest diameters. The dura showed no vessels of any size crossing to the leptomeninges and peeled away from its attachment over the right frontal lobe with ease. Atrophy of the right frontal lobe was apparent but no ventricular dilatation or distortion was evident. Cystic areas were found in the leptomeninges and the cerebrum in the scarred area. Histological examination showed a typical meningocerebral cicatrix below the superficial

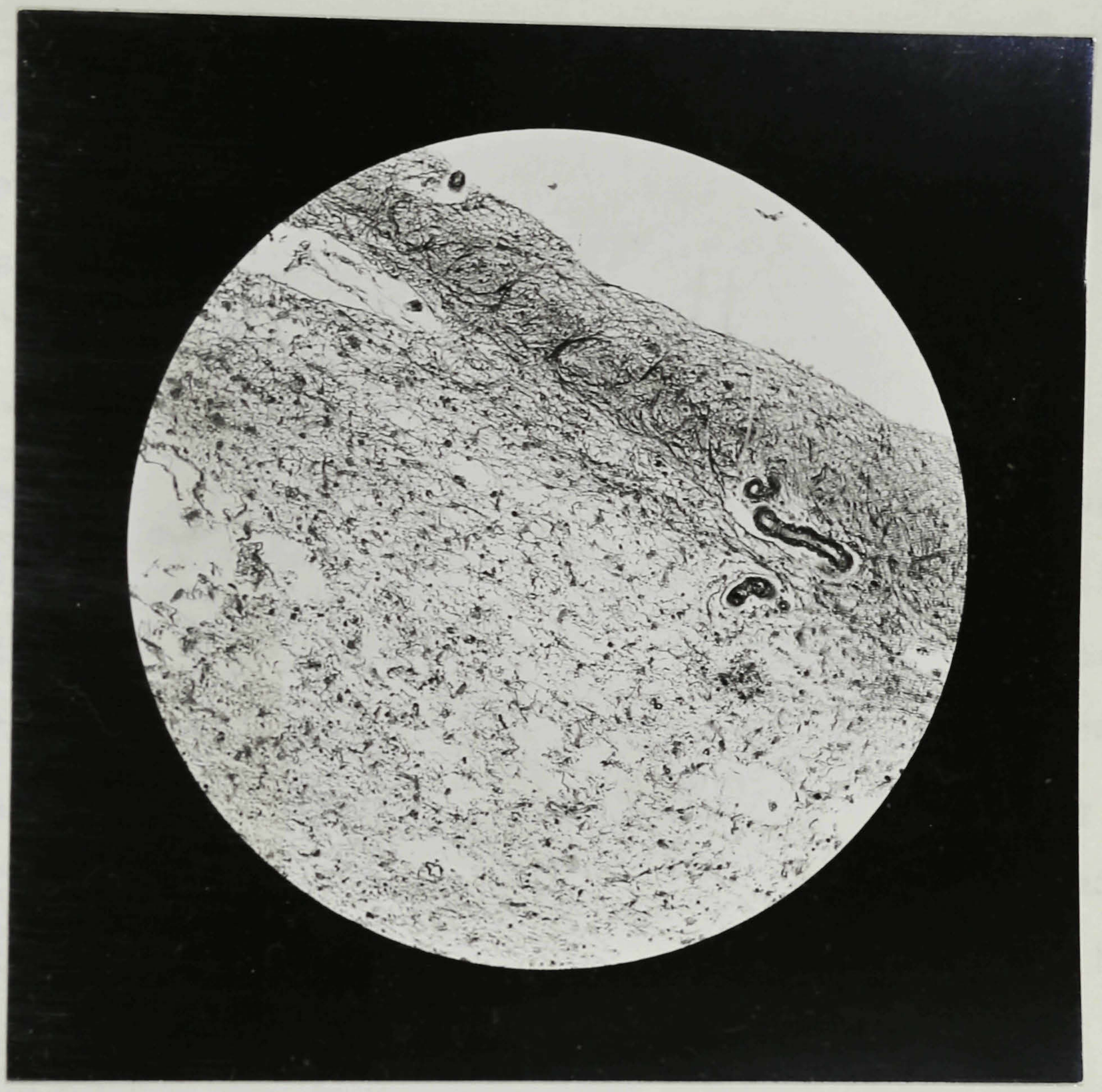
cysts, the leptomeninges being continuous with wedge-shaped interlacing network of collagen and reticulin fibers extending into the cerebral tissue. Many trabeculae of neuroglial and connective tissue were present in the atrophic region along with extra-cortical islands. Piloid glia were occasionally arranged in sheaves in such trabeculae (Fig. 50). Astrocytes in the damaged areas showed gliosis and the microglia were altered, there being scattered rod cells and compound granular corpuscles. Fat stains showed fat-filled compound granular corpuscles, scattered diffusely in the loose meshwork of atrophic cerebral tissue. Some such fat-filled phagocytes were found in adjacent perivascular areas. The latter finding was most prominent nearer the more normal adjacent brain.

Case 2 (N-2305, P.C.)

An 18-year-old malewas said to have been knocked unconscious when the bicycle he was riding collided with an automobile in May, 1934. The patient was immediately taken to the Homoeopathic Hospital where it was found that he had a laceration of the scalp in the left frontal region and X-rays showed a left frontal depressed fracture of the skull; he was transferred to the Royal Victoria Hospital at once.

Fig. 50.

Sheaves of piloid glia in cortex of old non-epileptogenic meningo-cerebral cicatrix. Note loose mesh of atrophic cerebral tissue.
Mallory's Phosphotungstic Acid Hematoxylin stain.



Objective findings showed stupor with periods of complete loss of consciousness; laceration of the scalp in the left frontal region; and, X-ray evidence of a depressed skull fracture in the left frontal region.

Operation: The depressed skull fracture was removed, softened brain aspirated, subtemporal decompression performed, and the laceration of the scalp sutured.

Operator: Doctor William Cone.

Postoperative Course: The patient improved steadily. However, it was noticed during his convalescence that he had a depressed type of personality and it was thought by Doctor Cone on subsequent occasions that the patient had schizoid tendencies. Otherwise he was considered normal until November 1936 ($2\frac{1}{2}$ years following skull fracture) at which time he was admitted to the Montreal Neurological Institute one-half hour after having shot himself in the left temple.

Objective findings showed a bullet wound in the left temple; coma; large hematoma in right temporal region; multiple retinal hemorrhages; acute papilloedema; and, flaccid limbs.

The patient expired 13 minutes after admission to the hospital.

Description of the Brain: A deficiency of brain tissue was noted in the left frontal pole over which the dura was adherent. A small opening marking

the point of entrance of the bullet was present at the anterior end of the left Sylvian fissure in the left frontal pole. The point of exit was found in a similar site in the right frontal lobe. Both the entrance and exit were moderately clean-cut.

Histological findings will be limited here to the region of the old scar following the depressed fracture of the skull. It might be said that no evidence of an inflammatory reaction was found in any of the many sections removed for histological study. A meningocerebral cicatrix in the left frontal lobe was found to contain islands of neuroglial tissue enclosed in a mesh of connective tissue. The surrounding brain contained many Nissl's plump astrocytes. Here again trabeculae of neuroglial tissue and extracortical islands were found.

Many compound granular corpuscles filled with fat were found scattered diffusely in the atrophic areas, particularly around irregular cystic regions (Fig. 51). These fat-filled phagocytes were also present in perivascular areas near the more normal cerebral tissue (Figs. 52 and 53).

Case 3 (M.P.-5-41, T.M.)

A 68-year-old male was said to have received a head injury in 1901 when he was kicked in the right frontal region of his head by a mule. He was admitted to the Notre Dame Hospital at that time, details of

Fig. 51.

Fat-filled compound granular corpuscles, both diffuse and perivascular in distribution, in an atrophic cerebral cicatrix of 2 years and 6 months' duration. Scharlach-R stain.

