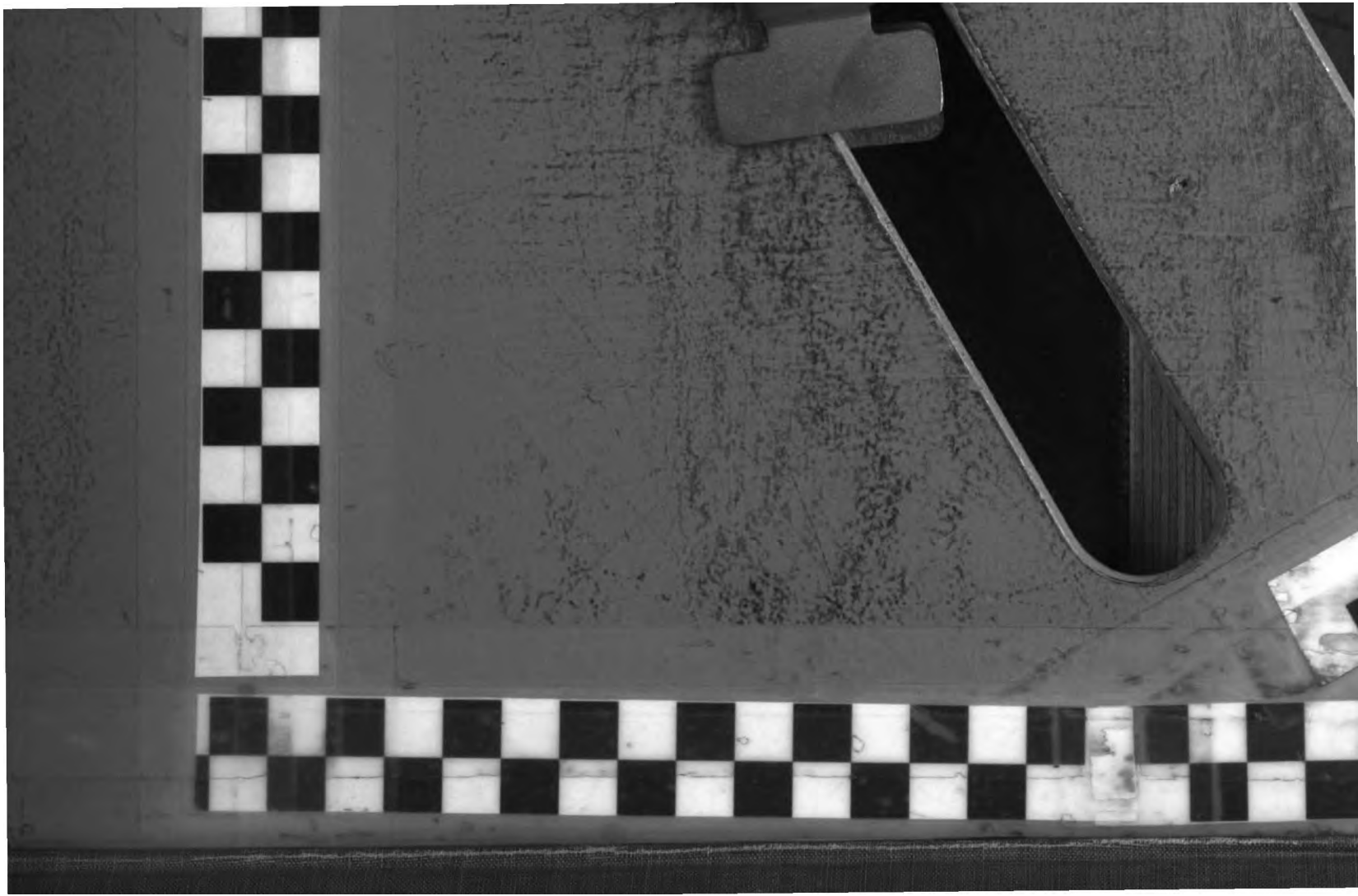
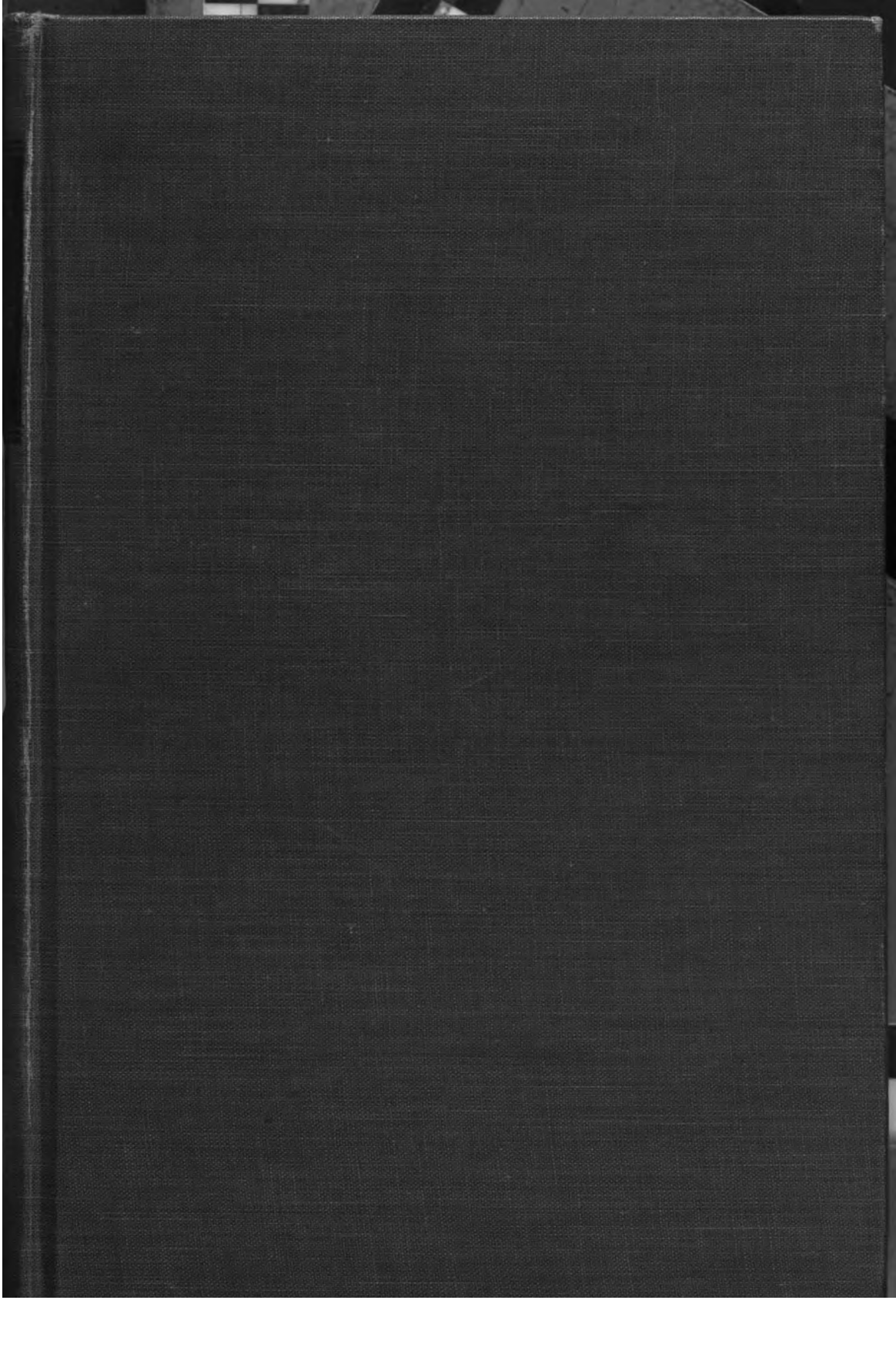
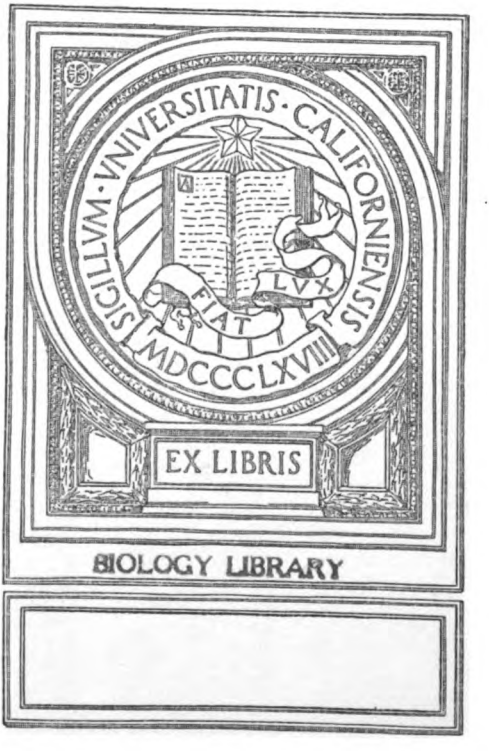
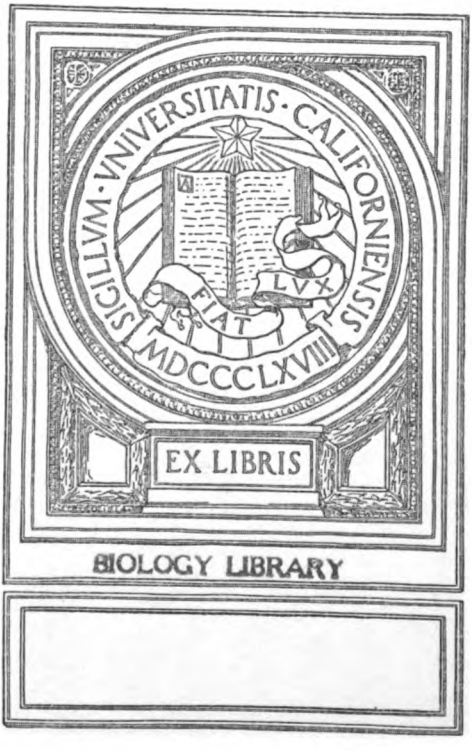
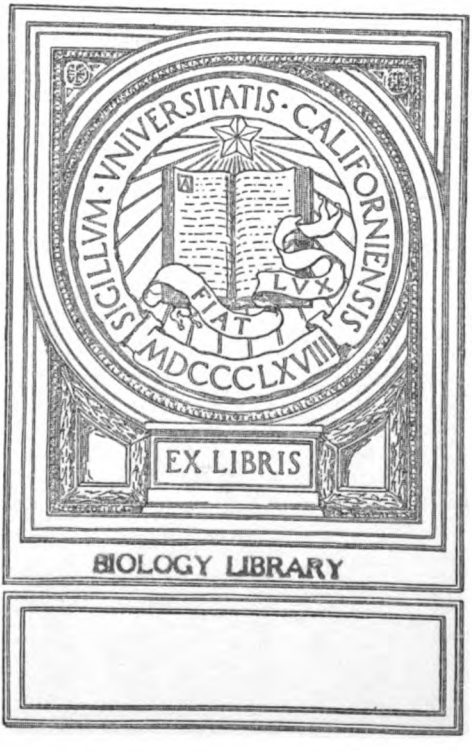





SIGILLVM · VNIVERSITATIS · CALIFORNIENSIS
LVX
FIAT
MDCCCLXVIII
EX LIBRIS
BIOLOGY LIBRARY


SIGILLVM · VNIVERSITATIS · CALIFORNIENSIS
FIAT LVX
MDCCCLXVIII
EX LIBRIS
BIOLOGY LIBRARY


SIGILLVM · VNIVERSITATIS · CALIFORNIENSIS
LVX
FIAT
MDCCCLXVIII
EX LIBRIS
BIOLOGY LIBRARY

TEXTBOOK OF NEUROPATHOLOGY

TEXTBOOK OF NEUROPATHOLOGY

By ARTHUR WEIL, M.D., *Associate Professor of Neuropathology, Northwestern University Medical School*

SECOND EDITION · REVISED AND ENLARGED

GRUNE & STRATTON · · · *1945*
New York

TEXTBOOK OF NEUROPATHOLOGY

By ARTHUR WEIL, M.D., *Associate Professor of Neuropathology, Northwestern University Medical School*

SECOND EDITION · REVISED AND ENLARGED

GRUNE & STRATTON · · · *1945*
New York

GRUNE & STRATTON, INC.
381 Fourth Avenue
New York 16, N. Y.

PRINTED BY
WAVERLY PRESS, INC.
U. S. A.

Dedicated to
the memory of
Walter Spielmeyer

GRUNE & STRATTON, INC.
381 Fourth Avenue
New York 16, N. Y.

PRINTED BY
WAVERLY PRESS, INC.
U. S. A.

Dedicated to

the memory of

Walter Spielmeyer

381 Fourth Avenue
New York 16, N. Y.

PRINTED BY
WAVERLY PRESS, INC.
U. S. A.

Dedicated to

the memory of

Walter Spielmeyer

PREFACE TO THE FIRST EDITION

NEUROPATHOLOGY has come into its own. With the development of neurology as an independent unit of the medical sciences, the accumulation of facts has progressed at such a rapid rate that it has become necessary to separate the fundamental branches of neuro-anatomy, neurophysiology, and neuropathology from the clinical teaching. Strümpell's ideal that the neurologist should be his own critic at the autopsy table and at the microscope has become difficult to realize in the present age.

The German medical schools were the first to recognize the need of a centralization of the different branches of neurology, and to effect this centralization have founded institutes of neurology. From these institutes neuropathology has received its most valuable stimuli and the wealth of the German literature and textbooks on the subject testifies to the success of fostering intensive research.

With the increasing appreciation of neurology as an entity in the medical schools of the United States, the need for textbooks in the English language on the fundamentals of neurology has gradually increased. This book has been designed to give a review of the present stage of our knowledge in neuropathology. It contains a collection of facts which have been scattered in the literature, and should enable the student to obtain a better understanding of the reactions of the nervous system in disease to guide him in his clinical work. At the same time it should help the neurologist to recall data and point out to him the many problems in the etiology of nervous disease which are still to be solved.

In order not to overburden the text, citation of literature is avoided as much as possible. However, the final chapter contains a collection of the more recent monographs on the different subjects. This will enable the more ambitious student to find the path back to the original observer of a given disease. Such a procedure prevents undue influence of an authoritative name in the discussion of different theories, and leaves it to the student to evaluate for himself the importance of the various facts which are cited in favor of a given theory.

The addition of chemical and physical data reflects the author's personal endeavor to study neuropathology not merely with the aid of the microscope but with every tool possible which modern biology puts at our disposal.

The chapter on staining methods is included to give a more complete understanding of the technique which was used in producing the slides

PREFACE TO THE FIRST EDITION

NEUROPATHOLOGY has come into its own. With the development of neurology as an independent unit of the medical sciences, the accumulation of facts has progressed at such a rapid rate that it has become necessary to separate the fundamental branches of neuro-anatomy, neurophysiology, and neuropathology from the clinical teaching. Strümpell's ideal that the neurologist should be his own critic at the autopsy table and at the microscope has become difficult to realize in the present age.

The German medical schools were the first to recognize the need of a centralization of the different branches of neurology, and to effect this centralization have founded institutes of neurology. From these institutes neuropathology has received its most valuable stimuli and the wealth of the German literature and textbooks on the subject testifies to the success of fostering intensive research.

With the increasing appreciation of neurology as an entity in the medical schools of the United States, the need for textbooks in the English language on the fundamentals of neurology has gradually increased. This book has been designed to give a review of the present stage of our knowledge in neuropathology. It contains a collection of facts which have been scattered in the literature, and should enable the student to obtain a better understanding of the reactions of the nervous system in disease to guide him in his clinical work. At the same time it should help the neurologist to recall data and point out to him the many problems in the etiology of nervous disease which are still to be solved.

In order not to overburden the text, citation of literature is avoided as much as possible. However, the final chapter contains a collection of the more recent monographs on the different subjects. This will enable the more ambitious student to find the path back to the original observer of a given disease. Such a procedure prevents undue influence of an authoritative name in the discussion of different theories, and leaves it to the student to evaluate for himself the importance of the various facts which are cited in favor of a given theory.

The addition of chemical and physical data reflects the author's personal endeavor to study neuropathology not merely with the aid of the microscope but with every tool possible which modern biology puts at our disposal.

The chapter on staining methods is included to give a more complete understanding of the technique which was used in producing the slides

from which the photomicrographs were made. A complete compilation of neurological technique is available in Spielmeyer's compendium, hence a lengthy description of methods is unnecessary.

Without the cooperation of the Neurological Service of Montefiore Hospital in New York and of the Departments of Pathology and Neurosurgery of Northwestern University, which enabled the author to study material from both chronic and acute diseases of the nervous system, this book could not have been written.

Sincere thanks are due to Helen Davenport for assistance in revising the text.

Chicago A. W.

PREFACE TO THE SECOND EDITION

THE decade that has passed since the publication of the first edition of this textbook has witnessed great strides forward in neuropsychiatry. The knowledge acquired through a better understanding of the vitamin deficiencies, the discovery of the sulfonamides and their contribution to the therapy of meningitis, the different forms of shock treatment applied to selected cases of neurosis and psychosis—these are some of the milestones on the road of progress.

Neuropathology has not been directly affected by these discoveries in therapy. Not much could be added to the resources of macroscopic and histologic diagnosis of organic nervous diseases. A better insight into the pathology of virus infections was gained through study of the different epidemics of encephalitis that appeared in this country during this period. The contributions of neuropathology were rather more in the experimental field: the investigation of the vitamin deficiencies, the experimental production of tumors of nervous tissue, the experimental study of the pathology of the different shock treatments, are some of them. Publication of the *Journal of Neuropathology and Experimental Neurology* has given great stimulus and encouragement to such research.

The author has tried to incorporate these new additions to our knowledge into this second edition. This endeavor is reflected in an increase in the number of illustrations from 260 to 287, and in a corresponding increase in the size of the book. He has tried to do justice to all the more or less benevolent critics of the first edition by following their constructive advice. The only judgment that he could not accept was that of a Southern colleague who wrote: "Since we had the textbooks of Jakob and Spielmeyer, there was no need for an American textbook of neuropathology." That others too could not share such a point of view is evidenced by the fact that since the publication of the first edition of this work at least four new textbooks of neuropathology have been published in the English language.

It is with great pleasure that I acknowledge the technical assistance of Miss Jane Bostroem, Mrs. Helen Dey, Miss Shirley James, and Mrs. Lilian Rohs, who helped to prepare the material on the study of which this book is based.

New York, February 1945 ARTHUR WEIL

CONTENTS

CONTENTS

INTRODUCTION

NEUROPATHOLOGY is the study of the nervous tissue in disease and the determination of deviations of its structures from the normal. This definition implies a conception that is an inherent obstacle to every comparative study—the fictitious standard "normal." When one compares things by measuring and weighing, averages and standard deviations within certain limits define the norm, but when one comes to compare structures of tissues, the norm can be determined only by the mental process of creating an imaginary average picture of numerous organs and slides from healthy cases that have been studied. Long experience and intuition replace the tape and the slide rule, and the deviations from the investigator's own conception of "normal" play an important role.

The task becomes more difficult if one remembers that the norm of the nervous system changes rapidly in the first months of life and that its histologic make-up undergoes constant changes even after growth has been completed in the adult. Our newer knowledge of the significance of the hemato-encephalic barrier, and of the influence of nutrition and internal secretion upon the chemical composition of the nervous system, tends to emphasize again the close relationship of the latter to its environment. It is necessary therefore to create from an imaginary average the concept of a normal nervous system of the same age as that of the pathologic one to be examined. The task, if it is undertaken with the true spirit of scientific investigation, sometimes appears insoluble when it comes to the study of finer histologic details of cellular changes. Our ever increasing knowledge of the rapid onset of postmortem pathology, and of the influence of fixatives and staining methods on the finer structures, makes us suspicious of the validity of many disease entities reconstructed from and theories built upon the authoritative statements of former investigators. Furthermore, the histologic changes of the nervous system, with its limited means of reaction and defense against disease, do not always allow a conclusion as to the etiologic factor. The pathologist, otherwise the final judge of the diagnostic ability of the internist and the surgeon, is obliged humbly to ask the clinician for a history of events and laboratory findings, and must be satisfied with merely a detailed description of the histologic picture.

Neuropathology is not histopathology only; the microscope is no longer the only tool at our disposal for study of disease processes. Though still in its infancy, the technic of chemical investigation of the nervous system is rapidly progressing, and it occurs to us that diseases in which the mi-

croscope does not reveal structural changes may perhaps be brought about by a change in chemical and physicochemical make-up. Our newer knowledge of the significance of the hemato-encephalic membrane barrier, of the influence of nutrition, of internal secretion, and of chemistry tends to emphasize again the close relationship of the nervous system to its environment. It will help to bring it back from its "splendid isolation" and will guide us in paying closer attention to its relationship with diseases of other organs of the body.

I

CHANGES THROUGH AUTOLYSIS AND FIXATION

Autolysis

One is sometimes amazed to see publications in which an attempt has been made to photograph or to describe the "real" structure of a living ganglion cell. These investigators do not realize that the life of a cell is quite different in its natural environment and after its removal from the body. Neither the most ideal nutritional fluid nor the exact preservation of body temperature ever prevents the explosive change of the cellular metabolism after the adult ganglion cell has been removed from the body. Neither photographs with ultraviolet light nor photographs in the dark field or taken with the cathod ray microscope help to improve the experimental conditions. A huge amount of controversy could have been avoided if the following facts had been remembered.

A few seconds after the removal of the brain of a rabbit or a cat from the skull, the lactic acid increases explosively and the maximum is established after thirty minutes. At the same time the free fermentable sugar disappears (within from three to five minutes in the dog's brain) and from 80 to 85 per cent of the glycogen is lost within fifteen minutes. About thirty minutes after death, phosphocreatine is found hydrolyzed in the dog's brain and adenosine triphosphate is partially decomposed. Another source of water-soluble phosphorus compounds during the process of autolysis are the phospholipids, while the amount of galactolipids is not appreciably diminished two hours after death.

Table 1 gives an example of these abrupt changes in the chemical composition of the brain.

The breaking down of phospholipids in an experiment of longer duration is illustrated in table 2.

It is evident that such chemical changes must result in physical changes of the structural make-up of a cell and that they will find their expression in the staining reaction. This is especially true of the varying amounts of inorganic substances found in different parts of the central nervous system—e.g., equal amounts of iron and copper are found in the gray and in the white matter of the cerebrum and cerebellum. The striate body contains more iron and copper, while most of the iron is found in the globus pallidus and the substantia nigra. Infant brains contain less iron and

copper than the adult brain, while the content of manganese is about the same at different ages. The change in the physicochemical structure of the plasma colloids will immediately result in a different affinity for dyes and even a supravital stain will not reveal the living structures. The slightest damage to the hypothetic cell membrane will change the relation of diffusion of extra- and intracellular fluids. In living animals one may obtain a more intense staining of ganglion cells with vital-staining dyes if

TABLE 1.—*Chemical Changes in Rabbit Brain within Two Hours after Removal (Jungmann and Kimmelstiel)*

One hemisphere was frozen immediately in liquid air; the other hemisphere was kept for two hours at a temperature of 40 C.