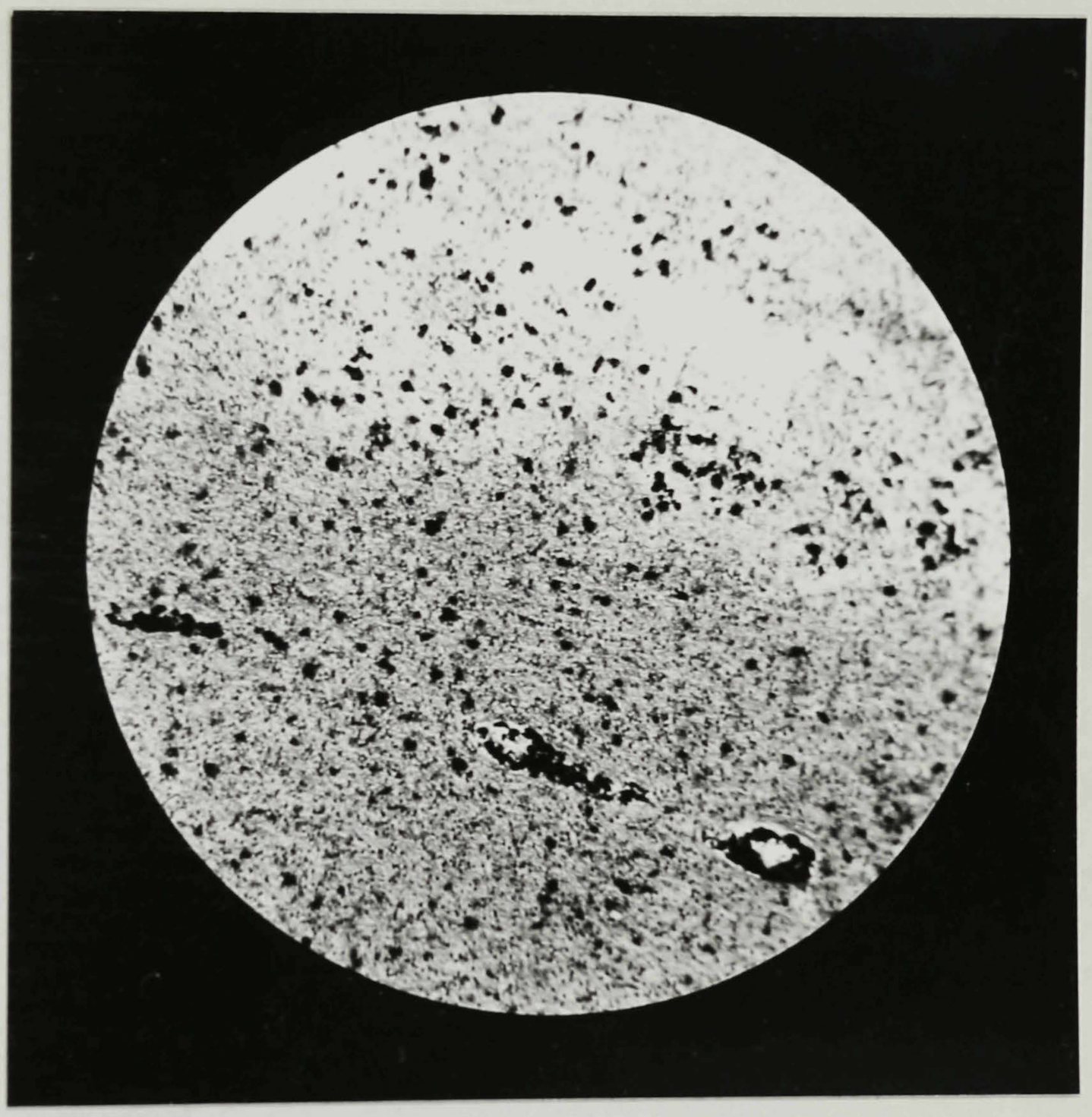


Fig. 52.

Perivascular compound granular corpuscles filled with fat in a non-epileptogenic cicatrix. Note the diffuse distribution of phagocytes.

Scharlach-R stain.

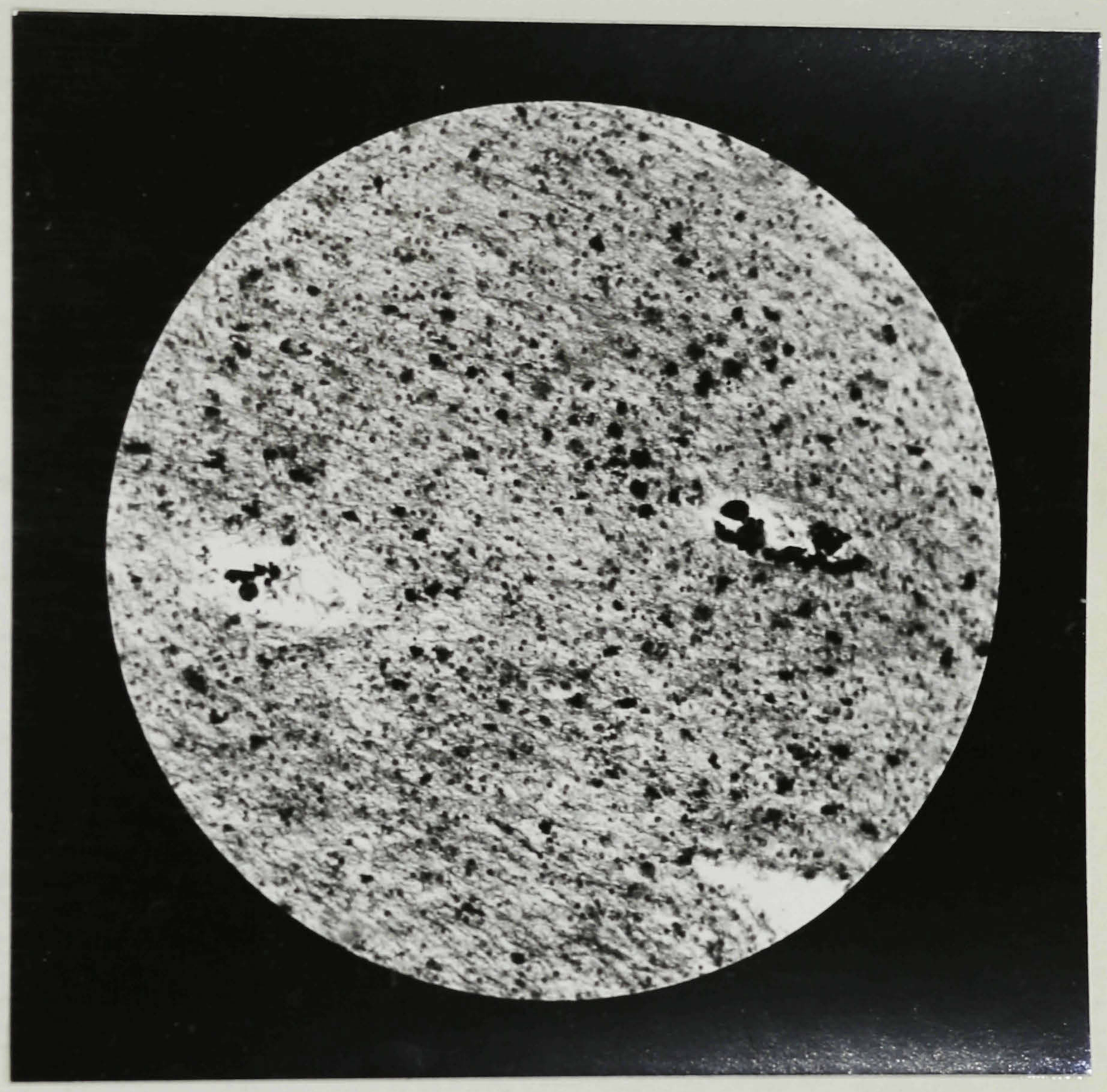
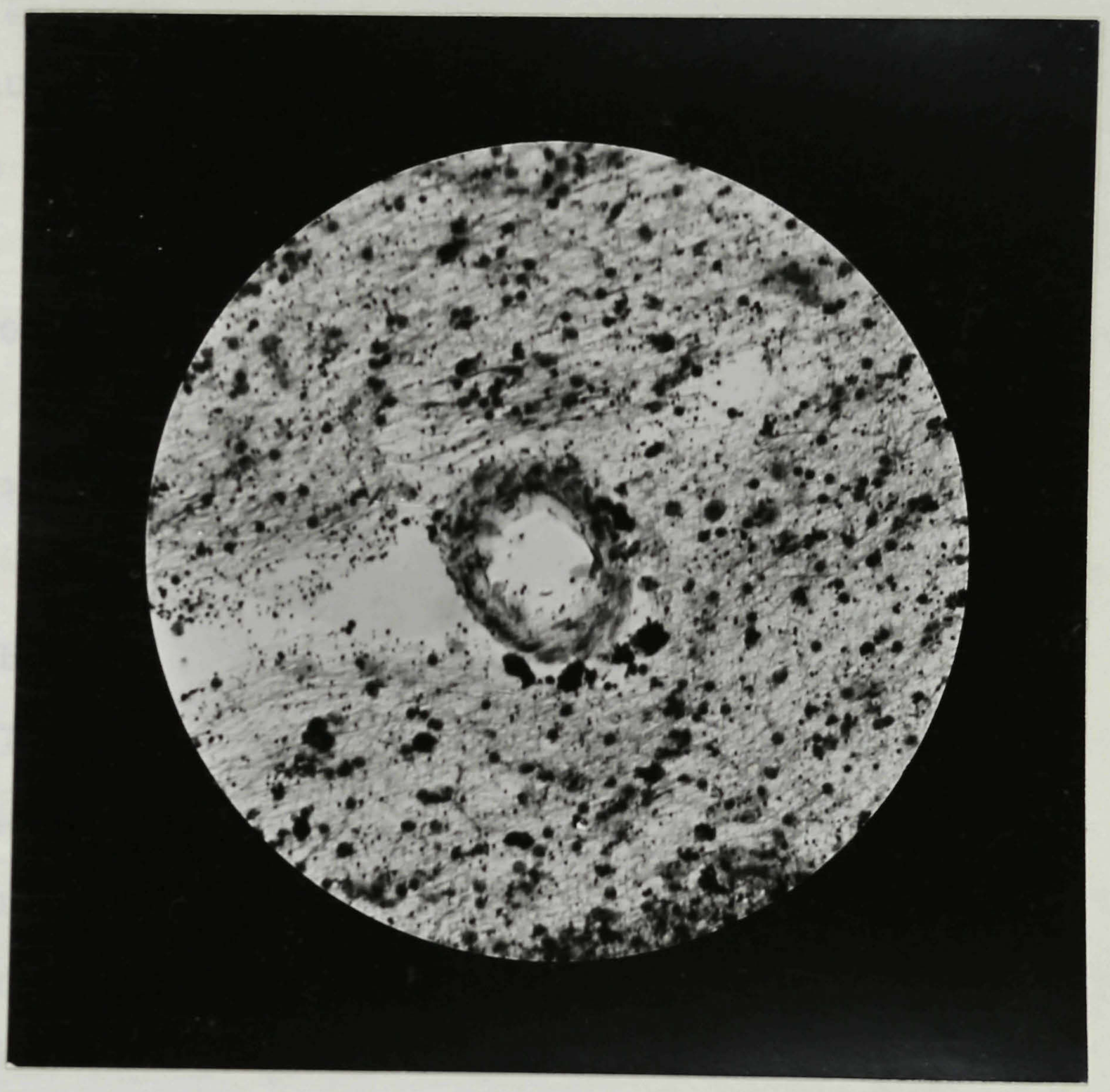


Fig. 53.

Fat-filled compound granular corpuscles in perivascular area in a non-epileptogenic meningocerebral cicatrix of 2½ years' duration.
Scharlach-R stain.



admission being unavailable. During the ensuing 40 years the patient had no known symptoms referable to his head injury. He and his wife stated when seen in the clinic of the Royal Victoria Hospital shortly before his death that he had had no seizures.

In March 1941 (40 years after the head injury) the patient was admitted to the Royal Victoria Hospital because of loss of weight, pallor, constipation, weakness and dizziness of several weeks' duration.

Objective findings other than an irregular depression in the right frontal bone (site of previous head injury) are not included here since they are irrelevant to the purpose of this report.

The following diagnoses were made:

(1) Bronchopneumonia.

(2) Idiopathic agranulocytosis.

(3) Malnutrition and general avitaminosis.

Regardless of extensive medical treatment the patient rapidly grew worse and expired one week after admission. General pathological diagnoses were as follows:

(1) Tuberculosis, miliary, spleen and liver.

(2) Tuberculous lymphadenitis, peribronchial and abdominal.

(3) Fibrinous pericarditis with hydropericardium.

(4) Bronchopneumonia.

(5) Arteriosclerosis, coronaries, cerebrals and aorta.

Description of Brain Pathology: Over the right supraorbital region there was a depression adjacent to the midline measuring 3 cm. in diameter, the center of which was 1½ cm. below the surrounding supraorbital skin. This area was found to be densely adherent to the underlying dura through a bony defect (old comminuted fracture) measuring 2½ cm. across (Fig. 55). In the right parieto-occipital region of the skull another bony defect measuring 2 cm. in diameter was found, having the appearance of an old burr hole. The undersurface of the dura at this site was smooth and free from the underlying arachnoid.

The tip of the right frontal lobe was bound to the thickened dura, filling the bony defect with many elastic adhesive bands. With traction on the frontal lobe the adhesions held firmly causing distortion of the frontal convolutions in this area.

The right frontal lobe was smaller than the left and on the undersurface of the frontal lobe a large, sunken, atrophic area was found measuring 2½ cm. in diameter (Fig. 54). The convolutions bordering this scar were much smaller than those of the opposite frontal lobe in a similar area (Fig. 54).

Histologically the scarred area showed a marked destruction of cerebral tissue consisting mostly of a veil-like mesh of atrophic cerebral tissue which contained many connective tissue strands. Overlying

Fig. 54.

Brain showing an atrophic cerebral cicatrix in right frontal lobe following depressed fracture of skull 40 years prior to death of patient.

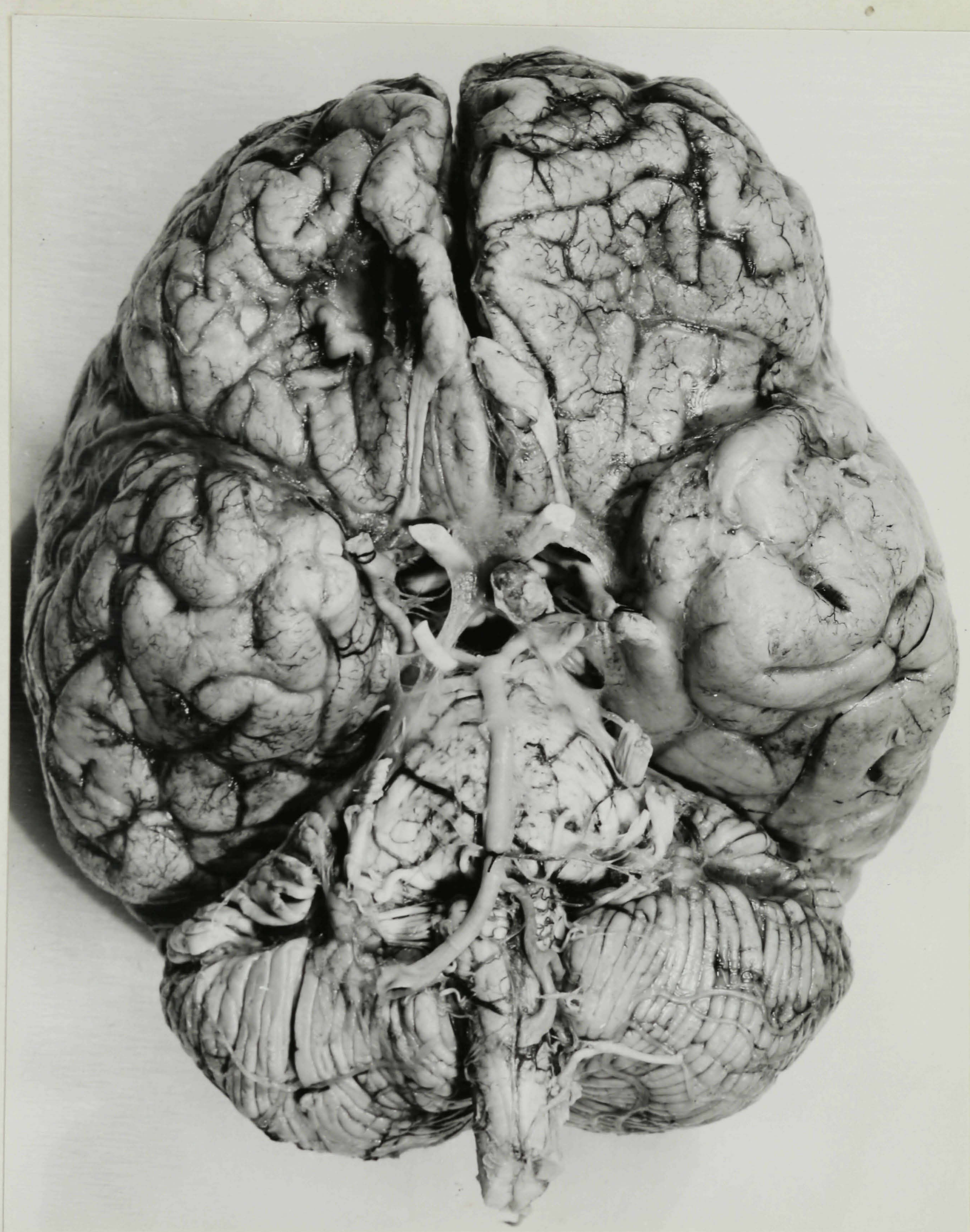
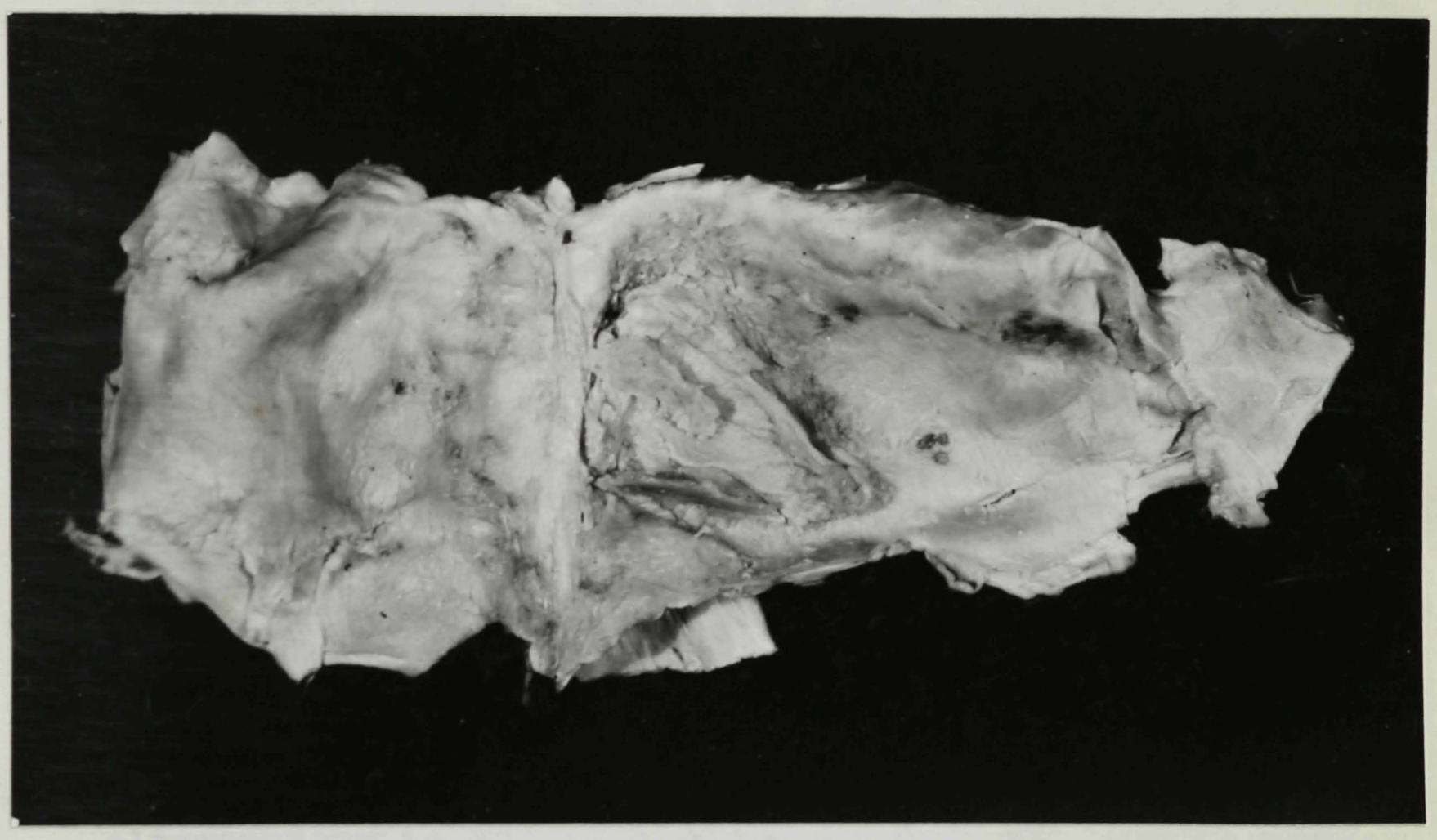


Fig. 55.