Rabbit Brain	Milligrams in 100 Gm. of Fresh Tissue			
	Glycogen	Lactic Acid	Cerebrosides	Phosphorus
Fresh	244	38	434	35
After 2 hr. at 40 C.	137	176	383	55

they are injected together with chloroform, which dissolves part of the "membrane" lipids, or with potassium chloride. Such changes in permeability of dead membranes have been particularly well studied. Therefore utmost care should be exercised in the evaluation of generalized ganglion cell changes in conditions in which the fluids of the central nervous system contained toxic substances, as in uremia, liver disease, septicemia,

TABLE 2.—*Autolysis of Nervous Tissue: Decomposition of Phospholipids*

Tissue kept in 0.9 per cent sodium chloride for twenty-four hours at 37 C. Percentage distribution of phosphorus after fractional extraction

Phosphorus	Brain		Spinal Cord	
	Normal	Autolytic	Normal	Autolytic
Water-soluble		76.0		62.6
Acetone-soluble	16.3	9.5	7.3	15.0
Alcohol-soluble	54.7	6.7	77.2	19.3
Residual	29.0	7.8	15.5	3.1

etc. It seems impossible to state whether or not some changes that will be described later have been produced by the change in permeability of the dead or of the living cell. For the same reason pictures of generalized paling of the outer zones of spinal cord sections stained for myelin sheaths make one suspect a postmortem change in permeability of the protecting meninges, permitting spinal fluid containing toxic substances to penetrate into the periphery of the spinal cord.

The influence of certain disease processes on postmortem changes has long been known. The rapid softening and cheesy changes of the brain

FIG. 1. PSEUDOHETEROTOPIA
Protrusion of softened spinal cord simulates tumor

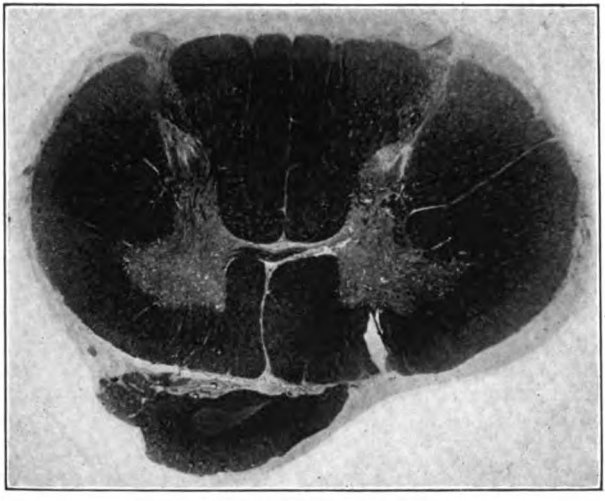


FIG. 2. PSEUDOHETEROTOPIA
Double spinal cord. Part of dorsal spinal cord was dislocated upward, where it was removed by pull

substance in tuberculous meningitis may be cited as examples. Sometimes only prolonged formalin fixation will bring out gross pathologic changes. The severe destruction of the striatum in double athetosis or in

certain diseases of the liver frequently is not detectable at the autopsy table. The same is true of the plaques in disseminated sclerosis and of the early stages of anemic softening. In the removal of softened spinal cords, displacement of white matter sometimes occurs; this after fixation may simulate a heterotopia (pseudoheterotopia) (figs. 1, 2).

POSTMORTEM INFECTION

A question still to be settled is that of postmortem infection. It has been demonstrated that foci of anemic softening may act even during life as "traps" for micro-organisms and may give rise to abscess formation. The

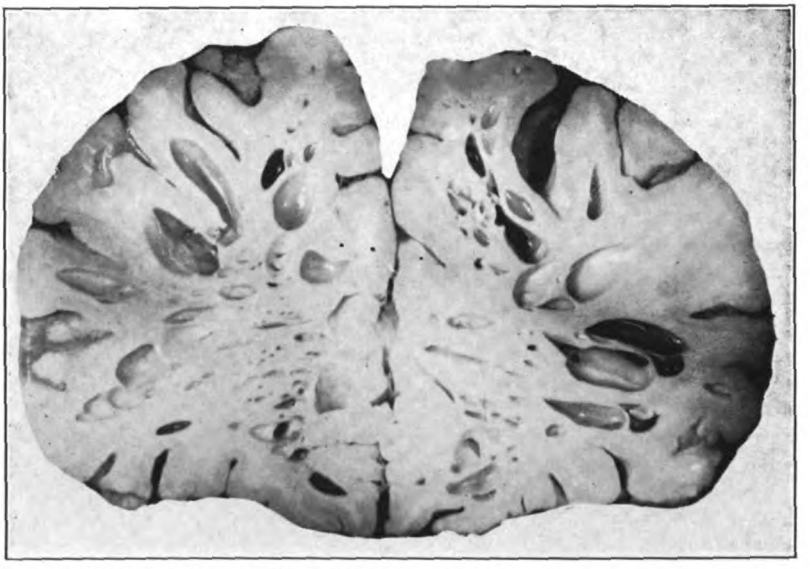


FIG. 3. GAS EDEMA OF BRAIN FOLLOWING INFECTED FRACTURE OF SKULL

demonstration of micro-organisms in foci of inflammation may readily be considered as evidence of a direct etiologic relationship. If, however, micro-organisms are demonstrated in regions that histologically do not show inflammatory changes, the possibility of postmortem migration from foci of infection elsewhere in the body or from the intestine should be considered. They are frequently found in the environment of abscess formation and purulent meningitis, producing a soft, creamy-like tissue. Such possibility is very likely following prolonged preservation of the body in warm weather. Gas-forming bacilli have been demonstrated in "gas edema" of the brain (*porose cérébrale*), another postmortem change, in which the manner of migration of the gas-forming bacillus has not yet been demonstrated (fig. 3). Clostridium welchii, Bacterium coli, and staphylo-

cocci are capable of invading the tissue of animals within from five to forty-eight hours after death if the temperature is kept at 25 C. Microorganisms that were inactive during life may multiply after death.

ACTION OF FERMENTS

Postmortem changes may also be produced by the presence of abnormal or increased ferments in certain diseases. Normally the cerebrospinal fluid does not contain proteolytic ferments; lipases seem to vary and may be absent in certain fluids; polypeptidases and diastases have been rather regularly found. The presence of proteolytic ferments has been demonstrated in different types of purulent meningitis and syphilis, but not in tuberculous meningitis. Monocytes contain pepsin (*p*H from 2 to 5); polymorphonuclear leukocytes also contain pepsin and trypsin (optimal *p*H, 3.5 and 8). During disintegration of nervous tissue, there is produced an ultrafilterable substance that possesses neurolytic properties; the amount resulting from gray matter is greater than that from white matter. The amount of lipase present in cerebrospinal fluid varies greatly. It is especially high in postoperative arachnoiditis, mildly increased in acute intoxications, diphtheria, acute leptomeningitis, and tetanus. It seems that ferments splitting tributyrin are diminished in cachexia, but increased in fat individuals. Two different phosphatases have been demonstrated in the brain of sheep, one active at an optimal *p*H of from 9.4 to 9.6, the other at a *p*H of 5.5. The concentration of ferments in the cerebrospinal fluid, like that of diastases, seems to be parallel to their concentration in the blood. Diastases have been found increased in general paresis, chronic alcoholism, diphtheria, dysentery, and tetanus.

FIXATION

EFFECT OF FORMALIN FIXATION

The idea that fixatives will preserve the living structures has been proved to be a delusion. Even formaldehyde, the most frequently used fixative for nervous tissue, has a destructive action upon part of the tissue. It can be demonstrated that the increase in acidity of the fixing fluid parallels an increase of water-soluble phosphorus compounds and a decrease in phospholipids that can be extracted. Many methods have been devised to overcome this undesired effect. Burke, for example, recommended a mixture of 75 parts of water, 25 parts of formalin, and 5 parts of pyridine. The latter, however, would act as a lipid solvent and interfere with the staining of myelin sheaths. In laboratory practice, storage of the formalin over calcium carbonate in brown bottles will prevent the formation of formic acid. Under certain conditions an acid fixative solution may even be desirable, as in staining of axis-cylinders or astrocytes by the Cajal method.

Examples of the process of phospholipid hydrolysis are given in tables 3 and 4.

That this decomposition of phospholipids is not due to postmortem autolytic changes can be demonstrated by treatment of boiled brain tissue with formalin, which results in the same gradual increase in water-soluble phosphorus.

TABLE 3.—*Influence of Formalin Fixation upon Phospholipids of Brain: Amount of Phosphorus Found in Fixing Fluid after Different Periods of Fixation*

	Days of Fixation					
	22	27	38	63	93	109
Milligrams of phosphorus per 1000 Gm. of fresh brain	340	378	400	429	476	532
Percentage of total phosphorus in 1000 Gm. of fresh brain	10.5	11.7	12.4	13.0	14.8	16.5

The gray matter of the brain is more involved in this process of splitting of phospholipids than the white matter. The galactolipids seem to be more resistant to the effect of formalin and their amount therefore relatively increases. After diseases of long standing the increase in phos-

TABLE 4.—*Fractional Extraction of Fresh and Formalin-fixed Nervous Tissue in Percentages of Dry Substance*

Water in percentage of tissue. Averages from three human brains

	Gray Matter			White Matter		
Days of Fixation	0	22	102	0	22	102
Water	82.0	85.3	84.3	68.6	72.7	73.1
1. Acetone extract	15.4	19.8	16.3	21.3	23.7	20.0
2. Alcohol extract	31.0	21.3	20.4	47.6	40.0	40.4
Acetone precipitate from 2	12.2	7.9	6.9	30.6	22.1	19.2
Residue of extraction	53.6	58.9	63.3	31.1	36.3	39.6

phorus in the fixing fluid seems to proceed more rapidly than in normal brains. It is possible that certain structures, such as "grapelike bodies," mucoid degeneration, mucin-like bodies, etc., which have been described in formalin-fixed brains and which stain metachromatously with toluidine blue, or red with mucin carmine, may be the result of such selective destruction of phospholipids (fig.4.). The galactolipids, which are relatively increased, stain intensely red with mucin carmine and purple with toluidine blue when thin smears of their solutions on slides are stained with these dyes. Structures that contain an abundance of galactolipids (myelin, possibly oligodendroglia) will more readily show these reactions. Un-

fortunately a great amount of effort has been spent on lipid analyses of formalin-fixed tissues. Acetone preservation should be used if such an analysis is desired.

The influence of formalin upon the solubility of lipids has also been demonstrated in other organs. Fresh livers give 33 per cent more ether and 100 per cent more alcoholic extracts than formalin-fixed livers. The ether extracts of fresh organs contain more phosphorus, cholesterol, and neutral fats than those from formalin-fixed livers (Mladenovic and Lieb).

Another influence of formalin fixation on nervous structures is represented by the change in volume. The maximum increase of approximately 10 per cent is reached after about a week of fixation, then a slight decrease sets in, with stability reached after three weeks. The binding power of brain tissue in relation to water is dependent upon the relation between proteins

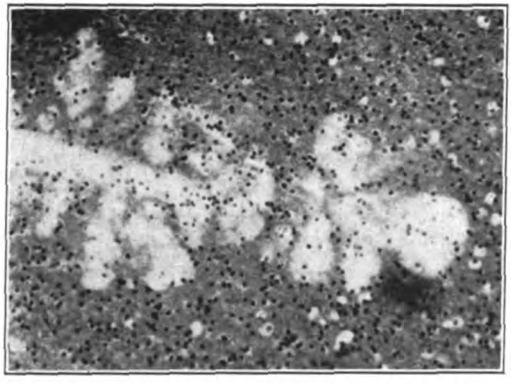


FIG. 4. "GRAPELIKE BODIES" (BUSCAINO)
Case of arteriosclerosis of brain (van Gieson stain)

and lipids. Extraction of brains with acetone and petroleum ether increases the ability to reabsorb water after desiccation. The brain of the newborn child contains a minimal amount of lipids and a high percentage (90 per cent) of water. This relation is gradually increased with growth. On theoretic grounds it may be assumed therefore that the increase in water during formalin fixation parallels the destruction of phospholipids.

Such a tendency to swell has also been described as a postmortem change in nonfixed brains, increasing with the time elapsing between death and autopsy (Ehrnrooth). The diagnosis of a brain swelling intra vitam, therefore, must take into consideration the time elapsing between death and examination of the brain. Changes in the blood urea, which is inincreased in brain swelling, and decrease in the freezing point of the plasma may be of some help in making a diagnosis. Much has been said about the

difference between edema and swelling of the brain. Edema has been defined as adsorption of water by osmosis, swelling as the colloid-chemical binding of water. Or, edema has been described as the increase of free intercellular tissue fluids, and swelling as the binding of water by the nervous tissues. Edema may be produced in inflammation or intoxication by an increased permeability of the damaged wall of the blood vessels. Increase in intracerebral and spinal fluid pressure will interfere with venous drainage; this is followed by escape of plasma through the capillary walls and leads to edema by stasis. The slowing of arterial flow will have the same effect. While edema leads to an increase in water content mainly, swelling is also accompanied by an increase in proteins and electrolytes.

Reichardt has devised a formula for the determination of *Hirnschwellung* by measuring the capacity of the skull in cubic centimeters and weighing the brain. Normally the weight of the brain in grams should be 90 per cent of the capacity of the skull (without dura) in cubic centimeters. A relationship of weight to capacity exceeding the normal range should be considered as swelling. However, the wide range in normal brains (from 84.3 to 102 per cent), and the known tendency of diseased brains or those taken after prolonged fever, alcoholic intoxication, etc., to swell more rapidly post mortem than normal ones, limit the value of such observations.

Pathologic lesions that occurred during life may show artificial changes produced by formalin fixation. The position of the head plays a role in the distribution of blood following cerebral hemorrhage; if a small amount of blood has invaded the ventricles, blood clots may sometimes be found in the tips of the posterior horns, while the anterior horns seem to be free of this, owing to the prone position of the body. When massive hemorrhages in the frontal lobes or the internal capsule break into the ventricles, the whole ventricular system, including the aqueduct and fourth ventricle, with the piarachnoid covering the pons and the base of the brain, may be filled with coagulated blood. Dissolution of the red blood cells is followed by a diffusion of hemoglobin into the region of the original hemorrhagic focus and under the influence of autolysis and formalin the red color is changed to a dark gray. For the same reason, small petechial hemorrhages may increase in size through such postmortem diffusion of hemoglobin.

Under the influence of formalin fixation, pigments are formed within the cytoplasm of ganglion cells in the neighborhood of foci of hemorrhagic softening. This granular pigment stains greenish black with toluidine blue, dark brown with hematoxylin-eosin. It seems to be hemoglobin that has become free and has penetrated through the outer border zone of the ganglion cell into the interior, following damage of the cellular membrane.

It is evident that such changes will deeply influence the staining qualities of the embedded nervous tissue. The destructive action of the formal-

dehyde upon the phospholipids is the reason for the difficulty of obtaining good myelin sheath or nuclear stains in brains that have been preserved for a year or longer. In sections stained with cresyl violet, the diffuse staining of the background in material that has been preserved for a long time in alcohol bears witness to such a process of gradual dissolution of lipid material (celloidin-embedded material therefore should be preserved in 50 per cent alcohol only). The decomposition of the phospholipids will liberate substances that have a reducing action on osmic acid and great care should be taken in the interpretation of Marchi granules in tissue that has been fixed in formalydehyde even for a short time. There is even a possibility of production of free fat granules staining with sudan III, if by reason of a preceding disease process the ground has already been prepared for the disintegration of the (hypothetic) lipin-protein compounds.

The coagulating action of most of the fixatives on the protein will produce shrinkage of the brain tissue as a whole if metallic salts are used or if this coagulation is combined with the dehydrating effect of acetone or alcohol. Not too much importance, therefore, should be attributed to pericellular or wide perivascular spaces in brains that were edematous or in infant brains. They may be due in adult brains to shrinkage of neurons following dehydration of the brain, e.g., after intravenous injections of hypertonic solutions.

If mucous material is present, in cyst formations or serous fluid, the sudden precipitation may produce all kinds of artificial structures. An illustration is the production of vacuolated areas in foci of Torula infection, which only after formaldehyde fixation become visible to the naked eye, owing to the precipitation of the mucus surrounding the yeast cells.

Any change in the osmotic equilibrium between the fixing fluid and the interior of the cell will tend to produce swelling or shrinkage with ensuing artificial changes of the histologic structure. After preservation in hypertonic solutions the disintegration of the nucleus may simulate "inclusion bodies." Hypotonic solutions or simple distilled water may produce disintegration of the Nissl bodies, with distortion of the cytoplasm (figs. 5, 6).

EFFECT OF ALCOHOL FIXATION

If alcohol is used as a fixative, the chemical changes that are produced by the phospholipid-splitting action of formaldehyde will be avoided. But the dissolution of the different lipoids will prevent subsequent staining of the myelin sheaths. Autolysis will not be entirely suppressed in the deeper layers of a block of tissue on account of the coagulating action of the alcohol in the outer zones and, therefore, retarded diffusion. In edematous brains and those of young children many artefacts may be produced by sudden

dehydration. These will be described later. Since the time of Nissl the "equivalent picture" (*Aequivalentbild*) of the chromatin bodies of the

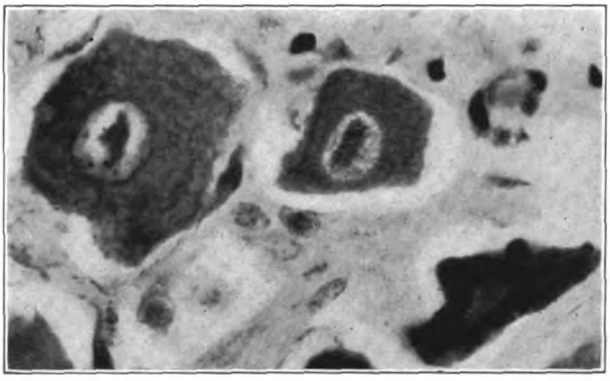


FIG. 5. EFFECT OF HYPERTONIC SOLUTIONS ON NERVE CELLS

Spinal root ganglion of turtle, kept in 5 per cent sodium chloride for 30 minutes, fixed in formalin, and stained with methylene blue–eosin. Chromatin of nucleus has shrunk away from nuclear wall and forms dense, dark-staining mass around nucleolus. Isolated round nuclear inclusions are seen

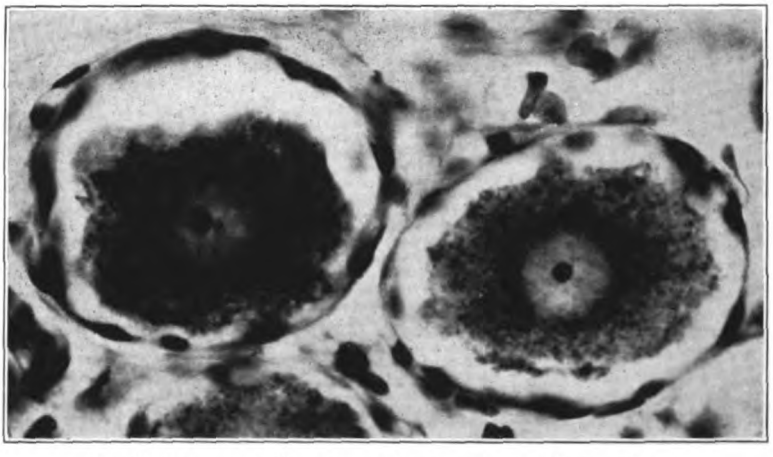


FIG. 6. EFFECT OF HYPOTONIC SOLUTIONS ON NERVE CELLS

Spinal root ganglion of cat, kept in distilled water for 30 minutes, fixed in formalin, and stained with cresyl violet. Cell cytoplasm has shrunk away from capsule. Nucleus is swollen

ganglion cells has been judged only from alcohol-fixed material. But Nissl himself pointed out that it is only in fresh animal material that

reliable normal histologic pictures can be obtained. Those who still adhere in an orthodox way to his first publications forget that only very seldom is alcohol fixation followed by the originally prescribed technic, i.e., cutting of the alcohol-fixed block, which is not embedded, but simply glued to a wooden block with gum arabic.

Equivalent pictures may be obtained after fixation by any method, provided that the normal control and the pathologic tissue are treated in the same way and that the time elapsing between death and fixation is the same in each case. The essential point is that the investigator be familiar with the histologic changes that may be produced by postmortem changes and by application of a given method of fixation.

Corpora Amylacea and Amyloid Bodies

At this point we may describe some concretions that are found in the central nervous system and that may be formed as a postmortem process by precipitation of colloidal material or intra vitam by physiologic degeneration of axis-cylinders (Saxén). They are referred to as corpora amylacea or amyloid bodies. The first name is taken from the laminated bodies first described in the prostate by Morgagni in 1723, in which Virchow demonstrated blue staining with iodine, and which were called by Purkinje "corpora amylacea." If one studies the neurologic literature it seems that both qualities, the laminated form and the staining reaction with iodine, were found combined or isolated in different structures that were called corpora amylacea. One type consists of round bodies surrounded by a pale-staining zone, as found in the posterior columns in tabes dorsalis, around the ventricles in multiple sclerosis, in the neighborhood of foci of softening in old arteriosclerotic cases, etc.; these stain dark blue with Delafield's hematoxylin or cresyl violet, and black in Bielschowsky preparations. The fact that thrombosed blood vessels in these foci are incrusted with a similarly staining material suggests that they are formed by precipitation of colloidal substances from the tissue fluids. Other forms are laminated structures that seem to have formed around dead cells, particles of nerve fibers, or thrombosed capillaries. In the fluids of cerebellar astrocytomatous cysts or cysts of the choroid plexus, there may be found laminated bodies that stain in van Gieson preparations but not with cresyl violet.