Portion of dura which overlies atrophic cerebral cicatrix resulting from depressed fracture of skull in frontal region. Note fragments of bone attached to dura near center.

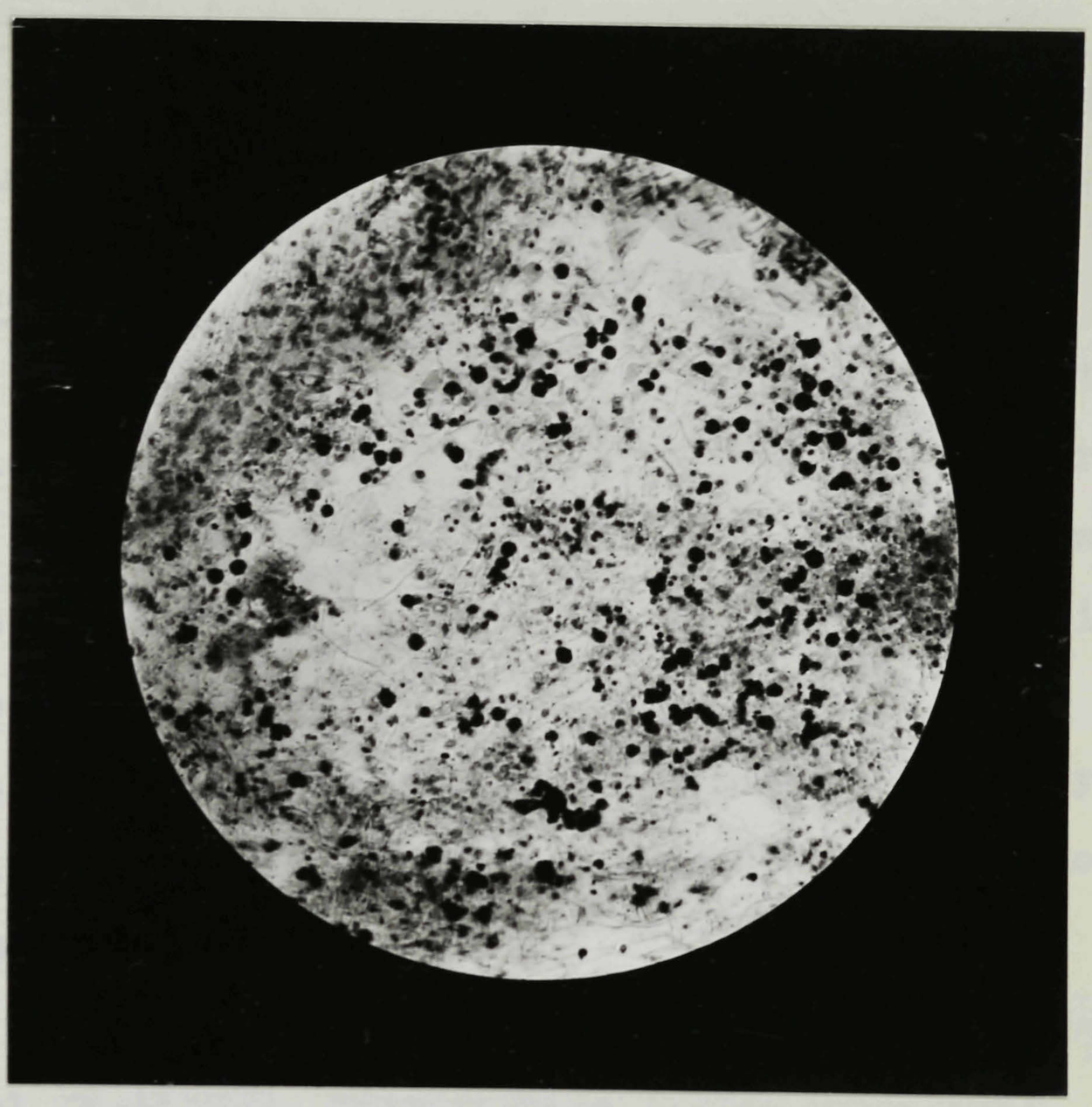


this were found a few trabeculae of neuroglia having a rather shaggy appearance (Fig. 61). Occasional piloid sheaves were seen in such trabeculae; however connective tissue fibers were far more predominant, being scattered in thin strands in several areas in the cortical margin. Here the piloid glia were intermingled with connective tissue strands which entered the cortex. P.T.A. and L.C.T. stains well illustrated this relationship.

Silver carbonate preparations well demonstrated various altered forms of microglia ranging from the normal to compound granular corpuscles. Altered microglia other than compound granular corpuscles were found diffusely scattered throughout the adjacent as well as more distant areas of gray matter, occasionally being arranged in small groups. Oligodendroglia throughout the section showed moderate swelling in other areas as well as in the scarred region. This swelling of oligodendroglia was also found in sections removed from the left frontal lobe. Scharlach-R preparations showed as many as 150 large, fat-filled compound granular corpuscles present in an area of destruction consisting of a loose mesh of neuroglia showing no neurons (Fig. 56). Portions of vessels were present in this region and many of the fat-filled phagocytes were adjacent to such vessels. Other than this area, most of the atrophic scar contained only minute particles of fat in altered microglia and many other areas of atrophy contained no fat.

Fig. 56.

Compound granular corpuscles filled with fat in atrophic region of cerebral cicatrix of 40 years' duration.
Scharlach-R stain.



The surrounding unscarred gray matter showed large amounts of fat in the neurons and many small granules of fat were seen in perivascular regions. This same picture was found in sections removed from the opposite (left) frontal lobe. Many control sections were made from the left frontal lobe which contained no scar and with no exception groups of fat-filled compound granular corpuscles could not be demonstrated.

2. Secondary to Ventricular Puncture.

Having reviewed the protocols in the Montreal Neurological Institute, the writer realized that brains which contained old posttraumatic scars and which were removed from patients having no history of epileptic manifestations were very few in number. For this reason it was planned to study cicatrices caused by ventricular punctures in non-epileptic patients who came to autopsy at least one year later.

The autopsy protocols in the Montreal Neurological Institute, representing approximately 650 brains examined from 1928 to 1941, were reviewed and cases having the following qualifications were chosen for study:

(1) History of ventricular puncture having been performed over one year prior to autopsy.

(2) History of patient having no seizures either before or after operative procedures.

The yield from this review was disappointing in that only 6 such cases were found; and, after careful repeated gross search for the scar of the needle tract, no scar was found which could be identified as a needle tract extending from the cortex to the ventricle. That it was possible to find a needle tract of long duration was known by the writer since one needle scar 3 years and 6 months old had been easily detected and studied. This was a case of astrocytoma and was discarded due to the fact that the patient had had seizures. (This scar showed similar areas of fat-filled compound granular corpuscles (Fig. 57) as the 3 non-epileptogenic scars described above).

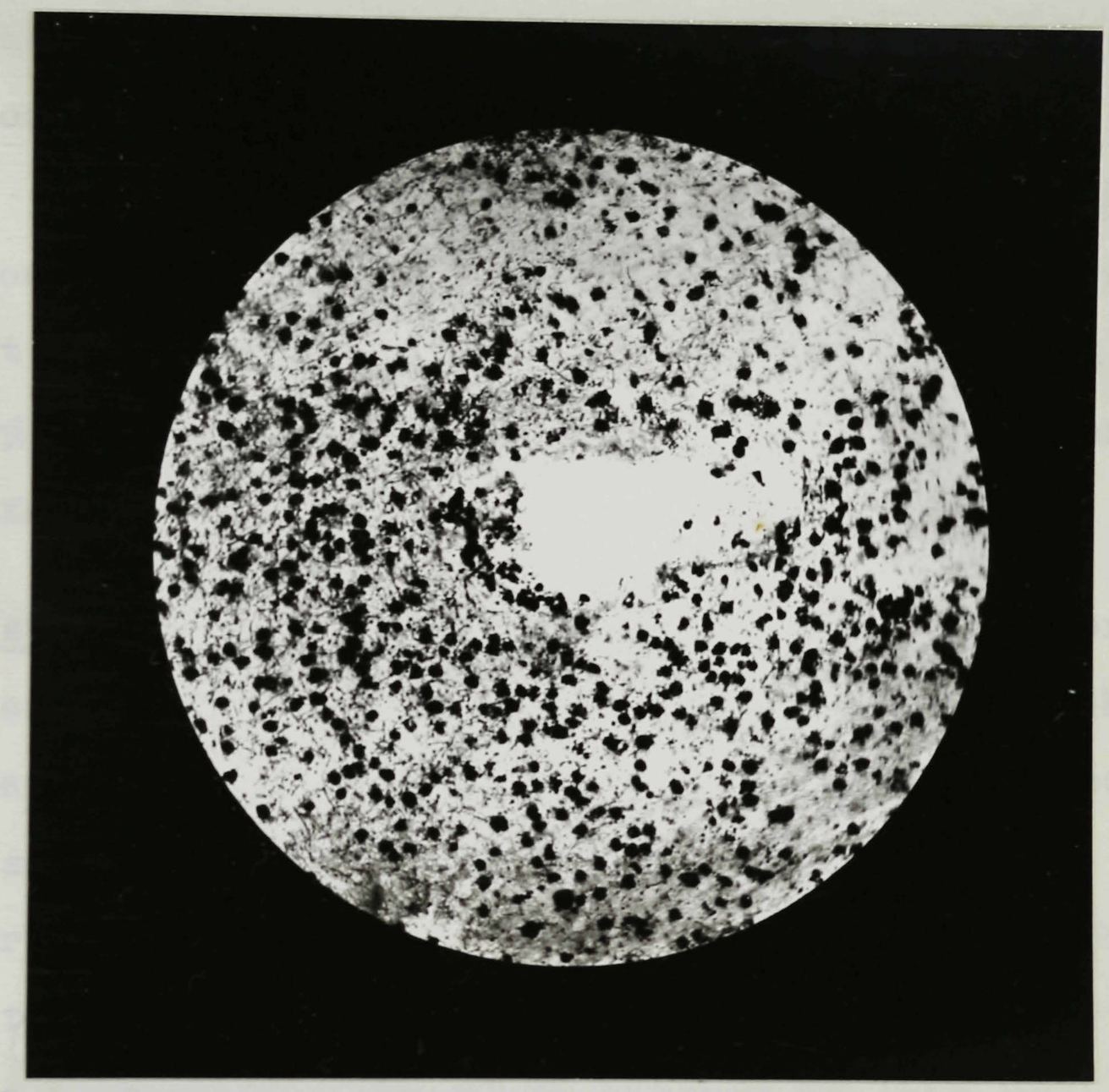
3. Non-epileptogenic Lesions in Experimental Animals.

Several brains of animals in which seizures were not observed were found in the Neurophysiology Department, having experimentally produced cerebral scars. Most of those available for this study, however, contained scars of a relatively short duration, that is, a few months prior to death of the animal. One cat brain containing a cortical scar of 3 years and 4 months' duration was selected for study.

In November 1937 a craniotomy was done by Doctor T.C. Erickson and a cerebral scar was produced by implanting three pieces of skin in the left frontal lobe. The animal recovered rapidly from the operation and appeared normal until December 1940 at which time

Fig. 57.

Fat-filled compound granular corpuscles in scar following needle puncture made 3 years and 6 months prior to death of patient. Scharlach-R stain.



a gradual weight loss became evident and 3 months later, in February 1941, the animal died. No seizures were observed by the animal house attendant during the 3-year and 4-month period following the operation.

Autopsy showed a few filmy adhesions over a scarred raised area measuring 5 x 5 mm. in the left frontal lobe (Fig. 58).

The brain was fixed in formalin ammonium bromide for 2 hours, after which time two blocks were cut from each frontal lobe and one of each placed in 10% formalin and formalin ammonium bromide for further fixation.

Histological Examination: A typical meningocerebral cicatrix was present consisting of a greatly thickened arachnoid containing much collagen and many connective tissue fibers, the latter running down into the cortex (Fig. 59). Large numbers of piloid glia were intermingled with the connective tissue fibers (Fig. 60). The cytoarchitecture about the scar was markedly disorganized, the neurons showing sclerosis and the surrounding glial nuclei being increased in number.

Beneath this scar several tissue defects were present surrounded by streams of piloid glia.

Silver stains showed the microglia in the scarred region to be altered and many compound granular corpuscles were demonstrable. Fat stains showed many fat-filled compound granular corpuscles

Fig. 58.

Cat brain showing scar of 3 years 7 months' duration in left frontal cortex.

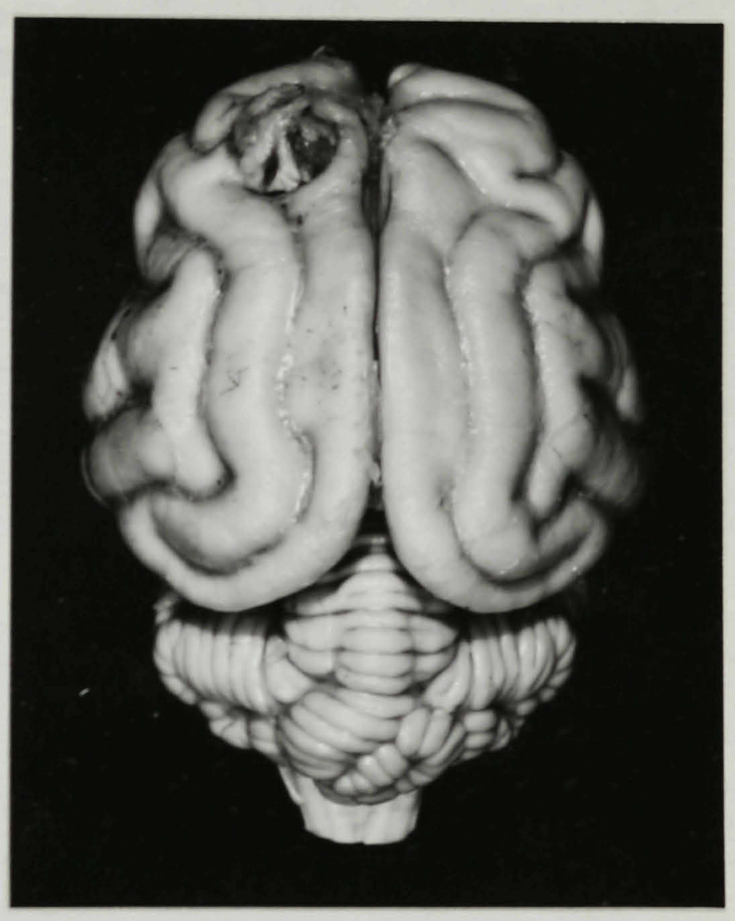
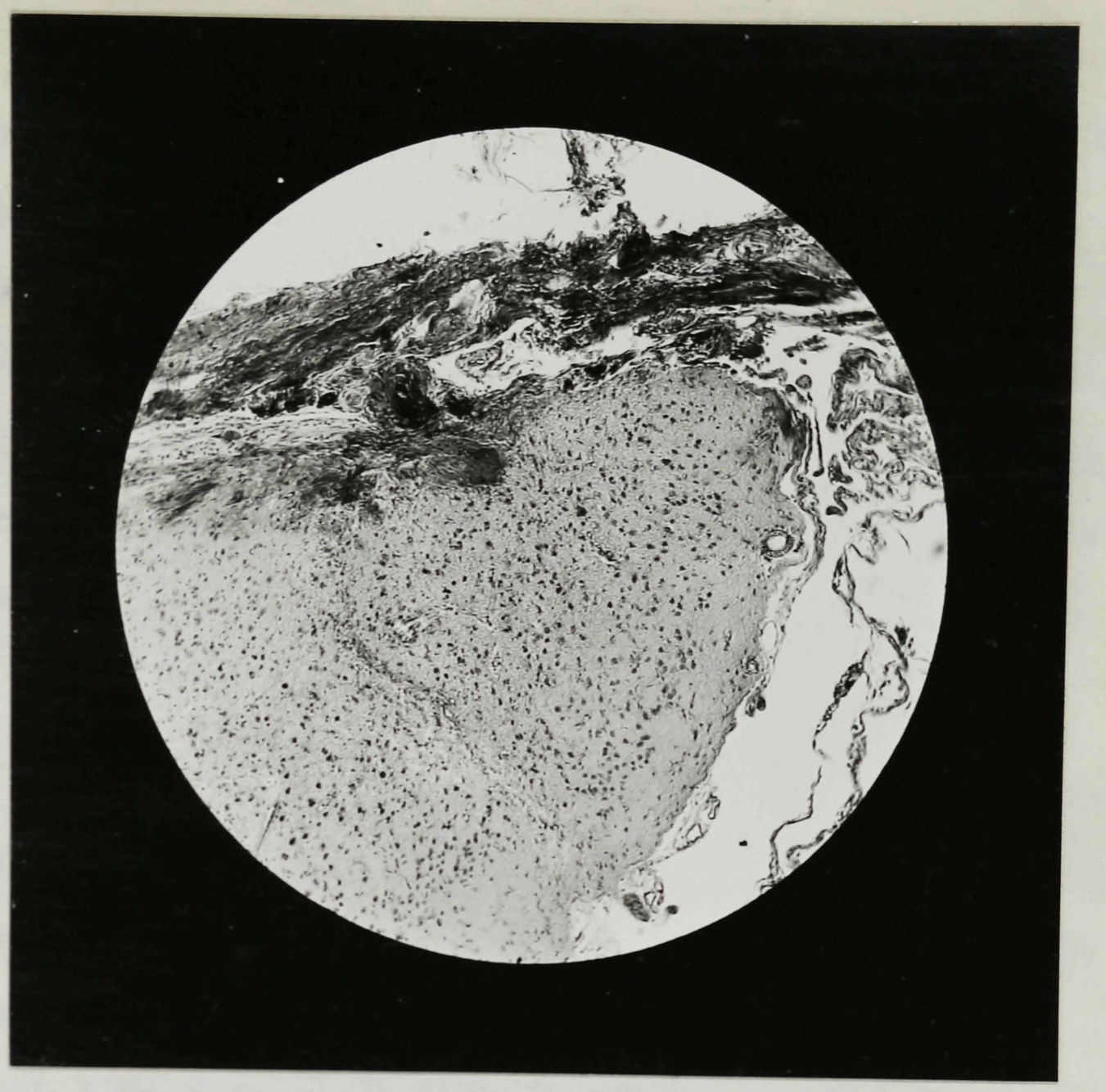