In the meninges of old people are found other, similar structures incrusted with calcium salts; these are the psammomatous bodies, which are also characteristic for certain types of meningiomas. More closely related to the corpora amylacea of the prostate is the "acervulus"—the laminated structures of the pineal gland. In view of these different types, of different etiology, it would be advisable to drop the term corpora amylacea al-

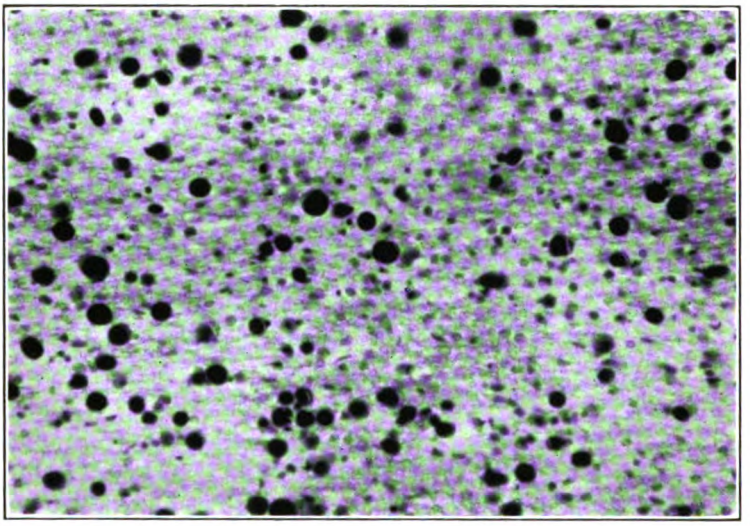


FIG. 7. CORPORA AMYLACEA (AMYLOID BODIES)
Posterior columns in tabes dorsalis. Hematoxylin-eosin stain

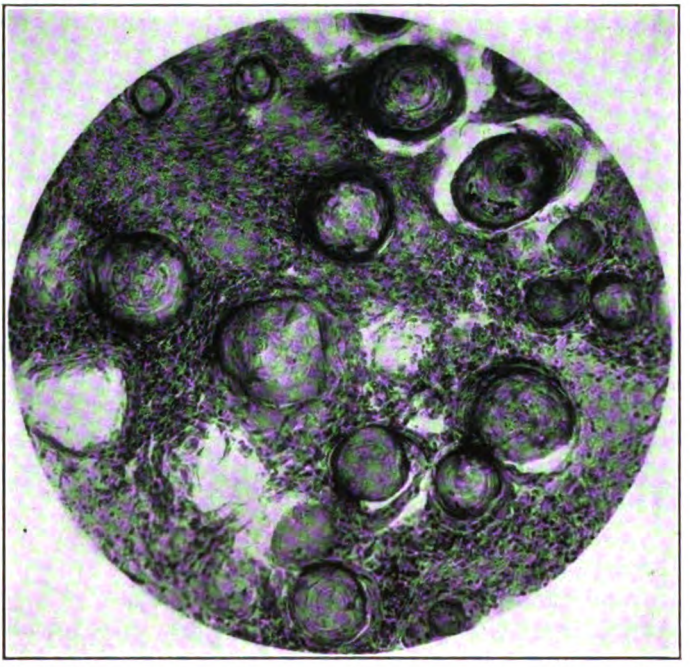


FIG. 8. PSAMMOMATOUS BODIES IN MENINGIOMA (VAN GIESON STAIN)

together, or at least to refrain from the attempt to reconstruct a common etiology (figs. 7, 8).

II

DISEASES OF THE NEURON

THE PROFOUND change that has taken place in the evaluation of histologic changes of ganglion cells will be immediately brought to mind if one compares the publications of the late nineties (Nissl, 1896) and the beginning of this century with modern investigations on the effect of anemia of short duration on these cells. In the earlier work an effort was made to correlate etiologic and time factors with different histologic pictures. Modern experiments have demonstrated that, side by side, "acute" and "chronic" neuronal disease may be found following the interruption of blood supply in a cat's brain for a few minutes; or changes that had been thought to require days may be found in the region of a needle puncture of the medulla oblongata that resulted in immediate death of the animal. Experimental experience has taught us that toxins may produce primary vascular damage and that under such circumstances the neuronal disease is only secondary to the nutritive disturbances. Recent attempts to correlate, in a large amount of human autopsy material, time lapse and histologic appearance of ganglion cell changes, have been a complete failure.

Besides the time-honored staining methods, microchemical analytic methods have more recently been employed for the study of cytologic changes of the neuron. Normally the cortex of the newborn child is rich in minerals, mostly concentrated in the nuclei. In the adult brain a shifting of these minerals takes place, the cytoplasm and dendrites of pyramidal, Purkinje, and anterior horn cells being rich in minerals, while the nuclei contain only minimal amounts. Disease of the neuron may lead to complete demineralization, e.g., in anemic softening and within the plaques of disseminated sclerosis. While collagenous fibers contain metal oxides, elastic fibers are free of minerals. Hypermineralization is found in brain tumors and in inflammatory foci (Alexander and Myerson).

The well established names given to the different histologic pictures of neuronal changes should be preserved as a matter of convenience and for mutual understanding of the condition that is described. But we should always be conscious of the fact that the suffixes of these terms do not have any bearing upon the etiology of the disease.

The following descriptions refer to sections from alcohol-fixed material stained with cresyl violet, or formalin-fixed material with silver impregna-

TABLE 5.—*Pathologic Changes of Neurons*

Type of Change	Cytoplasm	Nuclei	Conditions in Which Described
Acute neuronal disease (acute swelling) (figs. 9, 10)	swelling of cell and processes; Nissl bodies granular, later dissolved; cytoplasm stained homogeneously; neurofibrils unchanged; as end stage, shadow formation	preserved, with vacuolization; linin network stained; (mitotic figures in neuroglia)	various infections and intoxications; experimental states in overheated animals
Chronic neuronal disease (shrinkage) (fig. 11)	shrinkage of cell; dark-staining cytoplasm; dendrites stained darkly, neurofibrils diffusely, partly unstained; main dendrite tortuous; as end stage, sclerosis	elongated, triangular, or shrunken; darkly stained; nucleolus large, dark	various acute and chronic diseases—sometimes confined to neurons of second and third layer of cortex; traumatic and postmortem changes
Severe neuronal disease (liquefaction) (figs. 12–15)	rapid dissolution; formation of pale-staining, ringlike granules; neurofibrils not visible; as end stage, complete dissolution of cell	shrunken, containing dark-stained granules; nucleolus eccentric	acute infections and intoxications; swelling of brain
Ischemic neuronal disease (coagulation) (figs. 16–18)	loss of staining qualities; uniformly pale blue appearance; elongated, triangular; as end stage, liquefaction with final replacement by glitter cells, coffin formation by glia cells, or incrustation with calcium salts	shrunken; triangular; dark-stained; nucleolus large, eccentric	foci of anemic softening
Edematous neurons (figs. 6, 19)	outer zone of cytoplasm ringlike, dark-stained, separated by pale area from nucleus; granulation of neurofibrils	shrunken, karyolytic; nucleolus preserved	edematous brains; periphery of anemic foci; alcohol-fixed children's brains
Fatty degeneration (fig. 20)	mild swelling; alveolar or granular appearance; with fat stains, diffuse infiltration of lipoid granules, extending into dendrites	small, centrally located, dark-stained	various infections and intoxications of fulminant type
Pigment atrophy (fig. 21)	lipofuscin increased; alveolar appearance; with fat stains, granules localized mostly at one pole, producing bulging of cell	prominent, well preserved; in more advanced cases, shrunken	old age; senile dementia; general paresis; alcoholism
Retrograde degeneration (central chromatolysis) (figs. 22, 23)	central chromatolysis; swelling; later, homogeneous staining; central neurofibrils dustlike, preserved in periphery; as end stage, repair to normal, or vacuolization, shadow formation	swollen, pale, eccentric; nucleolus dark, prominent	experimental lesions of axis-cylinder; amyotrophies; various intoxications

tion (Bielschowsky, Davenport). Table 5 sets forth the different diseases in which such changes have been described. This does not exclude the

possibility that changes such as the "chronic ganglion cell disease" found in acute anemia may be seen in many other conditions.

These short descriptions follow in principle the outlines given by Spielmeyer. He emphasizes a strict adherence to the definitions of the different diseases of the neurons as they have been created by Nissl. The acute swelling is described as "swelling of the ganglion cells with its processes, dissolution of the basophilic substance, staining of the cytoplasm and dendrites together with parts of the nuclear linin network. The neurofibrils are well preserved. There are progressive changes with mitotic figures and regressive changes of the neuroglia. The ganglion cell disease is generally spread throughout the brain." The disease is rare and should be differentiated from manifold forms of acute swelling of the neuron with dissolution or fine granulation of the chromatin bodies as seen in different acute diseases, in which, however, the progressive glia changes and the staining of the nuclear linin network are absent (figs. 9, 10).

The "chronic ganglion cell disease" (shrinkage) has been referred to above, and it has been pointed out that the picture of hyperchromatic staining, with shrinkage of the neuron and dendrites, may be seen in very acute lesions; it may also be produced post mortem by traumatization of the brain. The outer layers of the cortex of a laboratory animal following formalin fixation will show "chronic ganglion cell disease," a fact that frequently has been overlooked (fig. 11).

The severe disease of the neuron is described as "rapid dissolution of the cytoplasm with formation of pale-staining, frequently ringlike granules, shrinkage and dark staining of the nucleus, and the dissolution or melting away of the cell body." It is accompanied by ameboid transformation of neuroglia with hyperchromatosis and karyorrhexis of the nuclei (figs. 12–15).

The ischemic disease of the cortical neurons is likened to the homogenization of the cerebellar Purkinje cells (figs. 16–18). The cytoplasm is homogeneous and pale-staining; the nucleus is shrunken and the nucleolus vacuolated. While, according to Spielmeyer, the ischemic disease of the neuron is produced only by circulatory disturbances, these changes of the Purkinje cells may be produced by a variety of disease factors.

Far advanced pigment atrophy is often difficult to differentiate from fatty degeneration. Microscopic examination of a section stained slightly with cresyl violet may help to demonstrate the greenish yellow lipofuscin (figs. 20, 21).

Normal Variations and Postmortem Changes

In order to be able to evaluate the pathologic significance of the various diseases of the neuron, two facts should always be remembered: (1) that

TABLE 5.—*Pathologic Changes of Neurons*

Type of Change	Cytoplasm	Nuclei	Conditions in Which Described
Acute neuronal disease (acute swelling) (figs. 9, 10)	swelling of cell and processes; Nissl bodies granular, later dissolved; cytoplasm stained homogeneously; neurofibrils unchanged; as end stage, shadow formation	preserved, with vacuolization; linin network stained; (mitotic figures in neuroglia)	various infections and intoxications; experimental states in overheated animals
Chronic neuronal disease (shrinkage) (fig. 11)	shrinkage of cell; dark-staining cytoplasm; dendrites stained darkly, neurofibrils diffusely, partly unstained; main dendrite tortuous; as end stage, sclerosis	elongated, triangular, or shrunken; darkly stained; nucleolus large, dark	various acute and chronic diseases—sometimes confined to neurons of second and third layer of cortex; traumatic and postmortem changes
Severe neuronal disease (liquefaction) (figs. 12–15)	rapid dissolution; formation of pale-staining, ringlike granules; neurofibrils not visible; as end stage, complete dissolution of cell	shrunken, containing dark-stained granules; nucleolus eccentric	acute infections and intoxications; swelling of brain
Ischemic neuronal disease (coagulation) (figs. 16–18)	loss of staining qualities; uniformly pale blue appearance; elongated, triangular; as end stage, liquefaction with final replacement by glitter cells, coffin formation by glia cells, or incrustation with calcium salts	shrunken; triangular; dark-stained; nucleolus large, eccentric	foci of anemic softening
Edematous neurons (figs. 6, 19)	outer zone of cytoplasm ringlike, dark-stained, separated by pale area from nucleus; granulation of neurofibrils	shrunken, karyolytic; nucleolus preserved	edematous brains; periphery of anemic foci; alcohol-fixed children's brains
Fatty degeneration (fig. 20)	mild swelling; alveolar or granular appearance; with fat stains, diffuse infiltration of lipoid granules, extending into dendrites	small, centrally located, dark-stained	various infections and intoxications of fulminant type
Pigment atrophy (fig. 21)	lipofuscin increased; alveolar appearance; with fat stains, granules localized mostly at one pole, producing bulging of cell	prominent, well preserved; in more advanced cases, shrunken	old age; senile dementia; general paresis; alcoholism
Retrograde degeneration (central chromatolysis) (figs. 22, 23)	central chromatolysis; swelling; later, homogeneous staining; central neurofibrils dustlike, preserved in periphery; as end stage, repair to normal, or vacuolization, shadow formation	swollen, pale, eccentric; nucleolus dark, prominent	experimental lesions of axis-cylinder; amyotrophies; various intoxications

tion (Bielschowsky, Davenport). Table 5 sets forth the different diseases in which such changes have been described. This does not exclude the

possibility that changes such as the "chronic ganglion cell disease" found in acute anemia may be seen in many other conditions.

These short descriptions follow in principle the outlines given by Spielmeyer. He emphasizes a strict adherence to the definitions of the different diseases of the neurons as they have been created by Nissl. The acute swelling is described as "swelling of the ganglion cells with its processes, dissolution of the basophilic substance, staining of the cytoplasm and dendrites together with parts of the nuclear linin network. The neurofibrils are well preserved. There are progressive changes with mitotic figures and regressive changes of the neuroglia. The ganglion cell disease is generally spread throughout the brain." The disease is rare and should be differentiated from manifold forms of acute swelling of the neuron with dissolution or fine granulation of the chromatin bodies as seen in different acute diseases, in which, however, the progressive glia changes and the staining of the nuclear linin network are absent (figs. 9, 10).

The "chronic ganglion cell disease" (shrinkage) has been referred to above, and it has been pointed out that the picture of hyperchromatic staining, with shrinkage of the neuron and dendrites, may be seen in very acute lesions; it may also be produced post mortem by traumatization of the brain. The outer layers of the cortex of a laboratory animal following formalin fixation will show "chronic ganglion cell disease," a fact that frequently has been overlooked (fig. 11).

The severe disease of the neuron is described as "rapid dissolution of the cytoplasm with formation of pale-staining, frequently ringlike granules, shrinkage and dark staining of the nucleus, and the dissolution or melting away of the cell body." It is accompanied by ameboid transformation of neuroglia with hyperchromatosis and karyorrhexis of the nuclei (figs. 12–15).

The ischemic disease of the cortical neurons is likened to the homogenization of the cerebellar Purkinje cells (figs. 16–18). The cytoplasm is homogeneous and pale-staining; the nucleus is shrunken and the nucleolus vacuolated. While, according to Spielmeyer, the ischemic disease of the neuron is produced only by circulatory disturbances, these changes of the Purkinje cells may be produced by a variety of disease factors.

Far advanced pigment atrophy is often difficult to differentiate from fatty degeneration. Microscopic examination of a section stained slightly with cresyl violet may help to demonstrate the greenish yellow lipofuscin (figs. 20, 21).

Normal Variations and Postmortem Changes

In order to be able to evaluate the pathologic significance of the various diseases of the neuron, two facts should always be remembered: (1) that

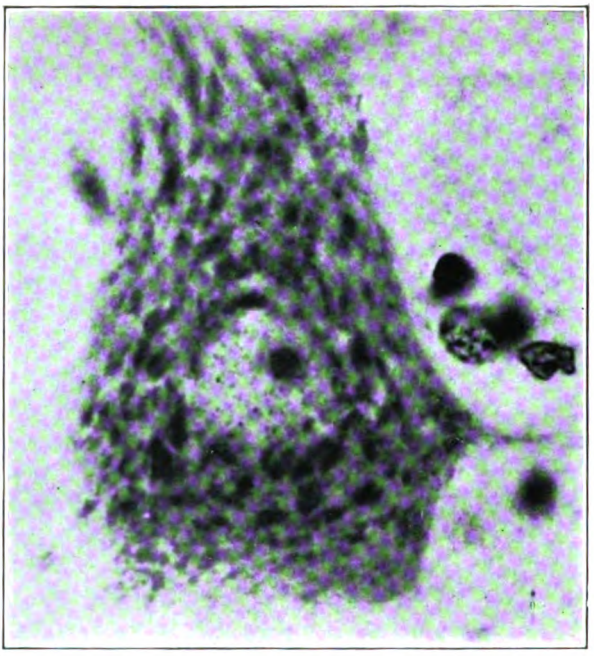


FIG. 9

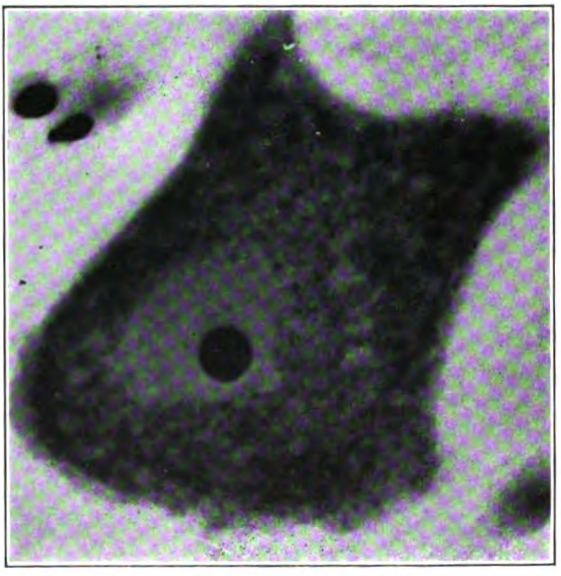


FIG. 10

FIGS. 9, 10. ACUTE SWELLING OF ANTERIOR HORN CELLS IN DOG, AFTER THREE HOUR ETHER NARCOSIS

Nissl granules have dustlike appearance. Nucleus and nucleolus are swollen. Cresyl violet stain. Figure 9, normal cell. Figure 10, diseased cell

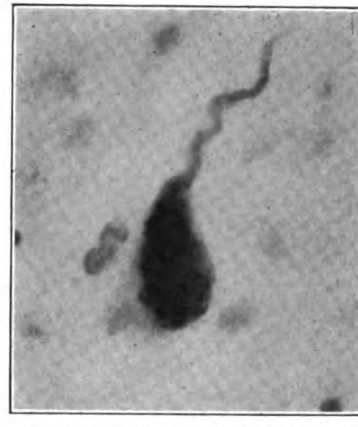


FIG. 11. CHRONIC DISEASE OF NEURON (SHRINKAGE)

Anterior horn cell in case of arteriosclerosis. Cresyl violet stain. Cell is shrunken. Nissl bodies are clotted and stained dark blue. Main dendrite shows corkscrew form and is prominently stained

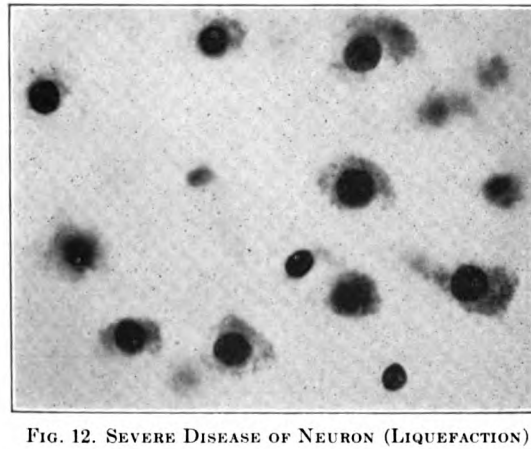


FIG. 12. SEVERE DISEASE OF NEURON (LIQUEFACTION)

Cortical neurons in case of purulent meningitis in child. Cresyl violet stain. Outlines of cells are indistinct. Cytoplasm is granulated or stained homogeneously pale. Nucleus is hyperchromatic, containing dark-stained granules

certain of these pictures may also be found under normal conditions, and (2) that sometimes they may be produced by postmortem changes.

One of the most difficult tasks confronting the neuropathologist is to decide whether the number and architectonic arrangement of the neurons in

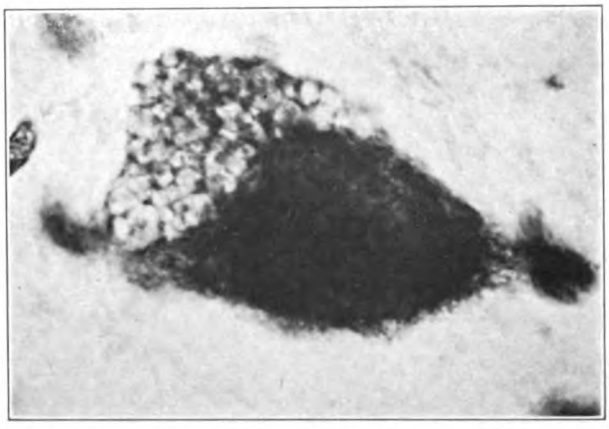


FIG. 13. SEVERE DISEASE OF NEURON (VACUOLIZATION)

Midbrain neuron in case of epidemic encephalitis (St. Louis). Cresyl violet stain. Cell shows foamlike vacuolization at one pole, with hyperchromatic staining of nucleus and of other half of cytoplasm

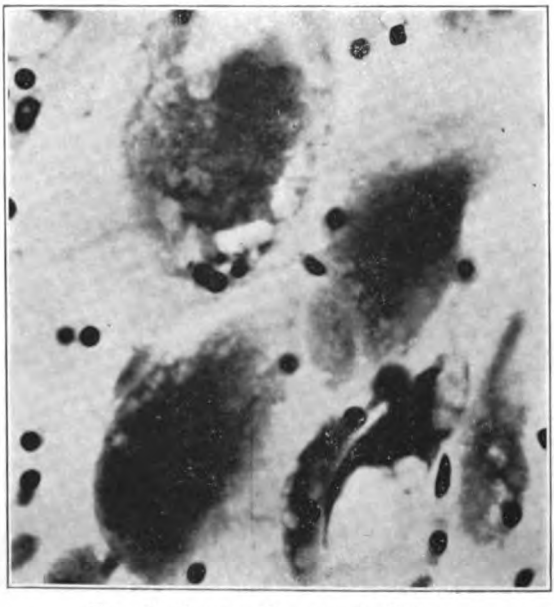


FIG. 14. SEVERE DISEASE OF NEURON

Postmortem changes in dentate nucleus of normal rat brain after preservation in ice box for 24 hours. Outer margin of cell shows large vacuoles. Central cytoplasm is darkly stained, granular

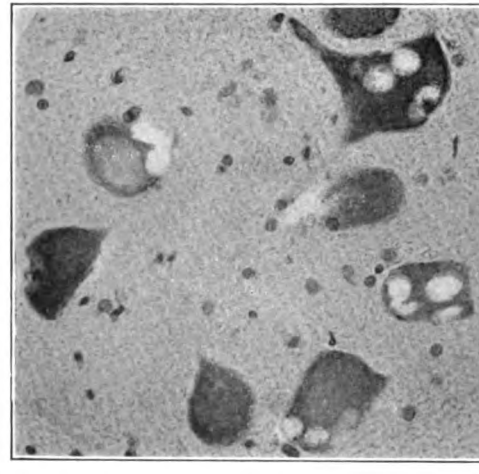


FIG. 15. VACUOLE FORMATION IN SWOLLEN ANTERIOR HORN CELLS OF LUMBAR SEGMENT

Case of amyotrophic lateral sclerosis. Hematoxylin-eosin stain

FIG. 16. ISCHEMIC DISEASE OF NEURON

Cortical neuron in neighborhood of organized focus of anemic softening. Cresyl violet stain. Cytoplasm of cell stained homogeneously pale. Nucleus is pointed, dark-stained. Nucleolus is large, intensively stained

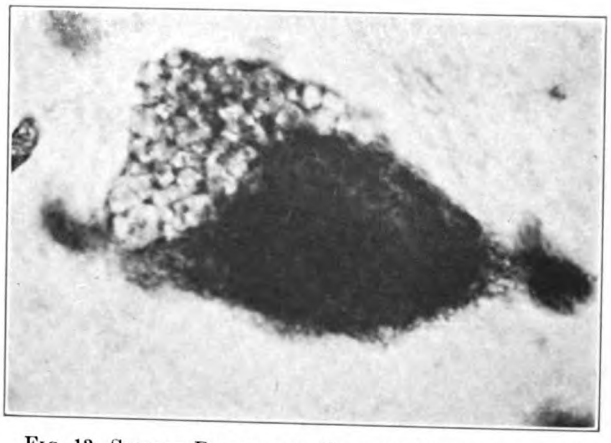


FIG. 13. SEVERE DISEASE OF NEURON (VACUOLIZATION)

Midbrain neuron in case of epidemic encephalitis (St. Louis). Cresyl violet stain. Cell shows foamlike vacuolization at one pole, with hyperchromatic staining of nucleus and of other half of cytoplasm

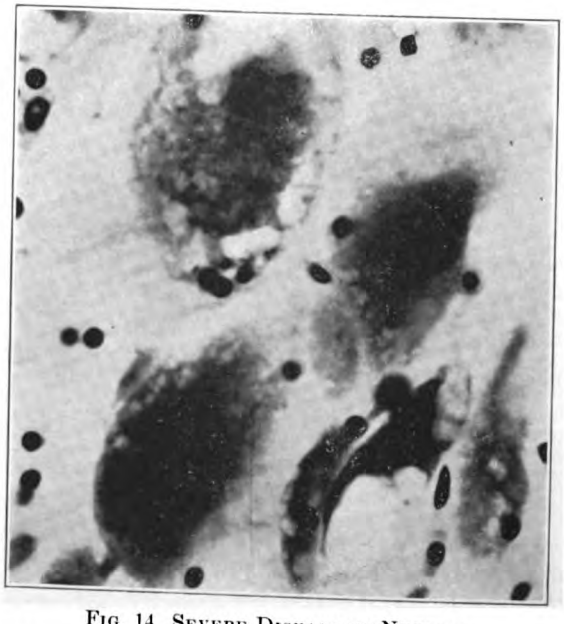


FIG. 14. SEVERE DISEASE OF NEURON

Postmortem changes in dentate nucleus of normal rat brain after preservation in ice box for 24 hours. Outer margin of cell shows large vacuoles. Central cytoplasm is darkly stained, granular

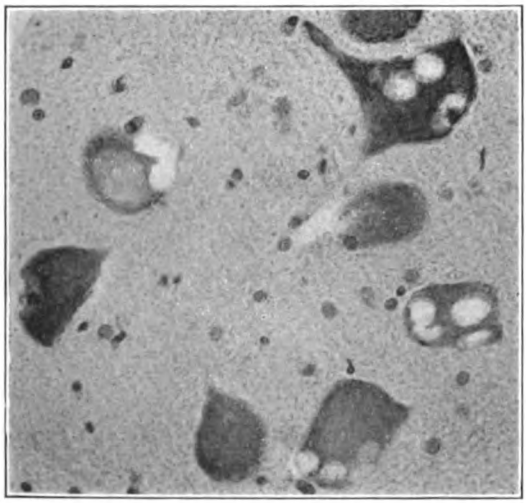


FIG. 15. VACUOLE FORMATION IN SWOLLEN ANTERIOR HORN CELLS OF LUMBAR SEGMENT

Case of amyotrophic lateral sclerosis. Hematoxylin-eosin stain

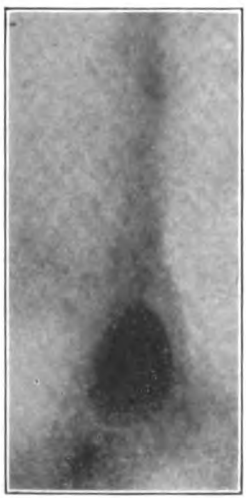


FIG. 16. ISCHEMIC DISEASE OF NEURON

Cortical neuron in neighborhood of organized focus of anemic softening. Cresyl violet stain. Cytoplasm of cell stained homogeneously pale. Nucleus is pointed, dark-stained. Nucleolus is large, intensively stained

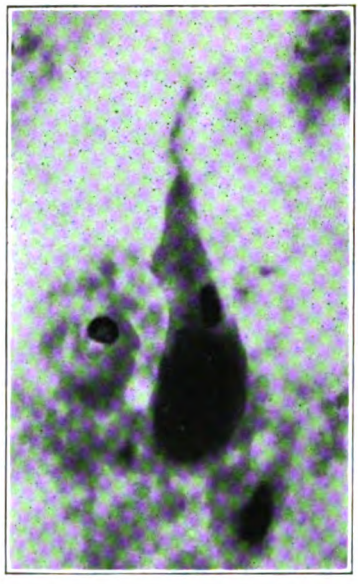


FIG. 17. INFILTRATION WITH BLOOD PIGMENT

Neurons and glia cells in neighborhood of hemorrhage in case of scarlatina. Cresyl violet stain. Cytoplasm stained homogeneously greenish

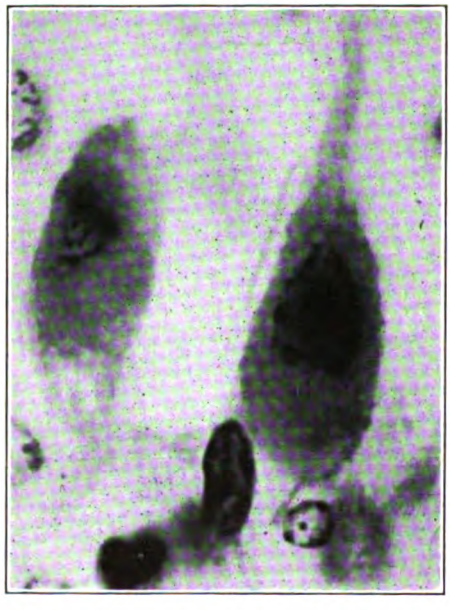


FIG. 18. HOMOGENEOUS STAINING OF PURKINJE CELLS (*Homogenisierende Zellerkrankung*)

Acute hemorrhage into cerebellum. Cresyl violet stain. Nissl bodies have disappeared, cytoplasm is pale-stained. Ring of granular chromatin surrounds shrunken nucleus

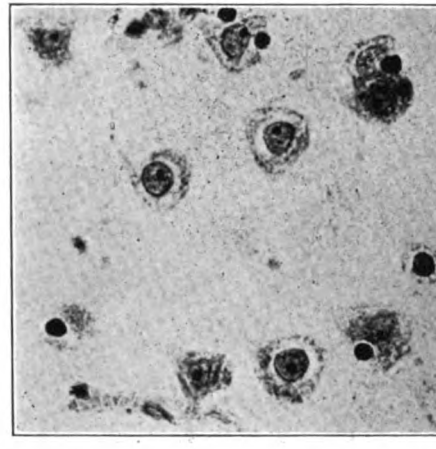


FIG. 19. EDEMATOUS GANGLION CELLS

Case of meningitis in child. Cresyl violet stain. Cytoplasm shrunken away to outer zone. Nucleus swollen

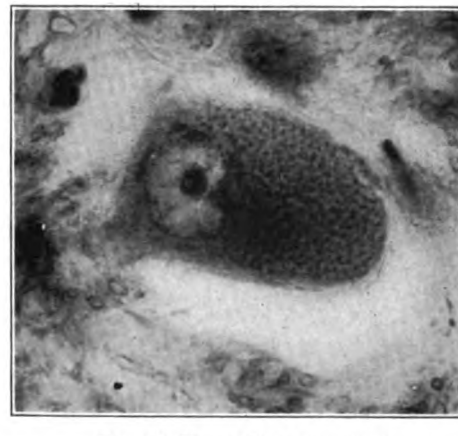


FIG. 20. FATTY DEGENERATION

Anterior horn cell of lumbar spinal cord in case of amyotrophic lateral sclerosis. Sudan III stain. Cytoplasm is filled with large fat granules stained brilliant red. Nucleus is pushed eccentrically, its membrane is folded

a given area of the cerebral cortex are normal. The extreme individual variations and the changes of old age should make one extremely cautious about making statements such as "number of neurons diminished" or "irregular distribution of neurons in a given area." Caution also should be

exercised in applying the diagnosis of *Lückenfelder* or *Ganglienzellausfall*, i.e., areas devoid of neurons. The history of neuropathology affords many examples in which statements like these, loosely applied, have been made the basis of assumption of an organic etiology of certain psychoses.

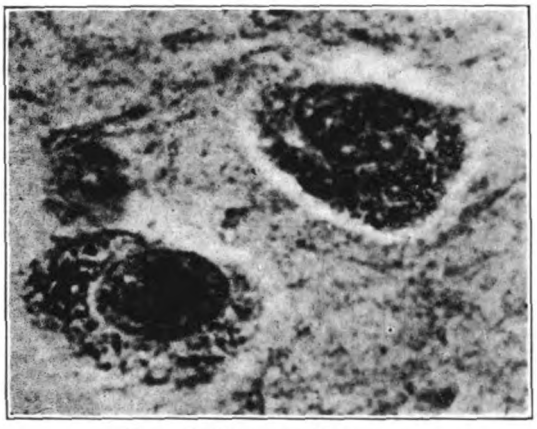


FIG. 21. PIGMENT ATROPHY

Neurons from deeper layers of frontal cortex in arteriosclerosis of brain. Sudan III stain. Lipofuscin is increased, replacing two-thirds and more of cytoplasm. It has been transformed into large droplets staining intensively with sudan III

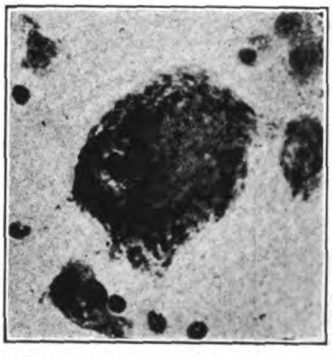


FIG. 22. CENTRAL CHROMATOLYSIS (RETROGRADE DEGENERATION)

Neuron from nucleus ambiguus in case of amyotrophic lateral sclerosis. Cresyl violet stain. Nissl bodies well preserved at periphery of swollen cell, dustlike in center. Nucleus situated eccentrically and mildly swollen

Neurons of Clarke's column, of the nuclei of Goll and of Burdach, of the raphe medullae oblongatae, of the substantia reticularis of the pons, and of the mesencephalic nucleus of the fifth nerve, present under normal conditions a picture resembling that of central chromatolysis with eccentric position of the nucleus (figs. 22, 23). In persons who did not manifest

neurologic diseases during life, there may be found anterior horn cells or ganglion cells of the lower layers of the cortex that are shrunken, stain darkly, and resemble cells with chronic neuronal disease. The lipofuscin (lipochrome) is regularly increased in the neurons of older persons and may occupy one-half or more of the cell. Even in younger persons the amount of lipofuscin varies considerably in different individuals; both pontine and bulbar nuclei offer many examples of a normally increased amount, as shown in the olivary nuclei.

In the absence of simultaneous progressive glia reactions or mesenchymal changes it is sometimes impossible to state whether acute swelling, liquefaction, vacuolization, or edema was produced intra vitam or post mortem. A well preserved nucleus usually speaks in favor of the latter process, while karyorrhexis or karyolysis is indicative of a change during

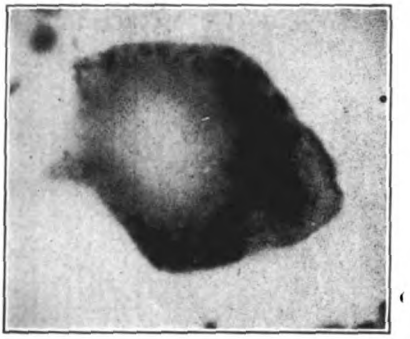


FIG. 23. CLARKE'S COLUMN CELL, DORSAL SEGMENT OF SPINAL CORD
Normal cell presenting picture resembling central chromatolysis. Cresyl violet stain

life. Other nuclear changes that point to a severe disease of the neuron are shrinkage, hyperchromatosis, or fragmentation of the nucleolus.

The condition in which the cytoplasm of the Purkinje cell becomes pale and uniformly stained, resembling the picture of ischemic neuronal disease, may be combined with a pale nucleus and enlarged nucleolus or with a shrunken, dark-staining nucleus. Both conditions are considered to be of intra vitam origin (fig. 18).

SPECIFIC REACTIONS

The question has frequently been discussed whether some neurons react in a specific way and whether some areas have a predilection for certain neuronal diseases. The homogeneous transformation of the Purkinje cells that may be seen in diseases of different etiology, is an example of such a specific cellular reaction. The neurons of the second and third cortical

layers have a tendency to shrink, presenting the picture of chronic disease of the neuron. The Betz cells of the precentral area react usually with central chromatolysis in response to a number of etiologic factors. The neurons of the striatum and pallidum show under different conditions a tendency to transformation of their cytoplasm into numerous basophilic globules. The pigmented cells of the substantia nigra and of the locus caeruleus lose their pigment, which is found in the form of fine black granules in the surrounding tissues. Other neurons will simply fade away and leave behind a structureless shadow. Such a reaction has been observed experimentally following transection of the hypothalamic-hypophyieal tract in the supra-optic nuclei. The reactive gliosis is very mild or may even be absent, resembling the homogenization of the pigmented cells of the substantia nigra in cases of idiopathic parkinsonism (fig. 202).

The earlier work on neuronal disease was mostly concerned with cortical neurons. Later, detailed work on the cerebellum (Scherer) and on the vegetative nuclei of the brain (Gagel) emphasized that each neuron reacts with the production of a definite pathologic cellular pattern, regardless of the nature of the etiologic factor producing the change. Comparative studies of neuronal diseases of the corpus striatum (Berlucchi) have demonstrated that similarity of histopathology does not always mean similarity of the pathologic physiology and clinical picture.

One of the few specific neuronal diseases is amaurotic family idiocy, and in this the etiologic agent does not act from without upon the cell, but from within in the form of a disturbance of the lipoid metabolism of the neuron itself (figs. 24, 204, 205).

The pictures that have been described represent changes of the cytoplasm and the nuclei. Under certain conditions, other cellular structures may be more affected by a disease process. Disease of the neurofibrils is a prominent feature in many cases of senile dementia and of Alzheimer's disease (fig. 25). In Bielschowsky preparations, usually in the frontal poles and the cornu Ammonis, one sees the prominent neurofibrils stained black, forming loops, baskets, or twisted cords. Similar changes may be seen in such cases in the glia, in the form of small rings and long threads, resembling the neuronal changes. According to Spielmeyer, the impregnation of the fibrils with argyrophile deposits is responsible for the intense staining. These deposits are the same as those found in the senile plaques. However, we are no longer so sure about the specificity of Alzheimer's *Fibrillenerkrankung*. It has even been claimed that the crumbling and thickening of the intracellular neurofibrils can be produced post mortem. Others have described such fibrillar changes in postencephalitic disease.

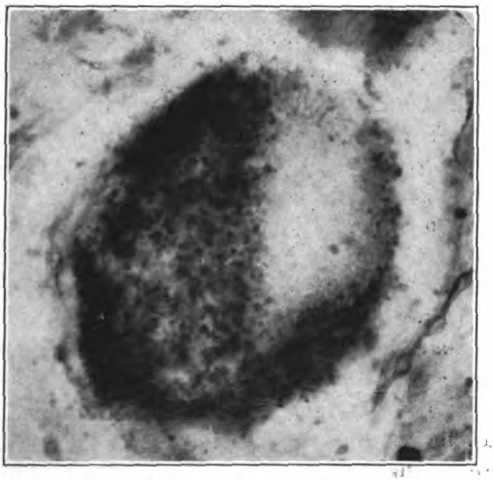


FIG. 24. AMAUROTIC FAMILY IDIOCY

Anterior horn cell, lumbar spinal cord. Iron hematoxylin stain. Formation of coarse granules, staining black

FIG. 25. ALZHEIMER'S DISEASE

Basket-like formation of neurofibrils in cortical neuron. Bielschowsky stain

INCRUSTATIONS

Incrustations with small globules or platelets supposed to be calcium salts have been described as the end stages of ischemic neuronal disease, of

sclerotic neurons in the neighborhood of abscess formation, or in degenerative diseases. In the region of hemorrhagic foci, blood pigments may be found in neurons (fig. 17). In rare cases large globoid bodies have been found embedded in the cytoplasm. They have been described as argyrophile by Spielmeyer in a case of muscular dystrophy combined with dementia. Lafora and Westphal found in myoclonus epilepsy round bodies in the neurons that gave the staining reactions of amyloid.

Vacuole formation may be found in the interior of ganglion cells under various conditions. They may be produced artificially by the dissolution of fatty substances in degeneration during the process of embedding. They are formed by liquefaction of the cytoplasm in severe neuronal disease or by postmortem changes, giving the cell a foamy appearance (figs. 13, 14). They may indicate cyst formation, accumulation of fluid within the cell during the process of digestion of intracellular inclusions. Spielmeyer has pointed out that the latter sharply defined spaces are not always indicative of neuronal disease (fig. 15).

Lipoids

Frequently the attempt has been made to determine the chemical changes that occur in diseased neurons with the help of different staining reactions. The method that is most frequently applied is staining with sudan III, scarlet red or, more recently, with oil red O in order to demonstrate "fatty degeneration." Neutral fats and the esters of cholesterol are stained brilliant red, while free cholesterol and the lipids (phosphatides and cerebrosides) do not stain. The lipochrome pigment stains more orange-red with these dyes. When the amount of this pigment is increased in old age or in pigment atrophy it assumes a dark red color, indicating a liberation of neutral fats or cholesterol esters. This pigment consists of a protein-like ground substance into which fat and other lipids are intermixed. The yellow color is part of the basic protein substance. The staining property of Nissl granules disappears in alcoholic solutions, but that of the lipofuscin does not. Osmic acid stains all the lipoids. After treatment with potassium bichromate, however, only neutral fat and mixtures of cholesterol with free fatty acids are stained. According to Lorrain Smith, nile blue stains fatty acids blue, neutral fats pink. Another means of differentiating between the various lipoids is the test for solubility. Table 6 gives some examples that may help to determine the chemical make-up of the "fat" in degenerated neurons.

It should always be remembered that the lipoids of the neurons as well as those of the myelin sheath are complex mixtures, partly forming emulsions, partly in closer chemical connection with the proteins of the cytoplasm. Fixation with formaldehyde changes profoundly their colloidal

make-up and their solubility. Therefore, micro-analytic studies should be carried out only on frozen sections of fresh, unfixed material. Even under such conditions one should consider autolytic liberation of lipoid substances in neurons already diseased. The same of course applies to the idea that micro-incineration will reveal the true intra vitam distribution of the different inorganic compounds within the living cell. The violent fluid currents arising when the cellular membrane is suddenly coagulated under the influence of formalydehyde or at the temperature of frozen carbon dioxide will of course destroy the physiologic pattern of the inorganic salts. The most one can expect is to obtain an equivalent picture by comparing sections from normal material with the pathologic.

The dark blue staining of incrustations of ganglion cells with hematoxylin has always been interpreted as a reaction with calcium salts. More

TABLE 6.—*Staining Reactions and Solubility of Different Lipoids**

	Scarlet Red	Double Refraction	Osmic Acid	Osmic Acid after Bichromate	Solubility in Cold		
					Acetone	Alcohol	Chloroform
Neutral fats	+	−	+	+	+	+	+
Cholesterol	−	+	+	−	+	+	+
Cholesterol esters	+	+	+	−	−	−	+
Phosphatides	−	+	+	−	−	+	+
Cerebrosides	−	+	+	−	−	−	+
Cholesterol and fatty acid mixtures	+	+	+	+	+	+	+

* From HURST, E. W.: A study of the lipoids in neurogenic degeneration. Brain *48*: 1, 1925.

recent investigations (Cameron), however, have taught us that this staining reaction is not specific and may also indicate the presence of iron. Alizarin is a more reliable indicator, especially for recently deposited calcium phosphate or carbonate.

GLYCOGEN AND AMYLOID

Glycogen is not present in normal ganglion cells. Under certain pathologic conditions (infections, diabetic coma) it may be demonstrated by the staining reaction with iodine or carmine in droplet form around the vessels of the gray matter and around or within glia cells.

It is doubtful whether amyloid occurs in neurons. The iodine staining reaction of the globular bodies described by Lafora and Westphal in myoclonus epilepsy does not by itself prove the chemical identity with amyloid (chondroitin-sulphuric acid-protein). Besides, in amyloid degeneration of other organs, this substance is found extracellularly.

III

THE GLIA AND ITS PATHOLOGY

At present, modern methods of silver impregnation have resulted in differentiation between three different glial elements: (1) astrocytes (classic glia, macroglia); (2) oligodendroglia (*oligos*, "few" [dendrites]); (3) microglia (Hortega cells, third element, mesoglia).

Astrocytes

Astrocytes occur in different forms, the protoplasmic and the fibrous type. The protoplasmic type is found in the gray, the fibrous type more frequently in the white matter. The first has only a small amount of cytoplasm, sending out numerous tortuous processes. The second has special, fine fibers that seem to be formed independently of the cytoplasm and that do not branch or form anastomoses. In the neighborhood of blood vessels, larger elements send off one or more thick processes forming T-like endings or feet that, taken together, form a membrane around the connective tissue sheath of the vessels (fig. 27). Under normal conditions the astrocytes are the framework of the central nervous tissue. Their nuclei are easily recognized in cresyl violet preparations by their large size and pale staining, since they contain only a few fine, dark-staining chromatin granules. Their fibers form a dense wall at the outer periphery of the spinal cord (marginal glia of Held) and at the outer border of the cortex. Structures that normally contain an abundance of fibrous glia are Goll's nucleus, the spinal nucleus of the fifth nerve, the upper olives, and the ventricular gray. Fibrous glia is scanty in the deeper layers of the cortex and in the neostriatum (caudate nucleus and putamen). The roots of the cranial nerves and of the spinal nerves proximal to their exit contain a glial meshwork instead of mesodermal pia and endoneurium surrounding the nerve fibers. The extent of this glial meshwork varies; in the eighth nerve it extends as far as 9 mm. from the exit of the nerves. In the spinal cord it is more extensive in the lumbar roots than in the cervical. This fact will help in our later discussion to explain the occurrence of gliomas in the proximal part of acoustic nerve tumors, and it has formed the basis for a theoretic explanation of the greater vulnerability of the optic nerve (which like the olfactory nerve contains only glia) and of the lumbar and dorsal nerve roots to the action of toxins circulating in the cerebrospinal fluid of the subarachnoidal spaces.

We do not know much about the normal function of the glia, but its behavior in disease has been fairly well investigated. The fibrous glia

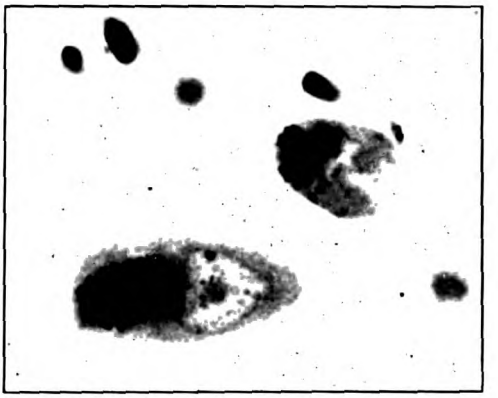


FIG. 26. PIGMENT INCLUSIONS IN NEURONS OF STRIATUM

Case of parkinsonism and arteriosclerosis of brain. Cresyl violet stain. Coarse, dark-staining granules, accumulated at one pole of neuron

FIG. 27. ASTROCYTES

Human cerebral cortex. Cajal gold sublimate method. Long processes are seen extending to blood vessel in center and surrounding it with large sucker feet

along with the mesenchymal tissues of the brain is the first to be called upon for defense in destruction of brain tissue. In the cerebellum it replaces Purkinje and granular cells in the form of a shrubbery-like syncytium

(*syncytiales Gliastrauchwerk*). Proliferation of Bergmann's cells leads to isomorphous gliosis; the nuclei disappear later and a fibrous scar remains (Scherer).