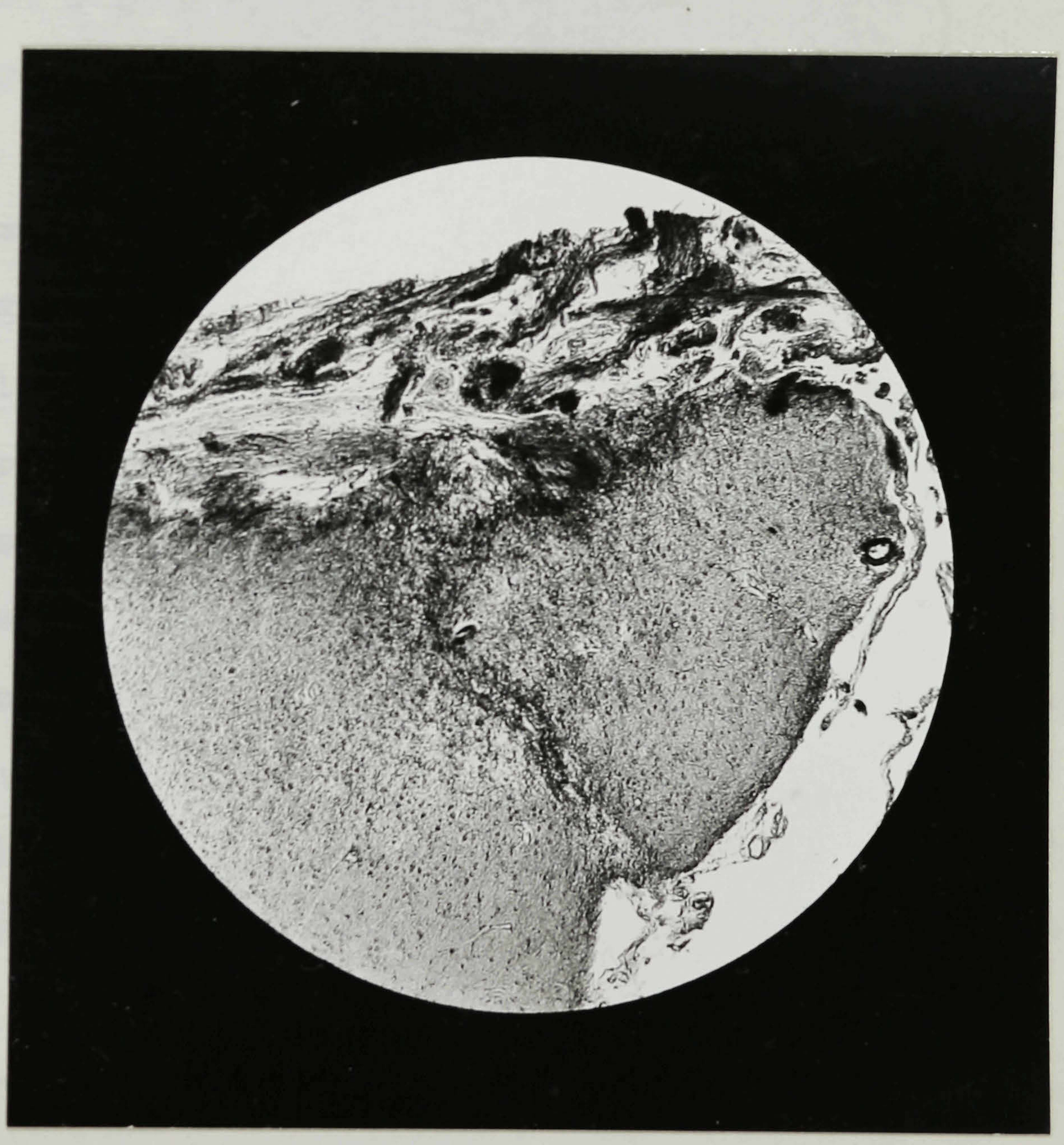
Fig. 59.

Meningocerebral cicatrix in cat. Age of scar 3 years and 7 months. Note ingrowth of connective tissue from pial surface.
(Hematoxylin and van Gieson stain).

Fig. 60.

Meningocerebral cicatrix in cat. Note presence of piloid fibrils intermingled with connective tissue fibers. (Compare with connective tissue stain, Fig. 59).
Mallory's Phosphotungstic Acid Hematoxylin stain.





in the scar; however, only rare fat-filled phagocytes were seen in perivascular areas in the border-zone between the scar and the adjacent normal cortex. Fat was also present in less altered microglial forms.

The oligodendroglia throughout the surrounding gray and white matter appeared normal; however, in the scar swollen oligodendroglia were present.

Discussion.

The cases presented well demonstrate that products of degeneration in compound granular corpuscles can be present in non-epileptogenic cerebral scars years after the production of the initial injury. The most pronounced constant finding is that of scattered, large, fat-filled compound granular corpuscles present in a loose mesh of cerebral neuroglia and connective tissue, most frequently showing few blood vessels. However, in regions adjacent to such degenerated areas many fat-filled compound granular corpuscles are arranged in groups in a perivascular distribution (Fig. 51). Past this zone of less destruction and entering the zone of relatively normal cerebral areas, such a perivascular arrangement of fat-filled phagocytes is again found. Silver stains show varied alterations of microglia, most of which contain small amounts of fat, increasing in quantity as the cell approaches the form of a compound granular corpuscle. It cannot be said here that such an evidence of tissue destruction is

entirely focal and not diffuse in its distribution. Many epileptogenic lesions examined by the writer also showed a diffuse rather than a primarily focal arrangement of such products of degeneration in the altered microglia (Fig. 49). Often fat-filled compound granular corpuscles were found in areas showing very few vessels, those present usually being large vessels (Fig. 56).

Such a picture recalls the findings of Spielmeyer (1922) in old foci of cerebral softening in which he described compound granular corpuscles containing products of degeneration present several decades after the initial injury. He stated that although it was by no means certain that such a picture represented a stationary one, it was certain that true terminal stages could show nests of compound granular corpuscles apparently "anchored".

This observation, together with those made by the writer, suggests the possibility of fat-filled compound granular corpuscles being left marooned in areas which showed marked degeneration due to the fact that alterations in the immediate blood supply left no means of elimination for the compound granular corpuscles containing products of degeneration. Would it then be possible for such fat-filled compound granular corpuscles to remain unchanged over a period of years?

The presence of fat-filled compound granular corpuscles and other altered forms of microglia around vessels which show no pathological changes, suggests

that such products of destruction are continually being emptied into the blood stream; however, when such cells are found in areas of almost completely avascular connective tissue structure, where the cortical capillary network has completely disappeared (Campbell, Alexander and Putnam, 1938), their ultimate destination is questionable.

It may be said here that in the report of Penfield and Humphreys many of the foci of destruction consisted of areas adjacent to intracortical islands of gray matter. In the non-epileptogenic scars studied no intracortical islands were seen. However, it is the writer's belief in regard to the hypothesis given in Chapter IV about such island formation that, since extracortical islands were found in these scars, intracortical islands were probably present at one time during the scarring process.

One may conclude from the cases presented that fat-filled compound granular corpuscles, and other fat-filled altered microglia, can be present in non-epileptogenic scars of long duration. The presence of these phagocytes in perivascular areas probably evidences progressive tissue destruction. Considering this observation the role played by progressive tissue destruction in the production of seizures is questionable.

Summary.

(1) The evidence for progressive tissue destruction in epileptogenic lesions is reviewed.

(2) 3 cases of non-epileptogenic lesions in the brains of human beings are presented showing similar evidence of tissue destruction present after 2 years and 6 months, 7 years and 4 months, and 40 years following the initial injury (meningocerebral cicatrix following depressed fracture of skull).

(3) The significance of such evidence of tissue destruction in old scars is discussed.

Fig. 61.

Trabecula of gray matter in non-epileptogenic scar of 40 years' duration. Note loose network of atrophic cortex in lower right-hand corner.
Hematoxylin and van Gieson stain.