In softening and abscess formation the glia forms a wall around the anemic or infected area, isolating it from the normal tissue. The same reaction is seen as a defense against certain invading tumors; sometimes the stimulus seems to be so intense that giant cells and fibers are produced (fig. 28). Where brain tissue is destroyed it forms a scar in which (fig. 29), after some time, the astrocytes begin to shrink and disappear, leaving

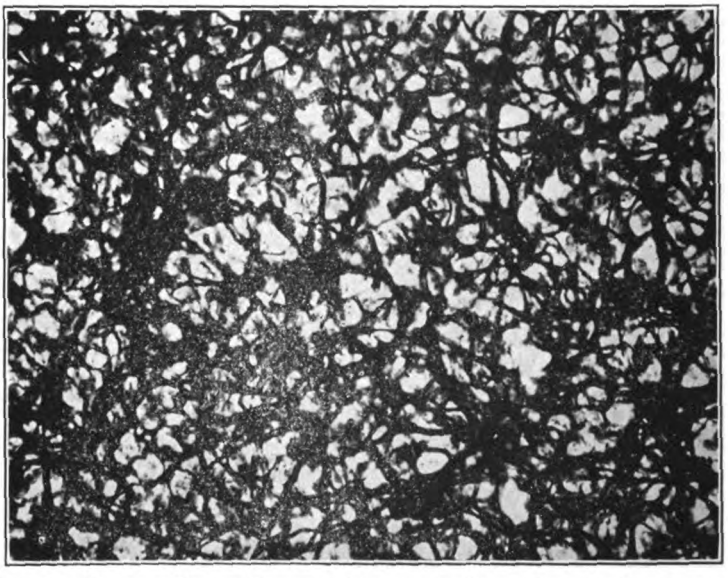


FIG. 28. WALL OF GIANT FIBROUS ASTROCYTES SURROUNDING METASTATIC CHORIONEPITHELIOMA (HOLZER STAIN)

a dense meshwork of glia fibers behind them. In secondary degeneration of nerve fibers, the same function is performed. The fibers adapt themselves to the original structure, forming, for example in the spinal cord, coarse longitudinal and fine transverse fibers (isomorphous glia). Under certain conditions the fiber formation may produce a dense structure. This led to the theory (later disproved) that in disseminated sclerosis proliferation of glia is the primary lesion, destroying the sensitive myelin sheaths (fig. 30). In tabes dorsalis the density of glia fibers in the posterior columns is much more pronounced than that usually seen in a simple secondary ascending degeneration (fig. 149).

The astrocytes do not seem to act as phagocytes. In the neighborhood of and within anemic foci one may see swelling of the astrocytes, which

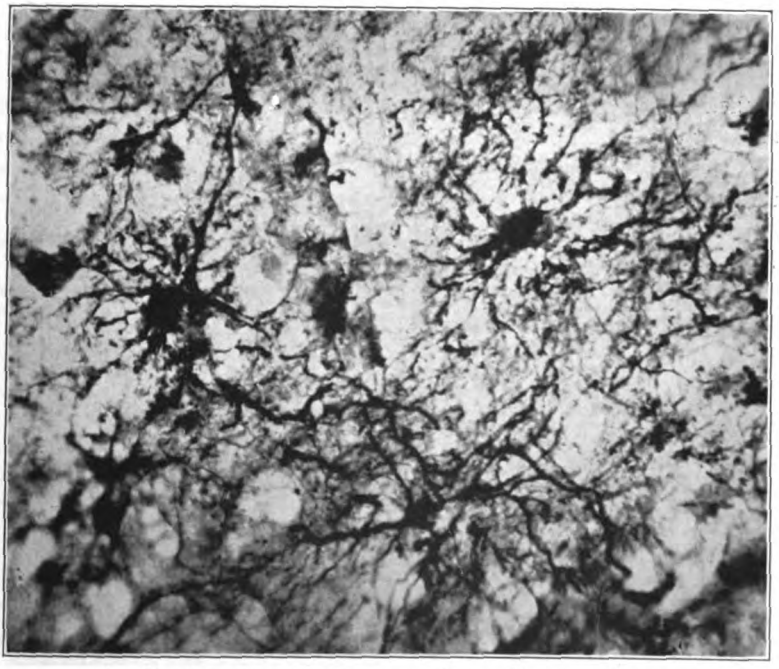


FIG. 29. ASTROGLIA SURROUNDING SMALL NECROTIC FOCUS
Epidemic encephalitis (North Dakota). Cajal astrocyte stain. (Cf. fig. 121)

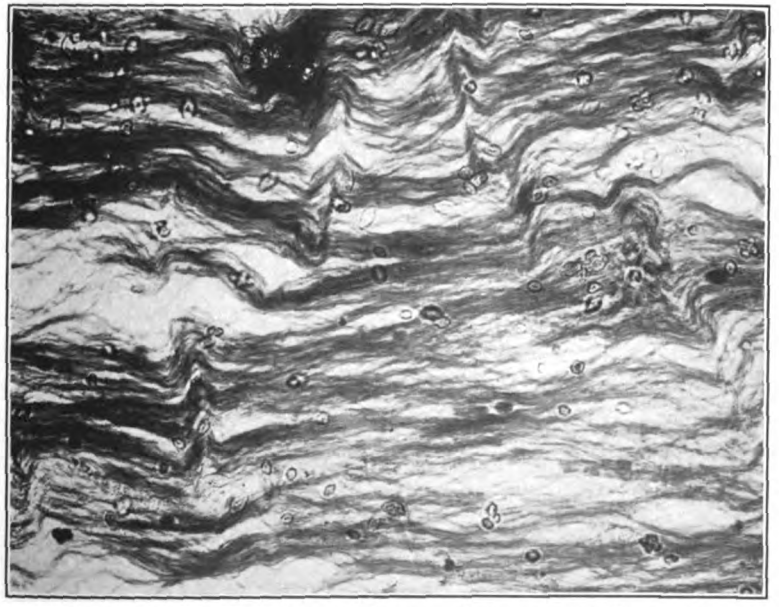


FIG. 30. INCREASE IN FIBROUS GLIA IN DISSEMINATED SCLEROSIS
Plaque in dorsal segment of spinal cord. Longitudinal section. Anderson's victoria blue stain

lose their processes and contain fat granules, but it does not seem that they assume the same role as the microglia. Sometimes it is impossible to decide whether a dense fibrous glia indicates merely protective scar formation or whether a neoplastic process is present. This is especially true in the environment of glioblastomas, and very often it may have happened that a piece removed at biopsy of a suspected tumor has been diagnosed as an astrocytoma. On the other hand, old astrocytomas may contain only a

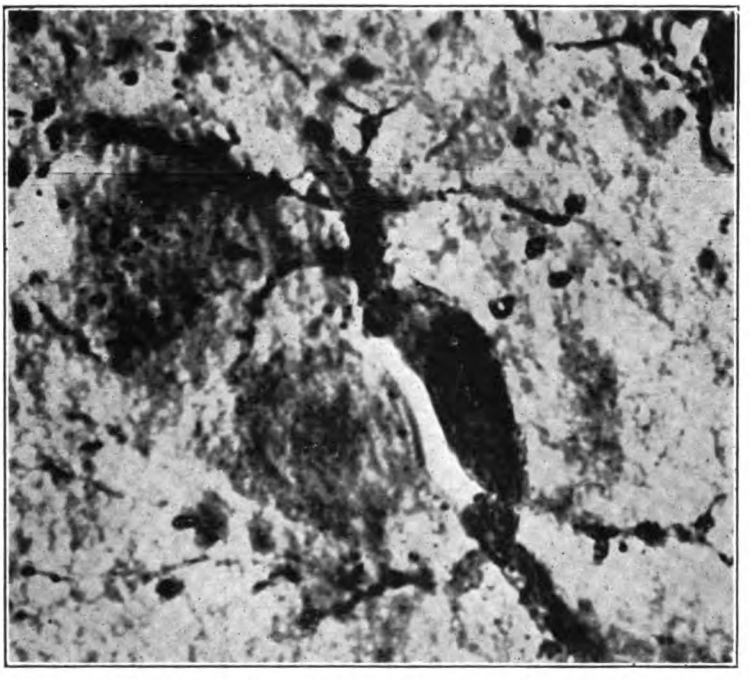


FIG. 31. SATELLITE GLIA CELL SURROUNDING CORTICAL NEURON
From human cerebral cortex. Stern method (Weil-Davenport modification)

few nuclei amid a dense fibrous meshwork—like those arising in the subependymal tissues of the ventricles—and may simulate scar formation.

Astroglia is very sensitive to the stimulus of metabolic disturbances and intoxications of the central nervous system. Physiologically, fibrous astroglia is increased in old age, especially in the lower layers of the cerebral cortex and within the white matter. Examples of astrogliosis following chemical stimulation will be discussed later in the chapter on intoxications.

OLIGODENDROGLIA

Oligodendroglia appears, in silver-impregnated sections, as cells with large round nucleus, scanty cytoplasm, and a few fine fibers streaming out

in different directions. In sections stained with cresyl violet the spherical nuclei are differentiated by their dark staining from the paler and larger astrocyte nuclei (fig. 32). Their situation around neurons facilitates identification; earlier observers have described them as lymphocytes. Oligodendroglia has different functions. Its accumulation around larger neurons of the cortex and the basal ganglia (perineuronal satellites) and along the myelinated nerve fibers of the white matter indicates that there is an intimate correlation between these different structures. Satellites are especially abundant around the nerve cells of the lower layers of

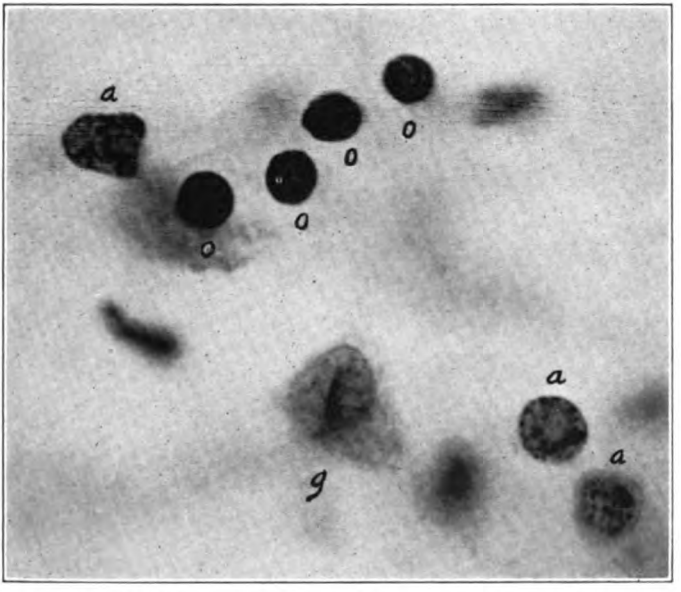


FIG. 32. GLIA NUCLEI IN SECTIONS STAINED WITH CRESYL VIOLET
a = astrocytes. o = oligodendroglia. g = neuron

the cortex at the borderline of the white matter. This may explain why neuronophagia takes place so readily in these regions when the neurons are diseased. The theory has been advanced that oligodendroglia cells (types 3 and 4 of Hortega) regulate the myelin formation of the nerve sheaths and that they act as intermediary agents in the exchange of metabolic products between neurons and brain fluids. After myelinization has been accomplished, they act as "drainage" cells (Belezky), forming sinuses around blood vessels and nerve fibers (fig. 38).

It seems that the stimulus that brings the oligodendroglia into action is

different from that which produces the fiber formation of the astrocytes. Under the influence of certain toxins that destroy neurons but leave the oligodendroglia intact, the latter acts as a different type of scavenger cell. The satellite cells increase rapidly and either surround (coffin formation) or cover the cell and its dendrites (or other large glia cells), which gradually disappear, leaving in the final scar only the accumulation of oligodendroglia (and microglia). This process of *neuronophagia* (and gliophagia) may frequently be seen in certain infectious diseases and intoxications. The best examples are found in the midbrain nuclei in epidemic encephalitis or around anterior horn cells following poliomyelitis (figs. 35, 36, 117). It seems that the stimulation that produces proliferation of oligodendroglia

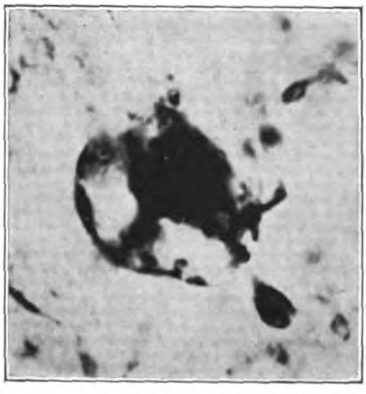


FIG. 33. SWELLING OF OLIGODENDROGLIA

Cerebral cortex in case of arteriosclerosis of brain. Stern method (modified). Similar pictures are frequently seen following formalin fixation of brains that were not diseased

must be of a very acute and intense nature. Rarely does one see neuronophagia of the gradually degenerating nerve cells in arteriosclerotic brains, in the idiopathic type of amyotrophies, or in a cortex that has been invaded by a glioma. In certain intoxications the interfascicular glia of the white matter undergoes proliferation.

MICROGLIA

Microglia (Hortega cells, third element, mesoglia) is normally, in the adult brain, a resting cell seemingly without any important function. Its small, polymorphic nucleus (elongated, rounded, triangular, curved) may easily be distinguished from the astrocyte nucleus, and in silver-impregnated sections it appears as an elongated cell, poor in cytoplasm, that sends out long fine fibers. Four different types have been described (Del Rio

Hortega). The most frequent type is the multipolar cell that is found chiefly in the cerebral cortex and the nuclear gray matter (figs. 37, 38).

FIG. 34. HYPERTROPHIC OLIGODENDROCYTE
Central cortex in case of general paresis. Stern method (Weil-Davenport modification)

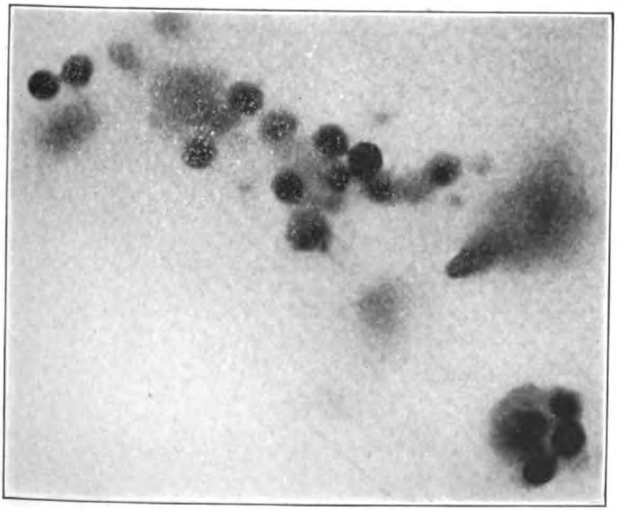


FIG. 35. COFFIN FORMATION OF GLIA CELLS AROUND DISEASED NEURON
Caudate nucleus in case of arteriosclerosis of brain with cirrhosis of liver. Cresyl violet stain. In right lower corner, three nuclei are seen surrounding small neuron. At upper left, small neuron is encircled by four nuclei

Three to six or more fibrous extensions may be seen radiating from the cell body, covered with fine, leaflike fibers. Unipolar and bipolar cells are less

different from that which produces the fiber formation of the astrocytes. Under the influence of certain toxins that destroy neurons but leave the oligodendroglia intact, the latter acts as a different type of scavenger cell. The satellite cells increase rapidly and either surround (coffin formation) or cover the cell and its dendrites (or other large glia cells), which gradually disappear, leaving in the final scar only the accumulation of oligodendroglia (and microglia). This process of *neuronophagia* (and gliophagia) may frequently be seen in certain infectious diseases and intoxications. The best examples are found in the midbrain nuclei in epidemic encephalitis or around anterior horn cells following poliomyelitis (figs. 35, 36, 117). It seems that the stimulation that produces proliferation of oligodendroglia

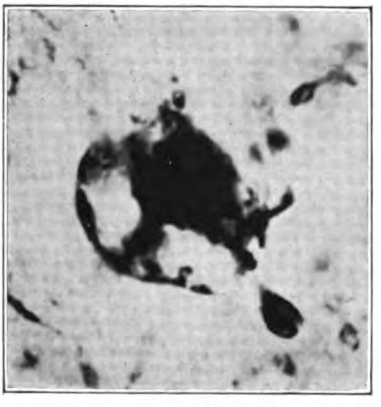


FIG. 33. SWELLING OF OLIGODENDROGLIA

Cerebral cortex in case of arteriosclerosis of brain. Stern method (modified). Similar pictures are frequently seen following formalin fixation of brains that were not diseased

must be of a very acute and intense nature. Rarely does one see neuronophagia of the gradually degenerating nerve cells in arteriosclerotic brains, in the idiopathic type of amyotrophies, or in a cortex that has been invaded by a glioma. In certain intoxications the interfascicular glia of the white matter undergoes proliferation.

MICROGLIA

Microglia (Hortega cells, third element, mesoglia) is normally, in the adult brain, a resting cell seemingly without any important function. Its small, polymorphic nucleus (elongated, rounded, triangular, curved) may easily be distinguished from the astrocyte nucleus, and in silver-impregnated sections it appears as an elongated cell, poor in cytoplasm, that sends out long fine fibers. Four different types have been described (Del Rio

Hortega). The most frequent type is the multipolar cell that is found chiefly in the cerebral cortex and the nuclear gray matter (figs. 37, 38).

FIG. 34. HYPERTROPHIC OLIGODENDROCYTE
Central cortex in case of general paresis. Stern method (Weil-Davenport modification)

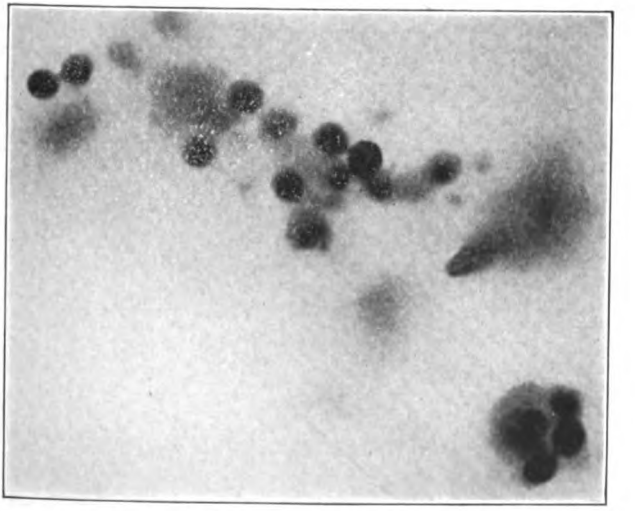


FIG. 35. COFFIN FORMATION OF GLIA CELLS AROUND DISEASED NEURON
Caudate nucleus in case of arteriosclerosis of brain with cirrhosis of liver. Cresyl violet stain. In right lower corner, three nuclei are seen surrounding small neuron. At upper left, small neuron is encircled by four nuclei

Three to six or more fibrous extensions may be seen radiating from the cell body, covered with fine, leaflike fibers. Unipolar and bipolar cells are less

frequent, the latter, with rodlike forms, predominating in the cerebellar cortex and the cornu Ammonis. Flat cells resembling endothelium—the

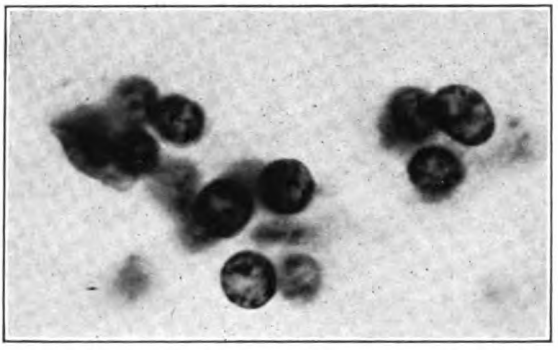


FIG. 36. NEURONOPHAGIA AFFECTING DISEASED NEURONS
Deeper layers of frontal cortex in case of yellow atrophy of liver. Cresyl violet stain

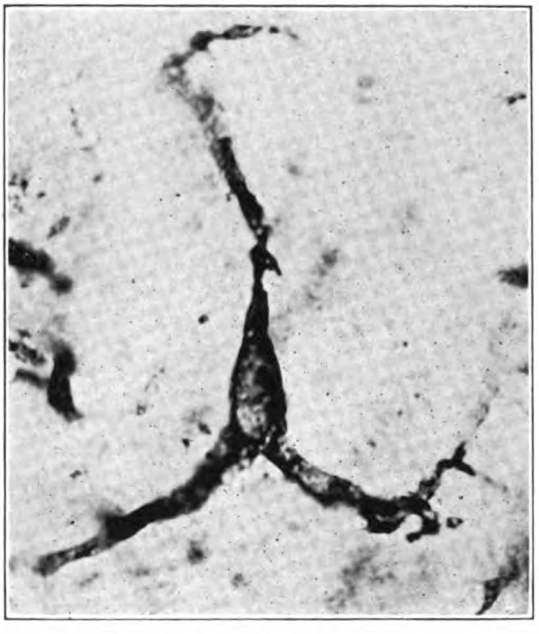


FIG. 37. HYPERTROPHIC MICROGLIA
Cerebral cortex in case of arteriosclerosis. Stern method (Weil-Davenport modification)

lamellar forms—are found in narrow interstices between the surfaces of nerve fibers in the brain stem and the corpus callosum. Microglia seems

to be less abundant in the white matter of the spinal cord than in the brain. It has also been found in the optic nerve and the retina.

The histogenesis of this cell is still a matter of discussion, some claiming that it is of mesenchymal origin (corresponding to the histiocyte of the reticulo-endothelial system) while others think that it belongs in the same group with the two other glial elements, being of ectodermal origin. It has been claimed that the microglioblast arises from the peripheral elements of the vessel walls very early in embryonic life (Bolsi). Del Rio Hortega thought that it is formed shortly before birth from meninges and tela chorioidea. This resting cell, which is normally difficult to stain in the

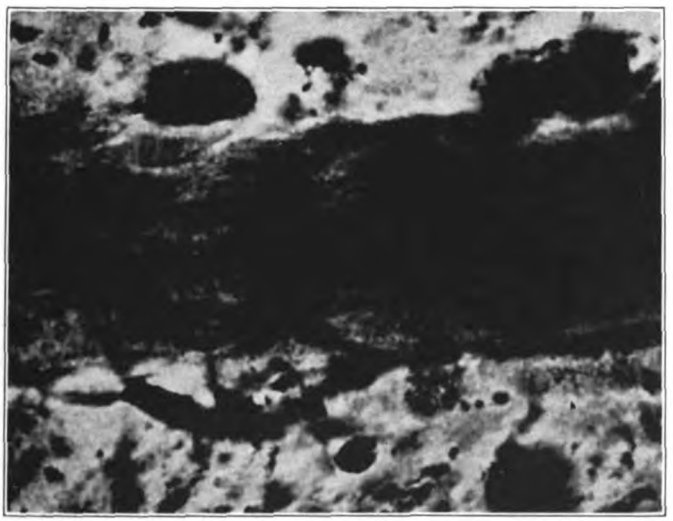


FIG. 38. MICROGLIA AND OLIGODENDROGLIA

Drainage cells attached to wall of small artery of white matter. Stern method (Weil-Davenport modification)

human brain, is suddenly aroused to great activity in the event of trauma, hemorrhage, or softening of brain tissue. It assumes in this case the role of a scavenger cell that takes up and digests the debris of the broken-down nervous tissue. Both the microglia that survives the damage and the normal cells of the region show thickening and retraction of their processes after twelve hours. Within thirty-six hours an anemic focus is filled with large round cells with peripherally located nucleus. In frozen sections stained with sudan III one sees them laden with fat droplets ("compound granular corpuscles") that are dissolved during the process of embedding. Therefore in paraffin or celloidin sections these cells contain a meshwork, resulting from the dissolved fat droplets, like a lattice—*Gitter* in German,

therefore "gitter cells"). Such scavenger cells may also originate from resting cells of the adventitia of blood vessels; the affinity of the mesoglial scavenger cell for trypan blue stain is less pronounced than that of macrophages (L. S. King). It is still a controversial question whether oligodendroglia or even astrocytes may be transformed into compound granular corpuscles, as has been claimed by different observers (fig. 40).

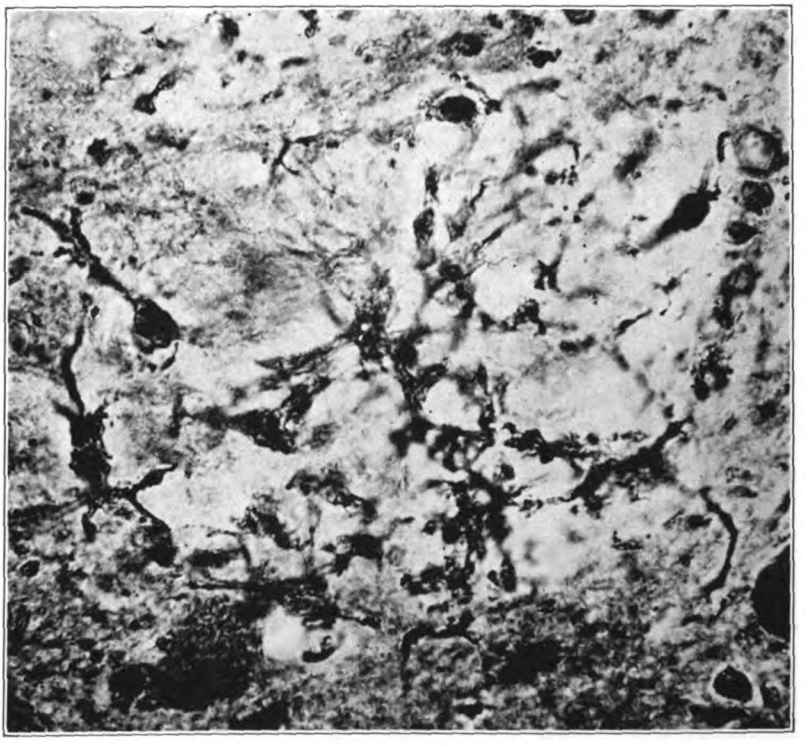


FIG. 39. SENILE PLAQUE

In cerebral cortex in case of Alzheimer's disease. Stern method (modified). Microglia surrounds and invades plaque; in center it breaks down, undergoing same process of degeneration as that which destroyed original tissue

In the brains of newborn animals, microglia appears in round forms with vacuolated cytoplasm containing fat granules and with round or irregularly formed nucleus, resembling a lymphocyte nucleus in its dark staining. In the white matter of newborn children accumulation of such microgliocytes has been thought by earlier investigators to indicate proliferation of lymphocytes and inflammation ("encephalitis interstitialis neonatorum"—

Virchow). Modern staining technic has revealed their true nature (Del Rio Hortega) (fig. 106).

In acute inflammations, microglia reacts by shortening and thickening of its processes and formation of elongated forms, but generally it does not proceed to the stage of the compound granular corpuscles. In chronic infections and in intoxications, it proliferates and, as in general paresis, forms numerous hypertrophic, elongated "rod cells" (*Stäbchenzellen* of Nissl) (figs. 143, 172).

The intensity and character of the stimulus seem to determine the function of the microglia as well as that of the oligodendroglia. Together with the latter it takes part in neuronophagia; with the oligodendroglia

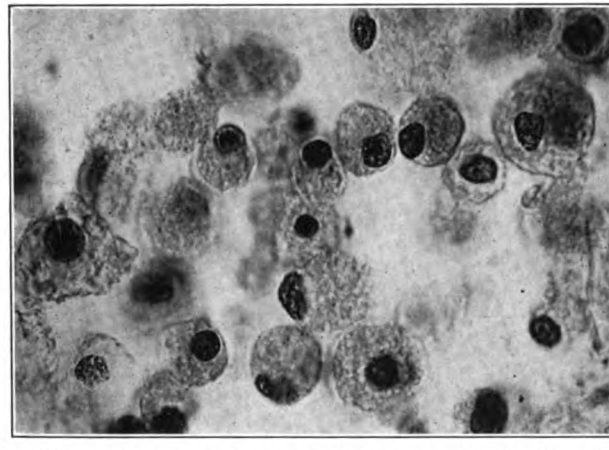


FIG. 40. COMPOUND GRANULAR CORPUSCLES (GITTER CELLS)
Focus of anemic softening in arteriosclerosis of brain. Hematoxylin-eosin stain

it forms the *Gliarasen* and the glia stars replacing dead nervous tissue. The term *Gliarasen* was created by Nissl to indicate the conglomeration of different glia cells into one cytoplasmic mass, with disappearance of the cell boundaries; it may also sometimes simulate a multinuclear giant cell. In the glia stars and nodules the single glia cell preserves its individuality (fig. 41). The final step in neuronophagia and star formation seems to be the gradual disappearance of the compound granular corpuscles that participated, leaving behind only a fine fibrous tissue; or they may themselves degenerate, breaking down before the process of repair has been definitely finished, as in the plaques of senile brains, in which the vitality of the compound granular corpuscles that try to invade dead tissue seems

also to have suffered (fig. 39). The formation of glia nodules may also proceed independently of destruction of nervous tissue. They are found in cases of chronic endocarditis (rheumatism), pneumonia, pellagra, in cancer, cachexia, and other diseases. With the improvement of staining technic it has been recognized that microglia takes part also in fiber formation, building, together with the astrocytes, the cicatrix around trau-

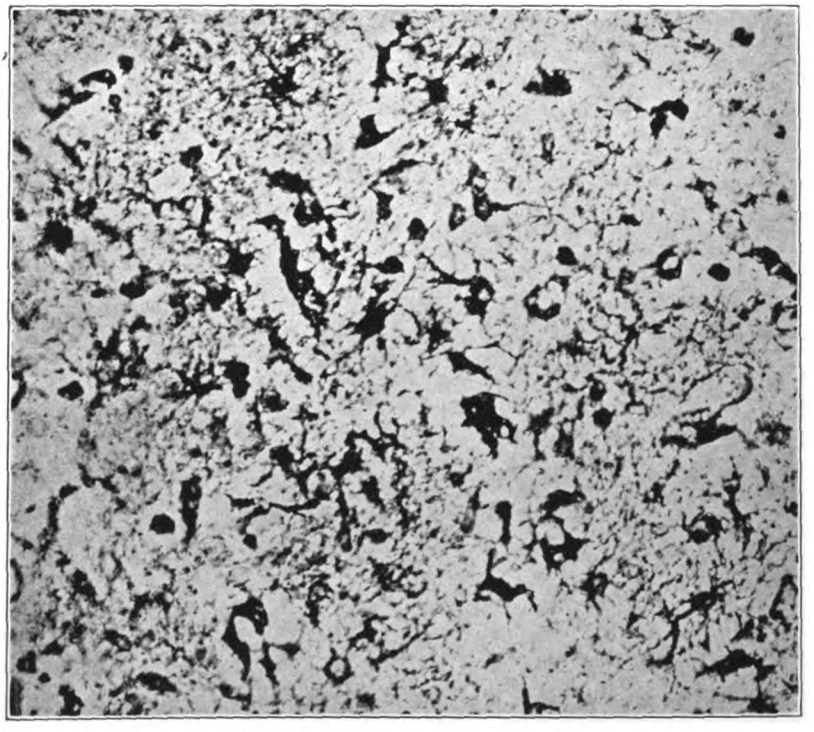


FIG. 41. PROLIFERATION OF GLIA

Midbrain in case of epidemic encephalitis (St. Louis). Stern method (Weil-Davenport modification). All three types of glia participate in formation of this nodule, refuting older theory that oligodendroglia only becomes hyperplastic, as based on study of sections stained with aniline dyes

matic lesions and anemic foci and producing sclerosis in certain chronic inflammations and disseminated sclerosis. Its active proliferation in acute inflammatory processes may be well studied in encephalitis following measles, where it plays a prominent role in the formation of the perivascular glia walls (fig. 157).

These different forms of glia reactions, constituting progressive glia

changes, are an important factor in histologic diagnosis and help us to supplement analysis of pathologic changes found in neurons. Their active proliferation is indicated by an increase of nuclei in cresyl violet-stained sections, in early stages by mitotic figures in microglia, by swelling and intense staining of the cytoplasm, with deeply staining nuclei, and by the presence of multinuclear cells. Mitotic figures may be detected in microglia in acute infections and intoxications of the cerebral and more frequently of the cerebellar cortex.

Degenerative (Regressive) Changes of Glia Cells

The same disease factors that produce pathologic changes of the neurons at the same time affect the glia. But there is not always the same response in both elements; certain factors (intoxication, mild anemia) that lead to the death of the neuron may stimulate the glia elements to proliferation (progressive changes).

Some types of nerve cell disease that have been described in the preceding chapter are accompanied by similar disease of the glia, which has been best studied in the astrocytes. Together with the "acute swelling" of neurons, mitotic figures in the surrounding glia nuclei or hyperchromatic staining of the nucleus or its wall is seen; this finally leads to pyknosis, atrophy, and dark homogeneous staining of the nucleus. Shrinkage and sclerosis of the irregularly outlined nucleus are seen together with accumulation of lipoids in the cytoplasm of the astrocytes under many pathologic conditions and with senile pigment atrophy of neurons. The severe neuronal disease is accompanied by similar destruction of the cytoplasm and karyorrhexis of the astrocyte nuclei. Liquefaction of the cytoplasm and foamy appearance, together with pyknosis of the nucleus, are seen as postmortem autolytic changes. Similar pictures of a liquefaction of the astrocyte cytoplasm, which assumes ameboid forms by the formation of pseudopodium-like processes, are found in many cases of intoxication (Alzheimer's *amöboide Glia*). Glia fibers cannot be stained under these conditions. In the interior of the cell, there are found vacuoles that contain, like the rest of the cytoplasm, small granules staining intensely red with fuchsin or, at a later stage of degeneration, blue with methyl blue or hematoxylin.

In anemic foci the astrocytes lose their processes, become rounded, and finally disintegrate. The gradual breaking up of the processes into fine globules may be studied in certain acute and fulminant infections or intoxications (clasmatodendrosis) (fig. 42). (Penfield and Cone consider Alzheimer's ameboid glia and Cajal's clasmatodendrosis to be identical processes.)

Regressive changes occur not only in normal glia cells but also following

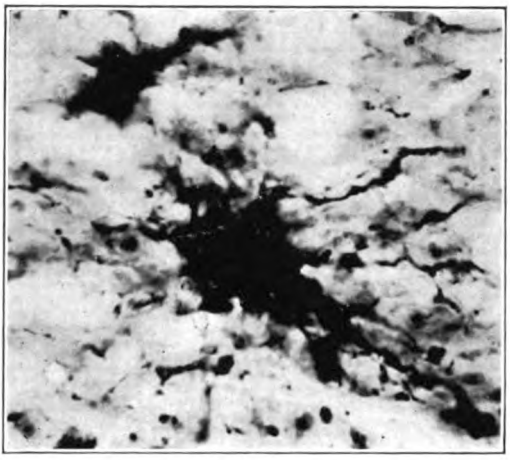


FIG. 42. CLASMATODENDROSIS

Astrocytes in white matter of cerebral cortex in case of encephalitis following measles. Cajal gold sublimate method. Swelling of cel and fragmentation of processes appear

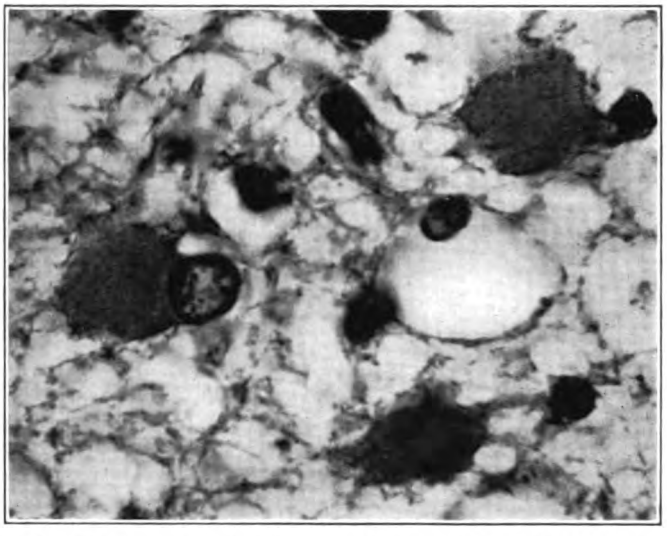


FIG. 43. SWOLLEN ASTROCYTES: FATTENED (*gemästet*) GLIA

Environment of hemorrhagic softening. Van Gieson stain. Cytoplasm of enlarged cell stained homogeneously. Nucleus eccentric

progressive reaction. In the neighborhood of anemic foci or of tumors, the proliferated astrocytes sometimes show a marked swelling of the cy-

toplasm, which stains intensively with eosin; the well preserved nucleus is dislocated peripherally (*gemästet*, i.e., "fattened" glia cell or "plump astrocyte") (fig. 43). The fiber-forming glia elements in scars or sclerotic foci frequently become atrophic and disappear, leaving behind only a dense fibrous meshwork with scanty nuclei.

Oligodendroglia seems to be very sensitive to postmortem autolytic changes. It becomes swollen and the processes undergo clasmatodendrosis. In senile brains, following chronic diseases, or in Schilder's disease, a polychromatic staining of the cytoplasm has been described—pink with toluidine blue or red with mucin carmine. The latter reaction has been thought to indicate mucin formation (Grynfeltt and Pelissier; Bailey

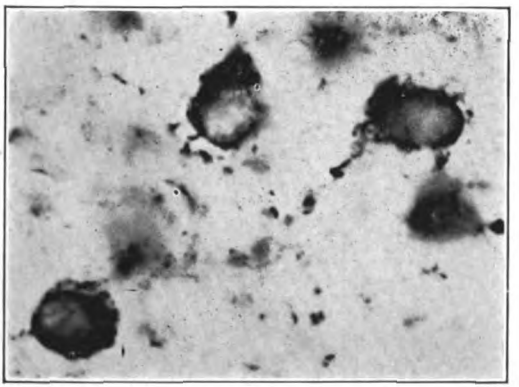


FIG. 44. SWOLLEN OLIGODENDROGLIA
Cytoplasm very pale, processes fragmented. Hortega stain (Penfield modification)

and Schaltenbrand), a fact that is doubted by others (Del Rio Hortega; cf. galactolipid reactions, chap. II) (fig. 44).

The swollen cytoplasm may become transparent (endolysis, acute swelling—Penfield and Cone), a process that is due perhaps not only to disease but also to agony and postmortem autolysis. Like the astrocytes, oligodendroglia may undergo fatty degeneration and show, in amaurotic family idiocy, the same products of disturbed phospholipid metabolism. The accumulation of fat granules or of iron is considered by some authors as a proof of phagocytic function, by others as a mere passive impregnation.

Atrophy of nuclei in sclerotic scars or shrinkage of the compound granular corpuscles after they have reached the perivascular spaces may be considered regressive changes of the microglia. The shrunken nuclei may still be found here many months after softening has occurred and may be

mistaken for lymphocytic nuclei. The presence in the scanty cytoplasm of fine fatty granules that stain with sudan III may help in making a differential diagnosis. In general, microglia seems to be more resistant than astrocytes. In foci of anemic softening where the latter are destroyed, or in the perivascular lesions of certain types of encephalitis (following measles), with clasmatodendrosis and swelling of the astrocytes, the microglia shows active proliferation (fig. 157).

IV

PATHOLOGY OF THE MYELIN SHEATH AND THE AXIS-CYLINDER

Experimental Demyelinization

One should always be conscious of the fact that the structure described as myelin sheath in sections of formalin-fixed material stained by special methods is only a distorted image of the original. First, the coagulating and hydrolyzing action of the fixative and, second, the lipolytic action of alcohol and xylol not only produce an artefact, but at the same time remove much of the lipid material that forms the main part of this structure. It is known that after preservation of fresh brain material in pyridine the myelin sheaths cannot be stained, while after formalin fixation, treatment with pyridine does not change their staining qualities. This indicates that the fixative must change the physicochemical character of the myelin sheaths, perhaps by precipitating part of the lipids together with the proteins, creating a compound insoluble in alcohol and other lipid solvents.

In test tube experiments it can be demonstrated that the myelin sheaths are easily destroyed by substances that are also hemolytic and that at the same time are mostly surface-active, i.e., increasing the surface tension of fluids. Most interesting from the biologic point of view is the myelolytic action of sodium salts of the bile acids—taurocholic and glycocholic acid. A similar action can be demonstrated in the serum and urine in experimental jaundice (figs. 45, 46).

Repeated intramuscular injections of aqueous emulsions and alcohol-ether extracts of sterile normal rabbit brain in monkeys will produce pathologic changes accompanied by destruction of myelin sheaths of the brain (Rivers and Schentker). Experimental demyelinization with mild gliosis may be produced by injection of potassium cyanide solutions in monkeys (Ferraro, Jervis, Hurst). Transitory interruption of blood supply leads to perivascular demyelinization (experiments of Putman and co-workers; Hurst and Cooke).

More recently, we have become aware of the extreme sensitivity of the myelin sheaths to lack of vitamin B_1 (thiamine). This vitamin acts as a coferment to carboxylase, a ferment essential in completely oxidizing the glucose of the nervous tissue (of the galactolipids, which are thought to

form one-third of the myelin sheaths). Lack of the vitamin leads to an accumulation of pyruvic acid, which probably acts destructively upon myelin sheaths (cf. chap. IX).

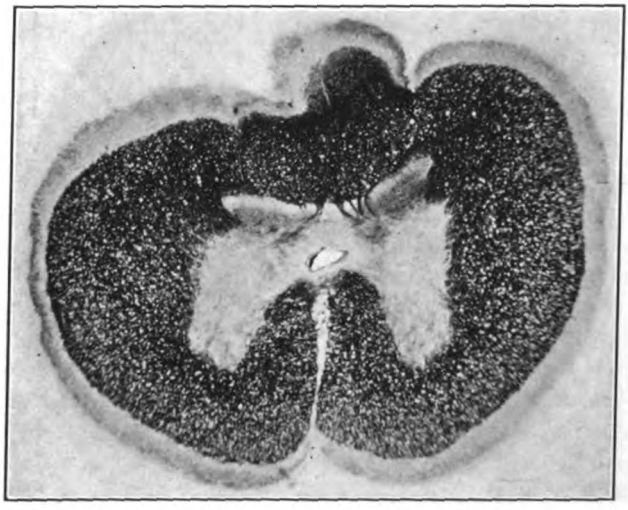


FIG. 45. EFFECT OF SAPONIN ON MYELIN SHEATHS

Test tube experiment. Rat spinal cord incubated with 1 per cent solution for 20 hours. Transverse section stained by Weil method. Dissolution of myelin sheaths in periphery of section

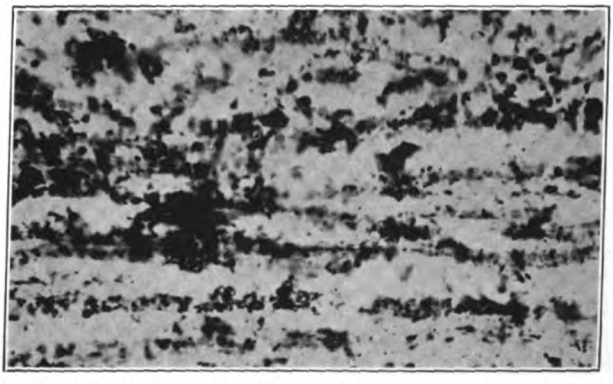


FIG. 46. EFFECT OF SODIUM TAUROCHOLATE ON MYELIN SHEATHS

Rat spinal cord incubated with 1 per cent solution for 20 hours. Longitudinal section stained by Weil method. Fragmentation and globulation of myelin sheaths

Disease of the myelin sheaths may be produced primarily by the action of toxic products in infections and intoxications, by nutritive disturbance

following anoxemia, by disease of the interfascicular oligodendroglia or the peripheral Schwann cells, by pressure, or by abnormal temperatures, high or low. Secondarily, decomposition of the myelin sheaths may follow disease of the axis-cylinder or interruption of a nerve fiber (wallerian degeneration).

Degeneration of the Myelin Sheaths

The decomposition of myelin sheaths under different pathologic conditions seems to follow a standard scheme. Whether we are dealing with a wallerian degeneration following lesion of a nerve fiber, or with the breaking

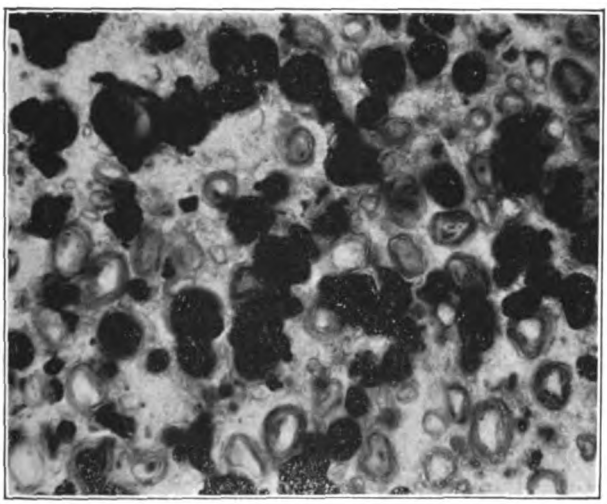


Fig. 47. Wallerian Degeneration

Rubrospinal tract of cat, 14 days after lesion of red nucleus. Transverse section of cervical spinal cord. Marchi method. Black-staining Marchi bodies and light-staining, preserved myelin sheaths

(*Courtesy Dr. W. R. Ingram*)

down of a nerve fiber in the region of an anemic softening, the first change will always be a swelling of the myelin sheaths, with loss of double refraction in polarized light. This is followed by fragmentation and formation of myelin globules, a process that in wallerian degeneration in the central nervous system seems to take place as early as two days following the lesion. These myelin globules stain black when the tissue is treated by the Marchi method (chromic acid followed by osmic acid, reduction of the osmium tetroxide, and formation of osmium dioxide, with black staining). Artefacts may be produced by trauma during autopsy or formalin fixation of long duration. The reaction is indicative of a chemical change of the lipoids of the myelin sheaths, perhaps liberation of unsaturated oleic

acid, because normal sheaths do not stain black with osmic acid after treatment with chromic acid. The optimal time for the reaction is approximately three weeks for the central nervous system and somewhat less for peripheral nerves (twelve days) (figs. 47, 48).