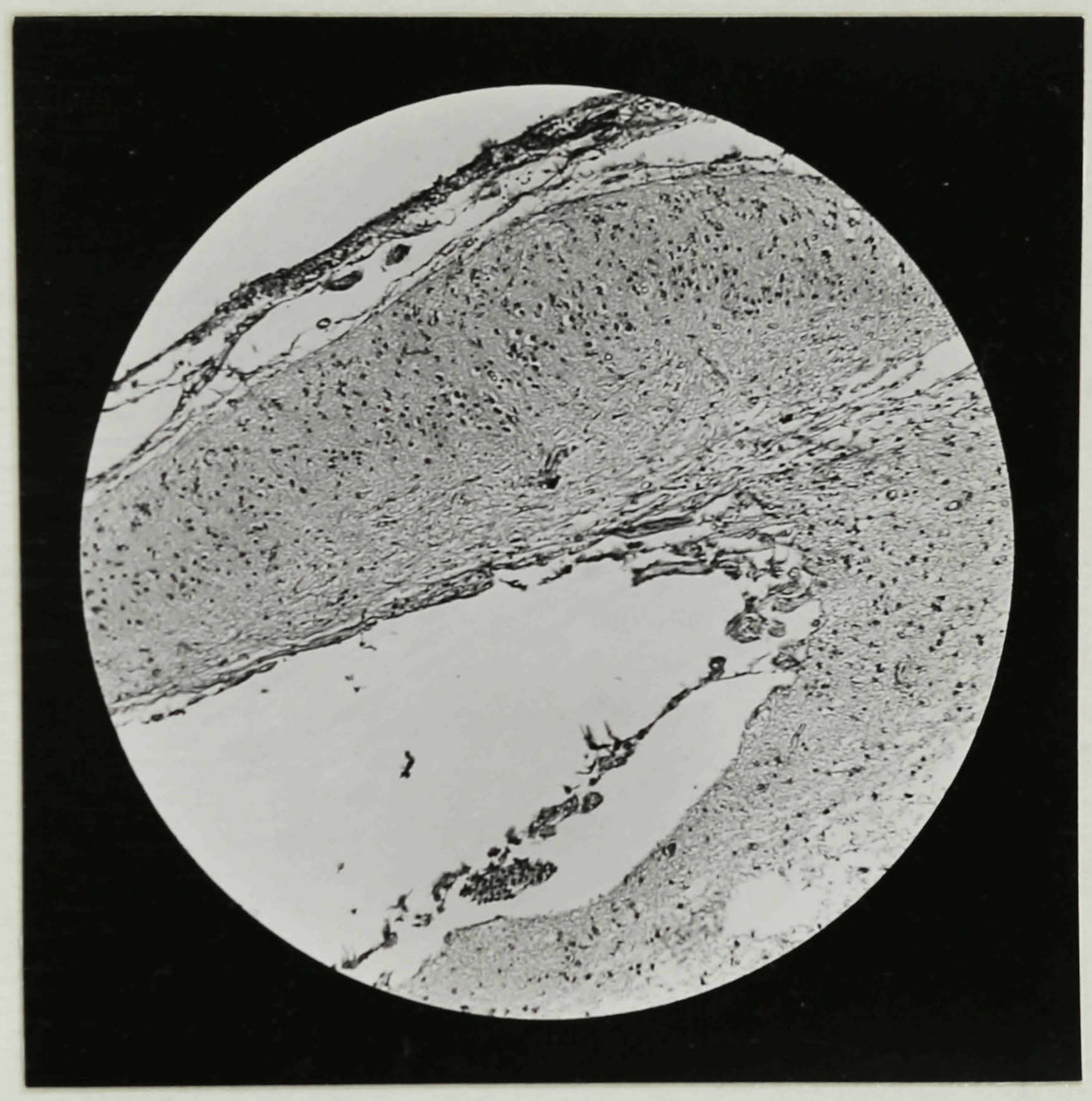


Fig. 62.

Minute extracortical island of gray matter containing neurons. Hematoxylin and van Gieson stain.

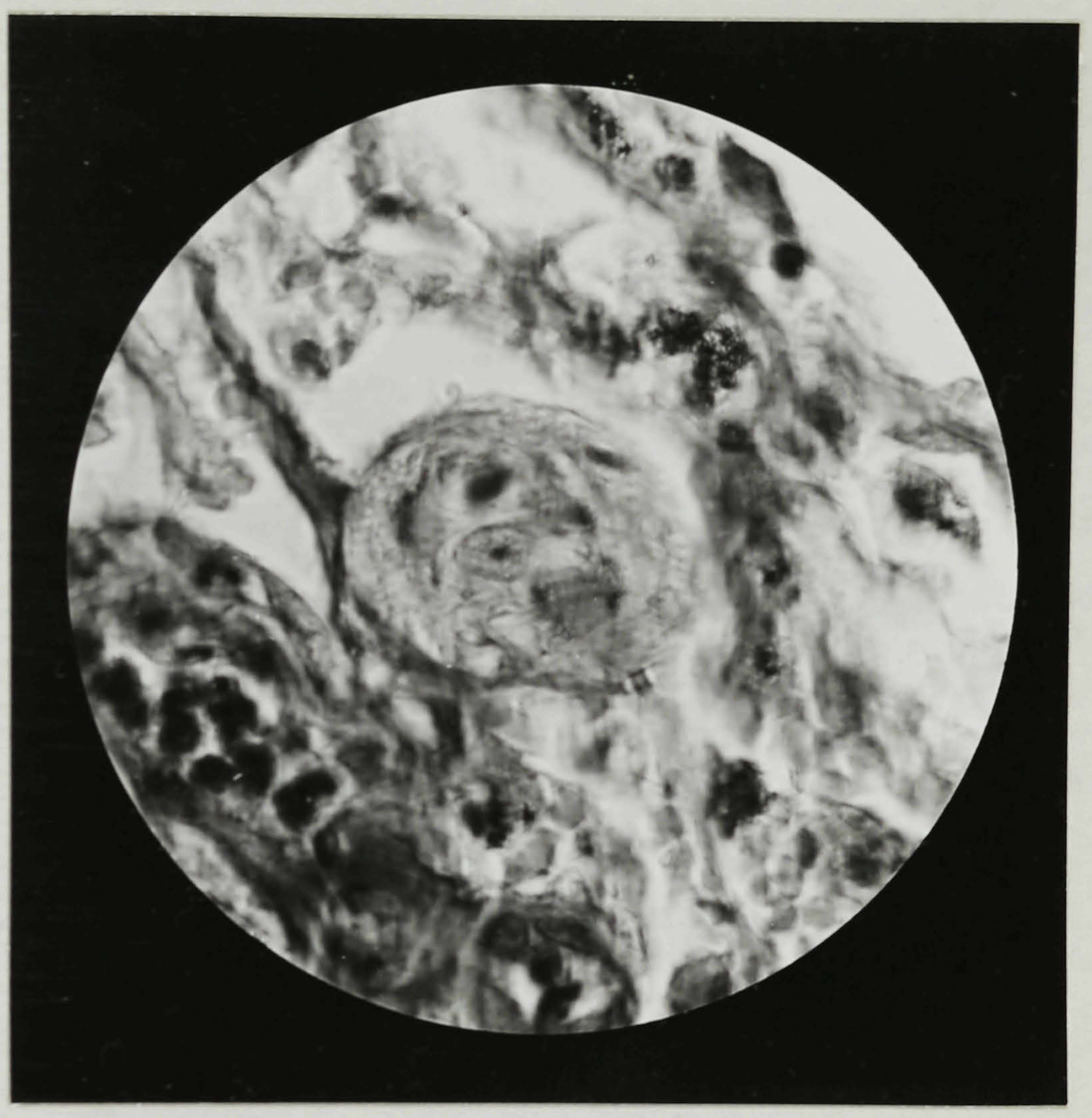


Fig. 63.

Numerous large vessels in region of trabeculae and extracortical islands.

Hematoxylin and van Gieson stain.

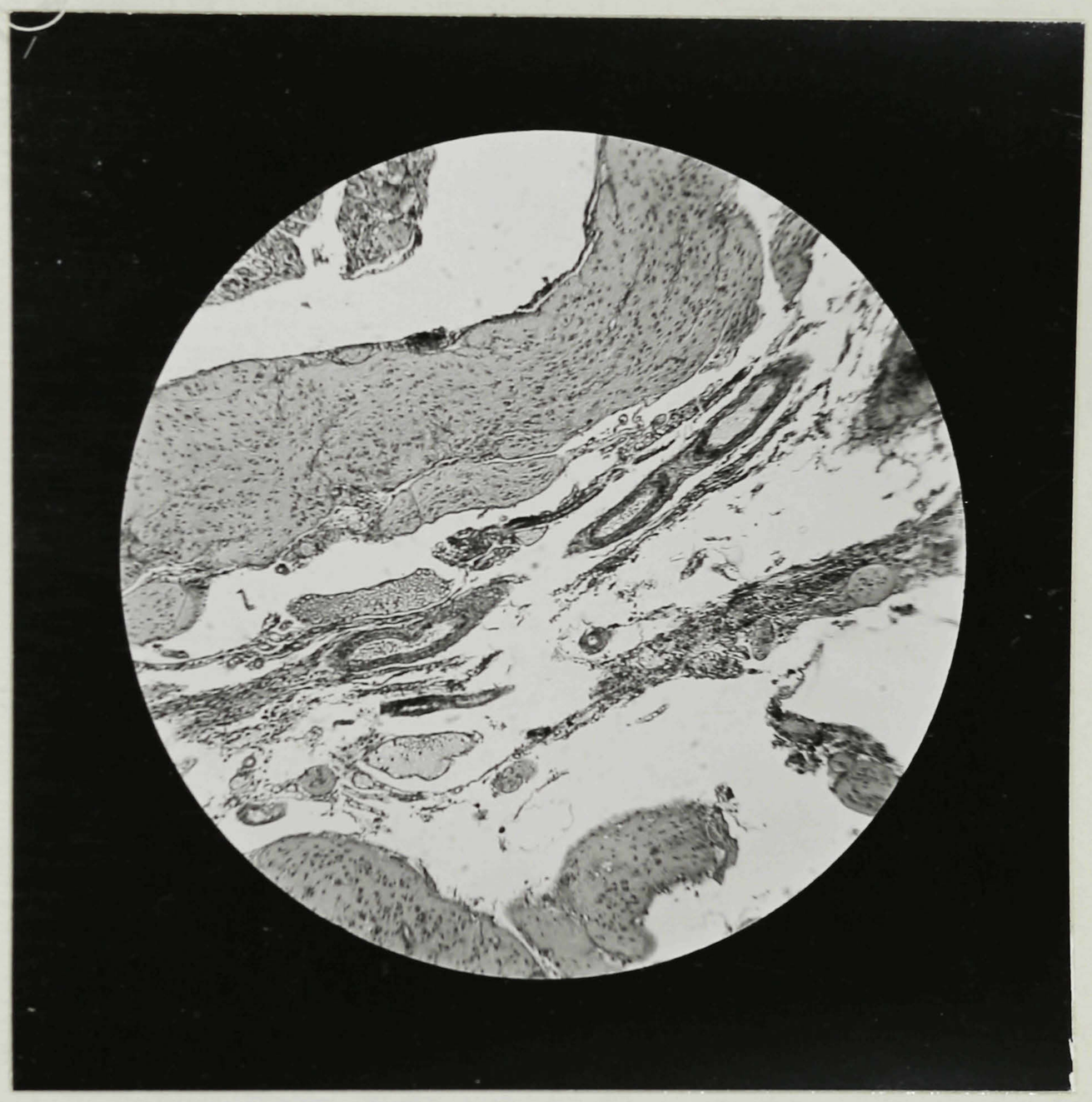

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Fig. 64.