In sections stained for myelin sheaths by the routine hematoxylin methods, the sheaths do not show loss of staining reactions up to the second week in wallerian degeneration. Later, the myelin globules stain paler and finally lose their affinity for iron hematoxylin. One should be aware of the fact that in old preparations stained for myelin sheaths certain fiber tracts will pale out earlier than others, e.g., the periphery of the brain stem

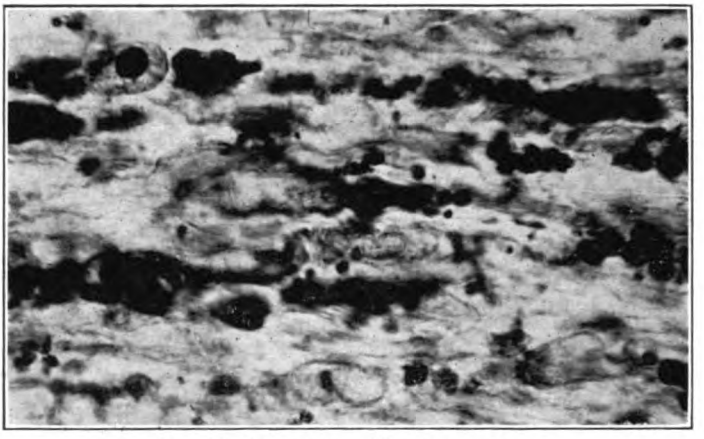


FIG. 48. WALLERIAN DEGENERATION

Optic tract of cat, 3 weeks after removal of eyeball. Longitudinal section. Marchi method. Degeneration of myelin sheaths more advanced than as seen in fig. 47. Myelophage in left upper corner.

(*Courtesy Dr. W. R. Ingram*)

and the spinal cord. Normally, Goll's tract in the cervical region stains lighter than its environment; the myelin sheaths are absent at the zone of entrance of the posterior spinal roots (Redlich-Obersteiner zone). In isolated instances certain fiber tracts may be devoid of myelin congenitally, as, for example, the Helweg or triangular tract of the anterolateral column of the spinal cord.

The end stage of degeneration of larger fascicles is characterized by unstained areas in which only isolated myelin sheaths remain (figs. 49–51). Chemically these changes are characterized by an increase in water and a loss of phospholipids and galactolipids. Tables 7 and 8 give some examples of such changes in lipid content under different experimental conditions. It was found that after removal of the products of degeneration, approxi-

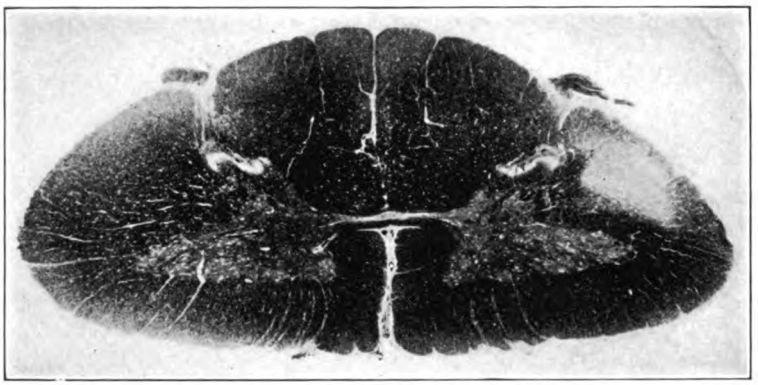


FIG. 49. SECONDARY DESCENDING DEGENERATION OF PYRAMIDAL TRACT FOLLOWING HEMORRHAGE INTO INTERNAL CAPSULE

Transverse section through sixth cervical spinal cord segment. Weil stain. Area of pyramidal tract is unstained

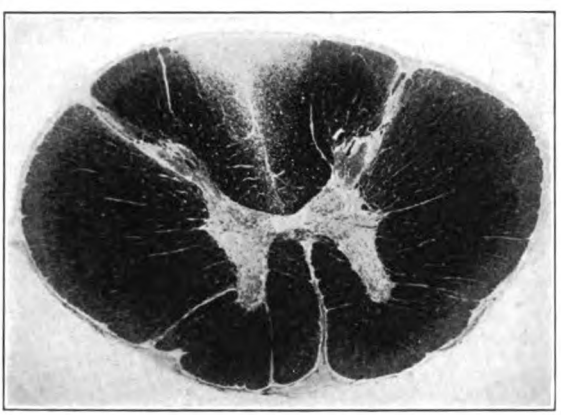


FIG. 50. SECONDARY ASCENDING DEGENERATION OF GOLL'S COLUMNS

Following destruction of lumbar vertebrae and compression of spinal cord by prostate cancer metastases. Transverse section through ninth dorsal segment. Weil stain. Unstained area in posterior columns corresponds to nerve fibers originating in spinal cord segments from sixth sacral to first lumbar

mately one month after the lesion, the water was decreased by 14 per cent and the total phosphorus by one-third, while the water-soluble phosphorus was increased by 35 per cent (May).

In the central nervous system the large myelin globules are gradually taken up by gliogenous scavenger cells (myelophages, gliophagocytes) that transform the debris into fine droplets, staining red with sudan III,

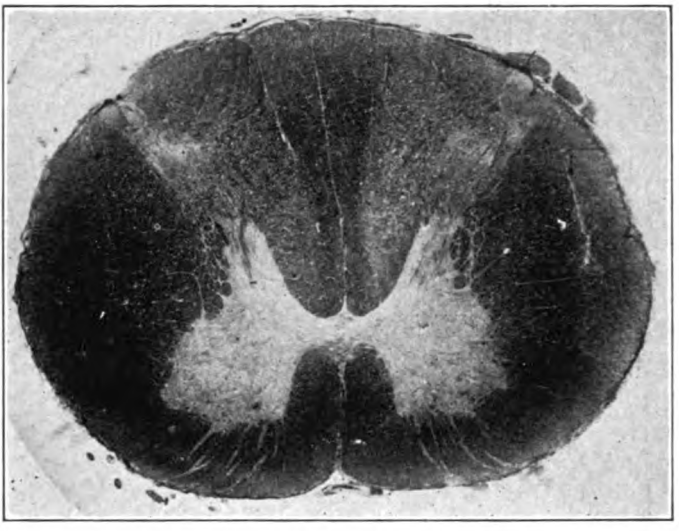


FIG. 51. SECONDARY ASCENDING DEGENERATION OF BURDACH'S COLUMNS (FASCICULUS CUNEATUS)

Following compression of spinal nerve roots of upper thoracic segments by breast cancer metastases to vertebrae of this region. Transverse section through seventh cervical segment. Weil stain. Both columns of Burdach are unstained

TABLE 7.—*Changes in Lipids of Spinal Cord: Descending Secondary Degeneration Following Transection of Both Cerebral Hemispheres in Dogs (Ranson and Weil*)*

	Weight of Extract in Percentage of Dry Substance			Grams of Phosphorus per 1000 Gm. of Dry Substance		
Survival Time (Days)	0	21	40	0	21	40
Acetone-soluble lipids	13.8	16.0	22.4	1.2	1.1	1.8
Alcohol-soluble lipids	60.1	58.2	49.3	13.9	14.2	10.1
Total lipids	73.9	74.2	71.7	15.1	15.3	11.9

* Unpublished.

in approximately four weeks following the lesion. These phagocytic elements assume the form of round compound granular corpuscles and carry the debris to the perivascular lymph spaces. It seems that different sets of glia cells are necessary for this process of repair; when one step in the digestion of the myelin has been completed, the cell breaks down and

its contents are taken up by another cell. Jakob differentiates between myeloclasts ("breaking up myelin"), myelophages ("eating myelin"), and, finally, compound granular corpuscles (gitter cells).

TABLE 8.—*Changes in Lipids of Spinal Cord Following Transection of Spinal Cord of Dog at Ninth Dorsal Segment* (Weil and McNattin†)*

Water in percentage of fresh substance, lipids in percentage of dry substance

	Normal	Transection of Spinal Cord	
		Above Lesion	Below Lesion
Water	68.2	70.2	76.0
Acetone-soluble lipids	13.8	18.4	25.5
Alcohol-soluble lipids	60.1	58.2	43.7
Total lipids	73.9	76.6	69.2

* Survival time, 5 days. † Unpublished.

In the peripheral nervous system the first changes of the myelin sheaths are accompanied by swelling and proliferation of the Schwann sheath cells. In the early stages they contain myelin globules and therefore correspond

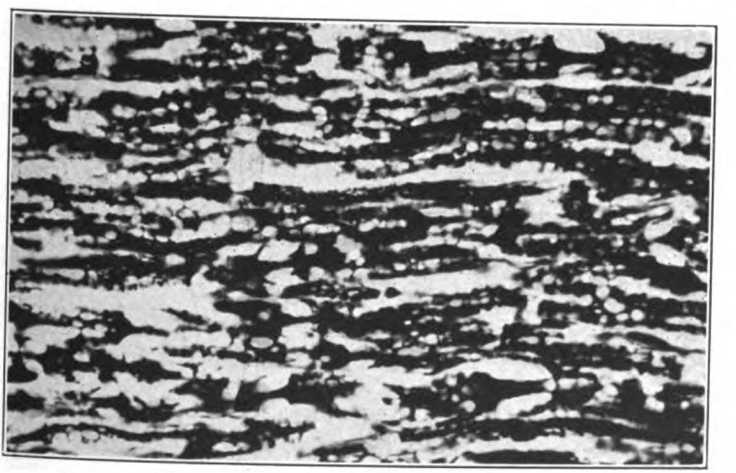


FIG. 52. WALLERIAN DEGENERATION OF MYELIN SHEATHS
Following transection of sciatic nerve of rat. Longitudinal section. Weil stain. Central stump after 7 days. Normal picture for comparison

to the myeloclasts of the central nervous system. It seems, however, that they do not carry out the transportation of the end products of decomposition of the myelin toward the perivascular spaces, but that this

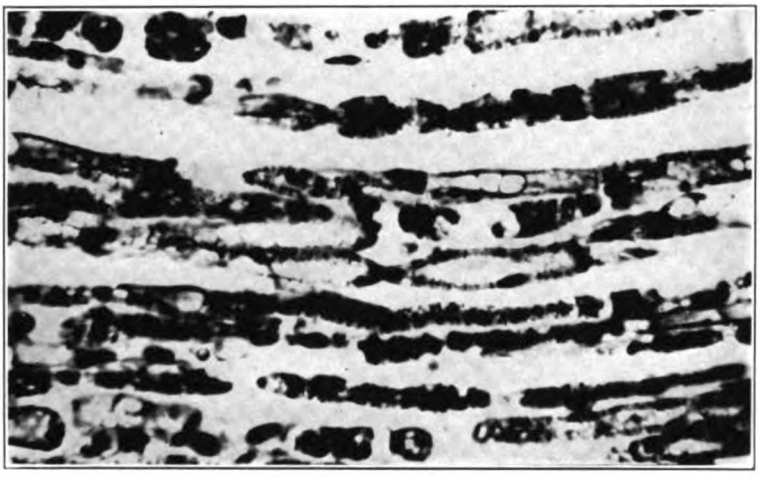


FIG. 53

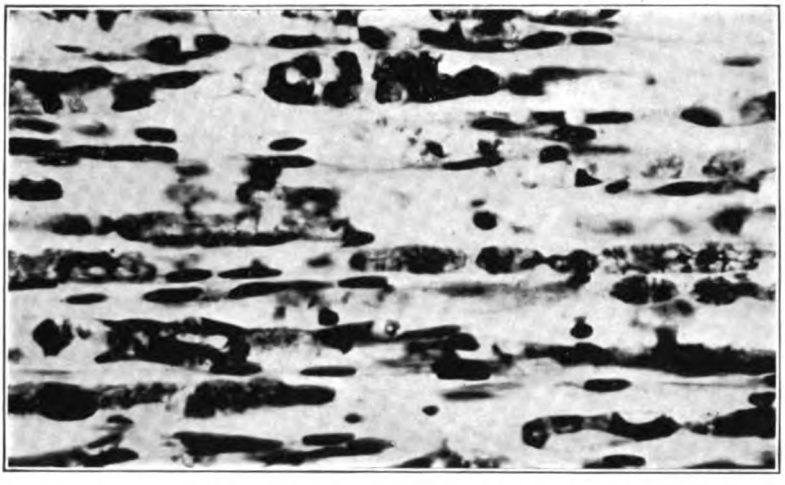


FIG. 54

FIGS. 53, 54. WALLERIAN DEGENERATION OF MYELIN SHEATHS FOLLOWING TRANSECTION OF SCIATIC NERVE OF RAT (CF. FIG. 52)

Fig. 53. Distal stump after 7 days. Swelling and fragmentation of myelin sheaths.
Fig. 54. Distal stump after 14 days. Dark-staining clumps of myelin inclosed in scavenger cells

task is taken over by mesodermal elements, histiocytes of the endoneurium, which assume the form of round compound granular corpuscles filled with the lipoid debris (figs. 52–54).

The intensity and duration of function of the destructive agent will determine the degree of damage and repair. Swelling alone may subside without any functional disturbance, as we know from observations in experimental ether narcosis, anoxemia of short duration, trauma, or transitory intoxications. Regeneration of completely destroyed myelin sheaths, however, does not seem to be possible in the adult central nervous system, while in the peripheral nerves other conditions prevail, as will be shown in a later chapter. An attempt has been made to interpret the presence of darkly stained condensed islands of myelin sheaths within large demyelinated areas in certain degenerative diseases (*état marbré* and *plaques fibromyéliques*) as myelin sheath regeneration. They are considered to be myelinated fibers that have grown within scars formed while the brain was still embryonic.

Disease of the Axis-Cylinders

Like the problem of the natural existence of Nissl bodies in the neuron, the problem of neurofibrils has long been the subject of ardent discussions. Recently, neurofibrils were demonstrated intra vitam in cultures of spinal ganglia from chick embryos. However, their morphologic picture changed from one day to another.

The pathology of the axis-cylinder is closely related to that of its myelin sheath. In many cases it is impossible to decide which was first attacked by the toxic agent. The close interrelationship between the two makes it probable that both are diseased together when nutritional or abiotrophic factors come into play, while toxins acting from without on the nerve fiber will attack the outer sheath first. Therefore a focus of anemic softening will show swelling of myelin sheaths and axis-cylinders at the same time. In secondary wallerian degeneration it seems that the axis-cylinder swells first and the myelin sheath changes follow later. But fragments of axis-cylinders may be found intact after the myelin sheaths have undergone globulation. Under conditions in which the myelin sheaths are destroyed and the axis-cylinders preserved, as in mild, slowly progressing compression by a tumor or in multiple sclerosis, there seems to be in the acute stages a bandlike swelling of the axis-cylinder, which only gradually subsides after the debris of the myelin has been removed and the effect of the toxic agent has ceased. A picture frequently observed in axis-cylinder disease is a rosary-like arrangement of globules. In anemic or hemorrhagic foci, bulb or loop formation may be seen preceding the final decomposition (figs. 55, 56). The first indication of axis-cylinder disease may be a change in staining qualities. Intense black staining in Bielschowsky or Davenport preparations, and red staining in Alzheimer-Mann or Mallory preparations, instead of the normal blue, have been described in different

pathologic conditions. However, more recently we have learned that such different shades of staining are due to the *p*H of the tissue as determined by postmortem and fixation conditions. Therefore the idea of staining with aniline dyes in buffer solutions at a given *p*H (thionin staining as devised by

FIG. 55. DEGENERATION OF AXIS-CYLINDERS

Neighborhood of hemorrhagic softening. Davenport stain. Loop, spiral, and bulb formations

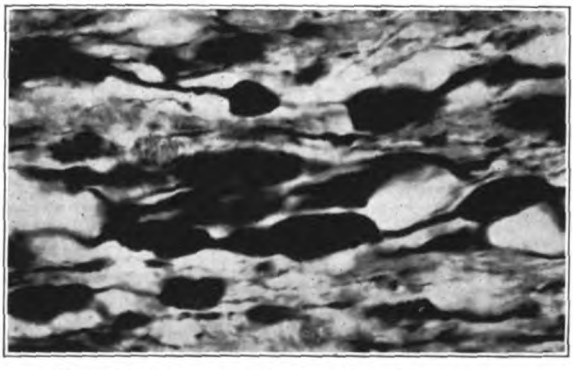


FIG. 56. DEGENERATION OF AXIS-CYLINDERS

Status spongiosus in brain of dog after experimental ligation of common bile duct. Davenport stain. Globular swelling (rosary formation)

Windle and his co-workers) should also be applied to the different methods of silver staining of neurons and glia.

The sequence of events in the destruction and absorption of the axis-cylinder is similar to what occurs in the case of myelin sheaths. Following

the swelling, which produces irregularly distributed globular enlargements, the axis-cylinder is broken up into numerous fine globules that are taken up and destroyed by the same type of scavenger cells as those described as operative in the process of myelin sheath decomposition (fig. 57).

Regeneration of axis-cylinders in the central nervous system, with restoration of physiologic function, does not seem to occur. It has been thought that the end bulbs, which are similar to those described in relation to regeneration of peripheral nerves, are indicative of an attempt at regeneration in the central nervous system. Experiments have been devised to prove the existence of such regenerative power in the brain. Elder marrow was placed in a wound of the cortex of an animal brain. When

FIG. 57. WALLERIAN DEGENERATION OF AXIS-CYLINDERS
Distal stump of cut sciatic nerve of rat after 14 days. Davenport stain. Swelling and fragmentation of axis-cylinders

removed after some time, it was found that axis-cylinders had grown into the meshes of the pulp. So far, however, we have neither histologic nor physiologic evidence that complete regeneration within the adult central nervous system, beyond such feeble attempts, is possible following lesion of a nerve fiber.

REGENERATION OF THE PERIPHERAL NERVES

A different picture of regeneration is seen in the myelinated fibers of peripheral nerves. After complete transection, both the sheath cells and the fibroblasts of the peri- and endoneurium begin to proliferate at the ends of the proximal and the distal stump. They cover the free ends of the nerve like a cap and their continuous proliferation finally forms a bridge connecting the separated ends (neuroma). Close to the surface of the proximal stump both medullated and nonmedullated fibers undergo de-

generative changes. In the latter segmentation appears; the medullated fibers begin to swell and to show a dissociation of the neurofibrils, which seem to be separated by an increased interfibrillar substance. The cellulip-

FIG. 58

FIG. 59

FIGS. 58, 59. REGENERATION OF PERIPHERAL NERVES

Transection of sciatic nerve of rat. Longitudinal sections of distal stump. Cresyl violet stain

Fig. 58. After 7 days. Intense staining of Schwann sheath cells of two medullated fibers. Between them, sheath cells of nonmedullated fiber.

Fig. 59. After 14 days. Schwann sheath cells of large medullated fiber at right are swollen and indistinctly stained. At left, newly formed, elongated cells, two of them connected by thin protoplasmic bridge

etal degeneration of the nonmedullated fibers may proceed as far as 2 cm. from the cut surface of the sciatic nerve of a dog (Ranson), but the degenerative changes of the medullated fibers seem to be confined to the zone of reaction in the immediate neighborhood of the cut surface (figs. 53, 54, 57).

After two weeks regenerative phenomena take place. Above the zone of degeneration the nonmedullated fibers begin to grow toward the cut end and, according to some observers (Cajal), to form branches. Part of the medullated fibers that did not show degeneration at the cut end grow peripherally as early as the second day, sending fine branches into the

FIG. 60. REGENERATION OF PERIPHERAL NERVES

Following 21 days after transection described under figs. 58, 59. Longitudinal section of distal stump. Cresyl violet stain. Formation of Büngner bands (*Leitbänder*). Section is overstained in order to emphasize protoplasmic bridges between elongated cells

outer zone. Others, cut at the peripheral lesion, develop very fine lateral branches within the sheath; these either grow within the old sheath, or penetrate it, forming spirals around it, or even grow centrally.

The medullated fibers of the peripheral stump first show darker staining and irregular outlines two days after the injury. From the fourth day on they are broken up into clumps of granules. Their myelin sheaths are

swollen, forming ellipsoid segments that as early as the fourth day separate and are surrounded by sheath cells together with the fragments of axons. The proliferation of sheath cells proceeds in a more harmonious manner in the distal than in the central stump. The cells undergo active division and act as scavenger cells taking up the debris of the degenerated nerve fibers. This process of disintegration is indicated by the appearance of fine droplets staining with sudan III or other fat stains, which finally are unloaded and may be found in neurilemma cells or around blood vessels. Later the proliferated oval sheath cells are united into a bandlike syncytium (Büngner's *Leitbänder*) (figs. 58–60).

After both ends of the cut nerve have been united again, the newly formed axons of the central stump change their direction. As though attracted by a magnetic force, they proceed into the peripheral stump and use of silver methods will soon demonstrate axons along the cytoplasm of the bands of the sheath cells. They gradually grow peripherally, myelin sheaths are formed around part of them, and after they have been united with the newly formed end organs, physiologic function is re-established (figs. 61–63).

The degeneration and regeneration of nonmedullated fibers in the distal stump proceeds in a similar way. There seems to be a difference between afferent, nonmedullated spinal fibers, which disintegrate during the first week, and nonmedullated sympathetic fibers, which disintegrate later. The latter may still be seen two weeks after the injury, staining uniformly without showing fragmentation. Both finally are broken up into segments and disintegrate into fine granules surrounded by the neurilemma sheath.

The time of regeneration depends upon different factors—the nature of the lesion, formation of a complete scar uniting the two ends after separation (neuroma), the vascular supply of this region and, finally, the type of nerve involved.