Extracortical islands surrounded by connective tissue. Note constrictions in trabecula caused by scarring.
Hematoxylin and van Gieson stain.



Fig. 65.

Thickened arachnoid beneath which are extracortical islands.
Hematoxylin and van Gieson stain.

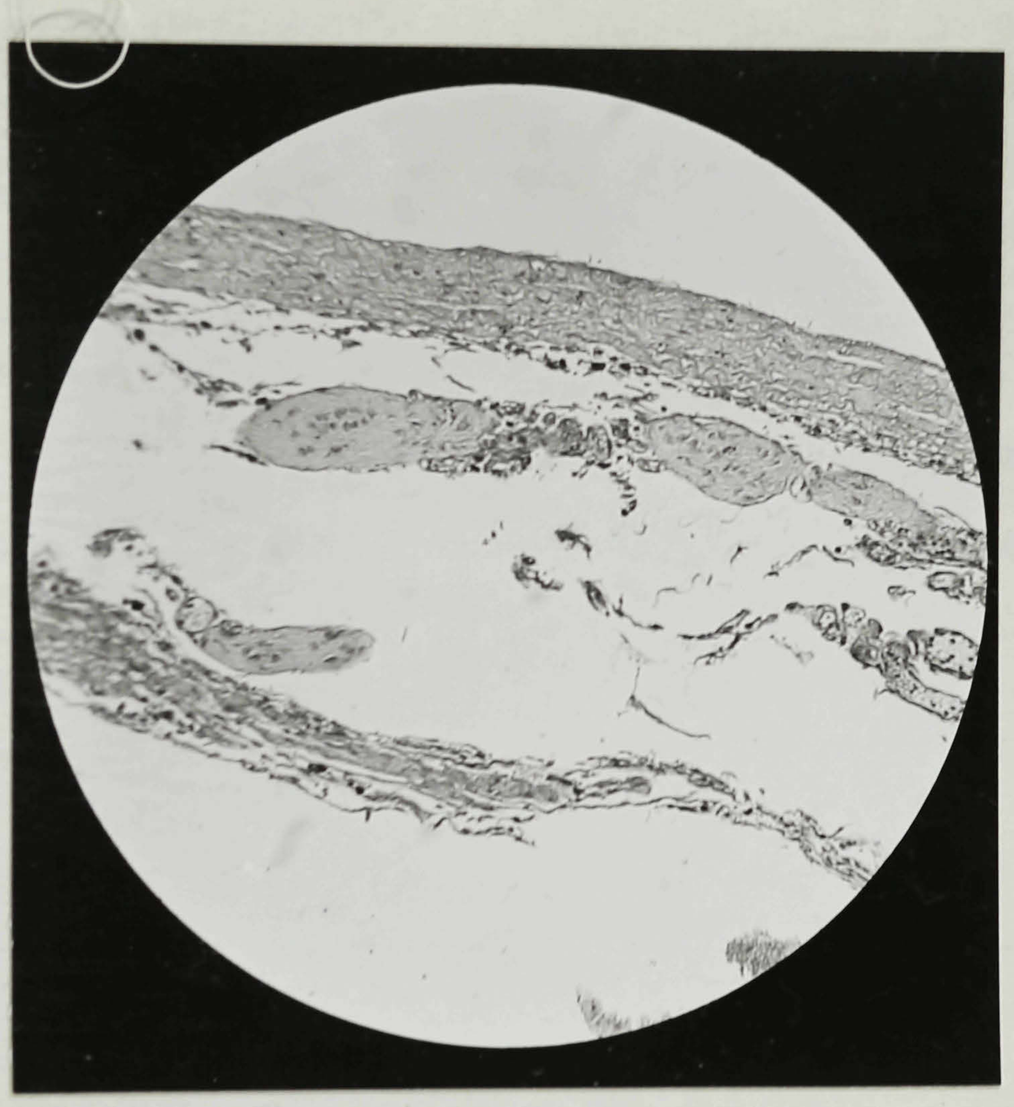


Fig. 66.

Trabeculae of gray matter and extra-cortical islands. Note islands not completely separated from trabecula and minute island (in center) containing neurons.

Hematoxylin and van Gieson stain.

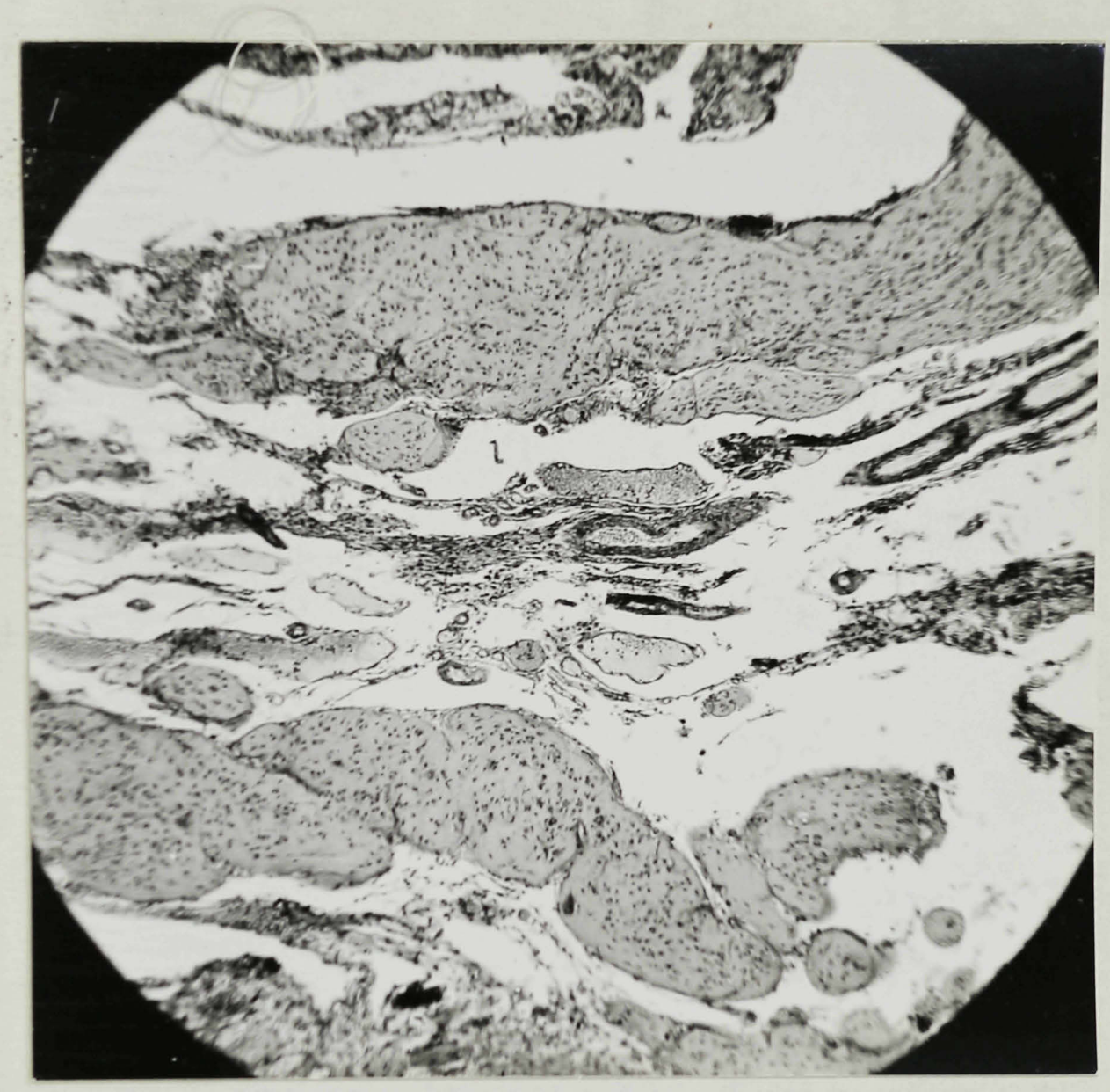


Fig. 67.

Strands of connective tissue entering cerebral cortex from pial surface, in meningocerebral cicatrix. Hematoxylin and van Gieson Stain.



VI. SUMMARY

I. The literature on the pathology of epilepsy has been reviewed and a further histological study of epileptogenic lesions has been presented.

II. In 12 epileptogenic lesions excised at operation circumscribed foci of neuronal destruction were found in the vicinity of the contained cicatrix. The histological picture of these foci simulated that frequently found following circulatory impairment.

It is suggested that such foci found near epileptogenic lesions give further evidence of a vascular spasm occurring at the border of epileptogenic foci.

III. In 7 epileptogenic lesions excised at operation varied sized islands separated from the cortex by scar formation are described. The presence of neurons in many of these islands is demonstrated. It is concluded that such extracortical islands originate from the cerebral cortex. A hypothesis concerning the formation of these isolated areas of gray matter is presented.

IV. The presence of progressive tissue destruction in 3 posttraumatic, non-epileptogenic cerebral cicatrices in human brains is demonstrated. The time intervals between the original trauma (depressed fracture of skull) and death of the patient varied from 2½ to 40 years. It is concluded that progressive tissue destruction can be present in non-epileptogenic as well as in epileptogenic lesions.

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VIII.

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