Regeneration after trauma without interruption of continuity occurs much more quickly than after separation. Such conditions have been studied following pressure upon or freezing of a peripheral nerve. The newly formed axis-cylinders do not have to traverse a dense connective tissue neuroma but grow directly into the paths of the Schwann cell syncytium, replacing the degenerated peripheral fibers. The older debate as to whether the axis-cylinders of the distal end really "grow" by extension of the proximal axons or whether they are formed by and within the Schwann cell syncytium of the distal end, is gradually disappearing from the literature. The fact is established that axis-cylinders in the peripheral end can be demonstrated only after a connection of the central fibers with the peripheral Büngner bands has been formed and after the "central stimulus" has been re-established. If such a reunion is prevented, either by dis-

location of both stumps, by formation of too dense a sclerotic scar tissue, or by inflammatory processes or vascular disturbances interfering with neuroma formation, the development of axis-cylinders in the peripheral stump does not take place. In such a case, the cellular syncytium begins to shrink and proliferation of the endoneurium takes place. The general

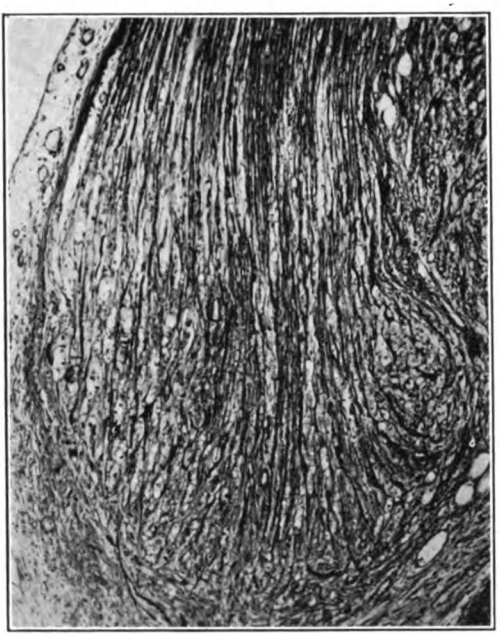


FIG. 61. REGENERATION OF PERIPHERAL NERVE

Central stump of sciatic nerve of rat, 6 days after transection. Davenport stain. Neuroma formation; proliferation of central axis-cylinders into newly formed connective tissue

structure of the nerve is preserved and even after years the longitudinal arrangement of the structures may be seen.

It has been taught that indicators of the peripheral extension of the central axis-cylinders are small ring- or globule-like protrusions that develop at the ends of the axis-cylinders as early as two days after the lesion. Cajal considered them as an essential factor of nerve growth. However, since they are found only in neuromas and not in regeneration after trauma without interruption of continuity (pressure, freezing), others think that they are indicative of the resistance offered by the newly formed connective

tissue, which does not allow a straight extension of the axis-cylinders. Larger end bulbs are considered to be an expression of degenerative changes. Such formations are also found in the central nervous system following interruption of a nerve fiber.

The attempt has been made, but abandoned, to render the formation of a neuroma unnecessary by intercalating agar tubes or pieces of peripheral

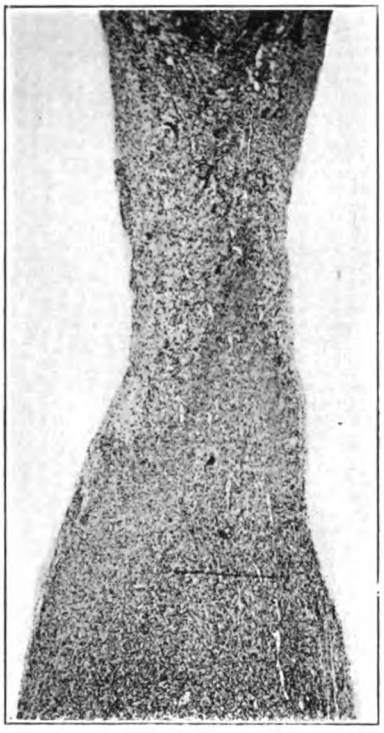


FIG. 62. REGENERATION OF PERIPHERAL NERVE

Section of sciatic nerve of rat. Connection of central and distal stump by neuroma, 14 days after transection. Van Gieson stain

nerves between the ends of the interrupted nerve. The newly formed axis-cylinders of the central stump do not grow into the agar, which, as a foreign body, is soon surrounded by dense layers of connective tissue. Opinions as to the value of intercalating pieces of nerves (auto-, homo-, or heterotransplantation) are divided. One group of experimenters reports favorable results and assumes that the sheath cells of the transplanted nerve survive and by their proliferation provide pathways for the extension of the central axis-cylinders or produce new neurofibrils. Another group

saw degeneration of the transplantate and believed that both alcohol-fixed and living nerves or spinal cords could fulfil the purpose of providing a tubelike conductor that would direct the outgrowing axons.

Inflammatory processes within the neuroma may interfere with regeneration in the same way as excessive scar formation following trauma of the surrounding tissue. Sutures that are not absorbed may, as foreign bodies, stimulate excessive connective tissue overgrowth. In younger persons the regeneration proceeds more quickly than in older ones. Animals show a more rapid restoration of physiologic function after nerve sutures than man.

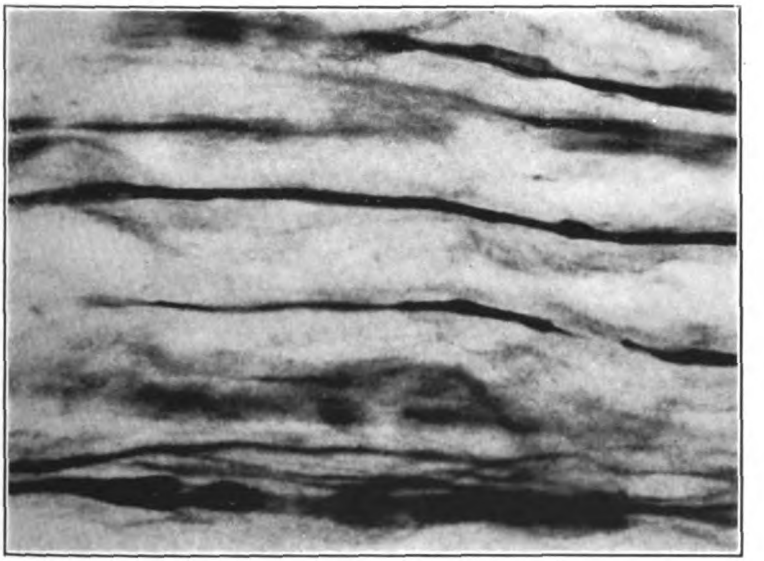


FIG. 63. REGENERATION OF PERIPHERAL NERVE

Distal stump of sciatic nerve of rat, 35 days after transection and suture of both ends. Bielschowsky stain. New formation of axis-cylinders

Regeneration of the radial and the musculocutaneous nerve seems to progress more rapidly than that of the ulnar, median, or sciatic nerve. Judging from the average of a large number of human cases, restoration of physiologic function seems to begin approximately six months following nerve sutures, with an optimum time of five weeks for the radial nerve (Spielmeyer) and a maximum of two and a half years after suture of the sciatic nerve. Regeneration of fibers of the autonomic nervous system following separation is accomplished within a shorter time. The cervical sympathetic nerve regains its function within a few weeks following transection; postganglionic fibers regenerate within several months.

The peripheral growth of newly formed central fibers into the distal stump is independent of the physiologic function of the latter. The experiment of Heidenhain is frequently cited. He united crosswise the cut ends of the lingual and the hypoglossal nerve; after electrical stimulation of the central stump of the lingualis following regeneration, contractures of the musculature of the tongue were noticed. It is also possible to form a junction between the vagus and the cervical sympathetic nerve, or between the latter and the chorda tympani or a somatic motor nerve.

V

ANEMIC SOFTENING

The Oxygen Consumption of the Brain

The brain ranks as that organ of the body which needs the highest amount of oxygen for maintenance of its function. The cortex uses nearly four times as much oxygen as the white matter, and the choroid plexus consumes as much per unit of weight as an equal part of total brain tissue, which indicates its active secretory function. It has been demonstrated experimentally that the brain of a dog receives, per 100 Gm. of weight and per minute, from 130 cc. to 140 cc. of blood. Removed from the body, the brain of a dog weighing 10 Kg. contains approximately 8.3 cc. of blood per 100 Gm. of brain. It has been stated that the average intracranial circulation time in experimental animals—monkeys or dogs—is three seconds (Wolff).

Table 9 gives comparative figures for the oxygen consumption of different organs.

Anatomically this difference between the gray and the white is expressed by the fact that the former is more abundantly supplied with capillaries (Cragie). According to Cobb and Talbot, the gray matter of the human cerebral cortex contains about 1100 mm. of capillaries per cubic millimeter of brain, the white about 300 mm. This relationship between the gray and the white matter is in the parietal region 2.33:1; in the nucleus trigeminus, 2.11:1; in the upper cervical ganglion, 1.18:1.

The respiratory quotient of normal brain tissue and spinal cord is 1 (Wortis); in B-avitaminosis it is 0.89. Injections of insulin diminish oxygen consumption. Addition of glucose or lactate to sliced brain tissue will increase the uptake of oxygen without changing the respiratory quotient (Dixon and Meyer).

Any diminution in the supply of oxygen will interfere with the normal function of the different parts of the nervous tissue. It seems that the neurons are more sensitive to temporary interruption of blood supply than glia cells. If all the arteries supplying a cat's brain are ligated for only 10 minutes (Cobb), complete cessation of the function of neurons may follow, while histologically many pictures of degeneration that have been described above may be seen.

Interruption of blood supply in a monkey's brain for 35 minutes produces

irreparable damage of cortical neurons (Müller.) The spinal cord neurons are more resistant. Compression of the abdominal aorta for 15 minutes did not lead to permanent damage of anterior horn cells (Tureen), while such an occlusion continued from 1 to 3 hours led to acute ganglion cell disease in anterior horn cells. In man compression of the abdominal aorta for more than 1 hour produced paralysis of the lower extremities. The cells of the sympathetic ganglion and the myenteric plexus seem to be more resistant to anoxemia (Drinker). Complete interruption of the cerebral circulation produced paralysis of the center of pupillary regulations after from 15 to 20 minutes, while the heart and vasomotor centers were still active after 30 minutes' interruption, and respiratory centers even

TABLE 9.—*Comparison of Oxygen Consumption of Organs in Situ with Normal Blood Supply in Different Animals at Rest (after Winterstein)*

Organ	Animal	Oxygen Consumption		
		Cc. per 100 Gm. and per Minute	In Comparison with Skeletal Muscle	Author
Striated muscle	cat	0.45	1.0	Verzár
Heart (vagus stimulation)	cat	1.10	2.4	Barcroft-Dixon
Liver	cat	1.10	2.4	Barcroft-Dixon
Intestines	dog	1.80	4.0	Brodie-Vogt
Kidneys	dog	2.60	5.8	Barcroft-Brodie
Salivary glands	cat	2.80	6.0	Barcroft-Piper
Suprarenal glands	cat	4.40	9.8	Neumann
Spleen	cat	5.00	10.1	Verzár
Pancreas	dog	5.30	11.8	Barcroft-Starling
Brain	rabbit	9.40	20.1	Yamakita
	dog	9.95	22.1	Gayda

after 1 hour (Heymans et al.). Neurons of newborn animals are much more resistant to interruption of oxygen supply than adult ones (Wertheimer). Their oxygen consumption is less than that of the adult brain, possibly owing to a less developed vascularization (Kabat and Dennis).

ANOXEMIA

If such a complete interruption of blood supply is confined to a limited part of the brain or spinal cord, the death of this area is followed by a process of repair originating in the surrounding normal tissue, and softening occurs. Between this complete destruction and the effects of a mild, transitory interruption of blood supply there are numerous intermediary stages producing different histopathologic pictures.

ETIOLOGY OF ANEMIA

The etiologic factors leading to a diminution or complete interruption of the blood supply of the brain are manifold. The most common one is the process of arteriosclerosis in aging blood vessels. It is quite unusual to find

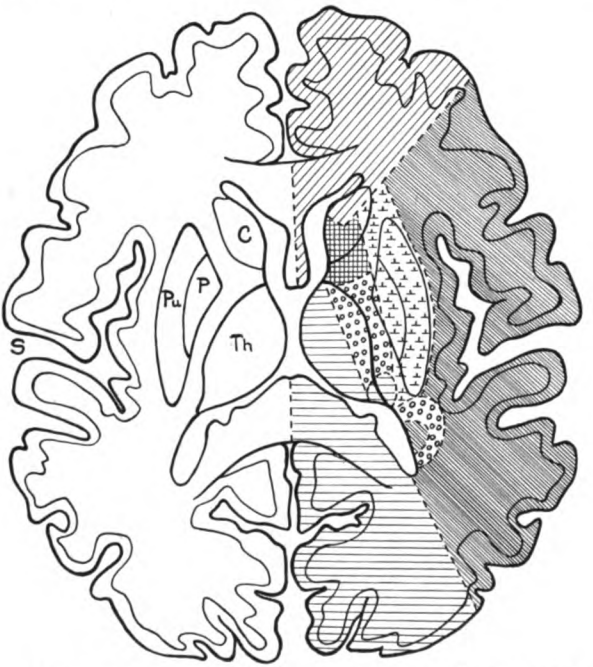


FIG. 64. DIAGRAM OF HORIZONTAL SECTION THROUGH BRAIN ILLUSTRATING DISTRIBUTION OF CEREBRAL ARTERIES

S = lateral cerebral fissure (fissure of Sylvius). C = caudate nucleus. Pu = putamen. P = globus pallidus. Th = thalamus

anterior cerebral artery

anterior choroidal artery

anterior communicating artery

superficial branch of middle cerebral artery

deep branch of middle cerebral artery

posterior cerebral artery

(After Foix and Schiff-Wertheimer: Rev. d'oto-neuro-opht. 4: 561, 1926. Courtesy Gaston Doin & Cie)

a brain of a person older than 60 years that does not show grossly a thickening and atherosclerosis of the larger arteries, especially the basilar arteries, with formation of yellow and whitish plaques within the vessel walls.

irreparable damage of cortical neurons (Müller.) The spinal cord neurons are more resistant. Compression of the abdominal aorta for 15 minutes did not lead to permanent damage of anterior horn cells (Tureen), while such an occlusion continued from 1 to 3 hours led to acute ganglion cell disease in anterior horn cells. In man compression of the abdominal aorta for more than 1 hour produced paralysis of the lower extremities. The cells of the sympathetic ganglion and the myenteric plexus seem to be more resistant to anoxemia (Drinker). Complete interruption of the cerebral circulation produced paralysis of the center of pupillary regulations after from 15 to 20 minutes, while the heart and vasomotor centers were still active after 30 minutes' interruption, and respiratory centers even

TABLE 9.—*Comparison of Oxygen Consumption of Organs in Situ with Normal Blood Supply in Different Animals at Rest (after Winterstein)*

Organ	Animal	Oxygen Consumption		
		Cc. per 100 Gm. and per Minute	In Comparison with Skeletal Muscle	Author
Striated muscle	cat	0.45	1.0	Verzár
Heart (vagus stimulation)	cat	1.10	2.4	Barcroft-Dixon
Liver	cat	1.10	2.4	Barcroft-Dixon
Intestines	dog	1.80	4.0	Brodie-Vogt
Kidneys	dog	2.60	5.8	Barcroft-Brodie
Salivary glands	cat	2.80	6.0	Barcroft-Piper
Suprarenal glands	cat	4.40	9.8	Neumann
Spleen	cat	5.00	10.1	Verzár
Pancreas	dog	5.30	11.8	Barcroft-Starling
Brain	rabbit	9.40	20.1	Yamakita
	dog	9.95	22.1	Gayda

after 1 hour (Heymans et al.). Neurons of newborn animals are much more resistant to interruption of oxygen supply than adult ones (Wertheimer). Their oxygen consumption is less than that of the adult brain, possibly owing to a less developed vascularization (Kabat and Dennis).

ANOXEMIA

If such a complete interruption of blood supply is confined to a limited part of the brain or spinal cord, the death of this area is followed by a process of repair originating in the surrounding normal tissue, and softening occurs. Between this complete destruction and the effects of a mild, transitory interruption of blood supply there are numerous intermediary stages producing different histopathologic pictures.

ETIOLOGY OF ANEMIA

The etiologic factors leading to a diminution or complete interruption of the blood supply of the brain are manifold. The most common one is the process of arteriosclerosis in aging blood vessels. It is quite unusual to find

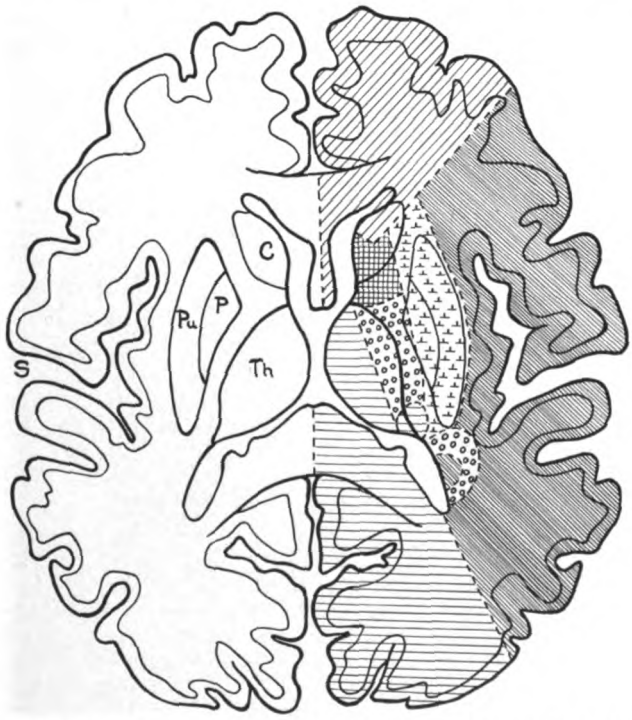


FIG. 64. DIAGRAM OF HORIZONTAL SECTION THROUGH BRAIN ILLUSTRATING DISTRIBUTION OF CEREBRAL ARTERIES

S = lateral cerebral fissure (fissure of Sylvius). C = caudate nucleus. Pu = putamen. P = globus pallidus. Th = thalamus

anterior cerebral artery

anterior choroidal artery

anterior communicating artery

superficial branch of middle cerebral artery

deep branch of middle cerebral artery

posterior cerebral artery

(After Foix and Schiff-Wertheimer: Rev. d'oto-neuro-opht. 4: 561, 1926. Courtesy Gaston Doin & Cie)

a brain of a person older than 60 years that does not show grossly a thickening and atherosclerosis of the larger arteries, especially the basilar arteries, with formation of yellow and whitish plaques within the vessel walls.

Hyperplasia of the elastic tissue of the intima to a greater or lesser degree is considered a physiologic change of advancing age. The vessel wall may undergo other pathologic changes that interfere with the free exchange of fluids. Calcification, localized or generalized (described as a familial form), may occur, even in young individuals (fig. 85). Toxins circulating in the blood affect the endothelium of the capillaries, producing swelling or even necrosis followed by hemorrhage or diapedesis of red blood cells. The

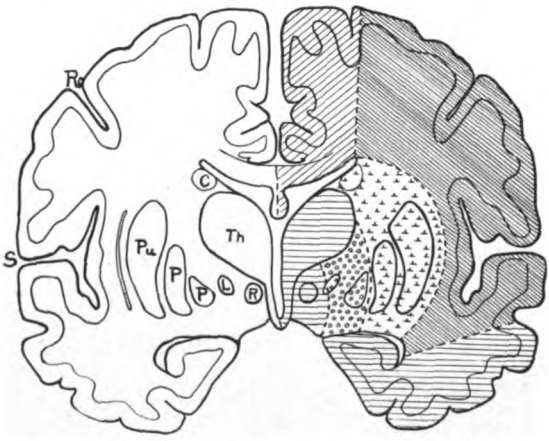


FIG. 65. DIAGRAM OF FRONTAL SECTION THROUGH BRAIN ILLUSTRATING DISTRIBUTION OF CEREBRAL ARTERIES

S = lateral cerebral fissure (fissure of Sylvius). Ro = central sulcus (fissure of Rolando). C = caudate nucleus. L = nucleus hypothalamicus (corpus Luysii). P = globus pallidus. Pu = putamen. R = red nucleus. Th = thalamus

anterior cerebral artery

anterior choroidal artery

superficial branch of middle cerebral artery

deep branch of middle cerebral artery

posterior cerebral artery

(After Foix and Schiff-Wertheimer: Rev. d'oto-neuro-optht. 4: 561, 1926. Courtesy Gaston Doin & Cie)

vessel wall may be affected from without by a rapidly growing tumor, by toxins circulating in the perivascular spaces, or by inflammatory processes.

Sudden and complete interruption of blood supply may be brought about by occlusion of a vessel by an embolus or thrombus. The former may arise from tissue of the inner wall or valves of a diseased heart or from the lungs. Thrombus formation may follow sudden coagulation of blood at a point where the lumen of an arteriosclerotic vessel abruptly becomes

narrower or where the inner surface has become roughened following disease of the intima (figs. 82, 139).

Vascular malformation is more frequently the reason for unusual clinical pictures of cerebral vascular damage than the average textbook description would lead one to expect. Figures 64 to 66 represent the average distribution of the more important cerebral vessels. But one should always have in mind the possible anatomic variations. The anterior cerebral

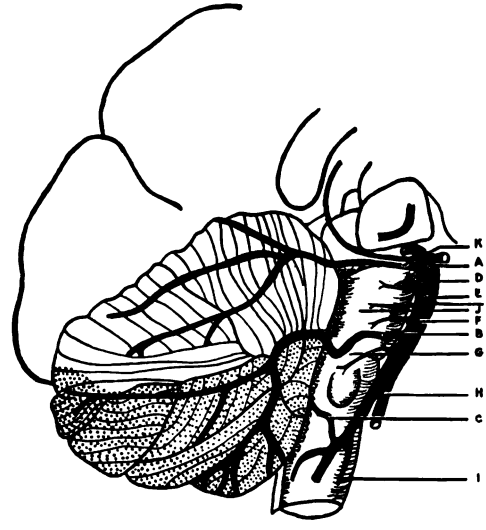


FIG. 66. ARTERIES OF CEREBELLUM, PONS, AND MEDULLA OBLONGATA

A = posterior cerebral artery. B = middle cerebellar artery. C = inferior cerebellar artery. D = transverse pontine artery. E and F = basilar artery (at E elevated to demonstrate paramedian artery behind it). G = lateral medullary artery. H = vertebral artery. I = medullary artery. J = pons. K = superior cerebellar artery

(*Foix, C., and Hillemand, P.: Rev. neurol., 1925. Courtesy Masson & Cie*)

artery usually arises from the internal carotid artery, but in exceptional cases it may arise from the middle cerebral artery or the anterior choroid artery. The posterior cerebral artery in 25 per cent of all cases branches off from the internal carotid artery. The anterior choroidal artery may be composed of two branches, one arising from the cranial division of the internal carotid artery to supply the paleostriatum and pyriform cortex, the other from the caudal division to supply the remainder of the choroidal field (Abbie).

The middle cerebral artery is more frequently the site of embolism than the posterior cerebral or the vertebral artery. The anterior cerebral

Hyperplasia of the elastic tissue of the intima to a greater or lesser degree is considered a physiologic change of advancing age. The vessel wall may undergo other pathologic changes that interfere with the free exchange of fluids. Calcification, localized or generalized (described as a familial form), may occur, even in young individuals (fig. 85). Toxins circulating in the blood affect the endothelium of the capillaries, producing swelling or even necrosis followed by hemorrhage or diapedesis of red blood cells. The

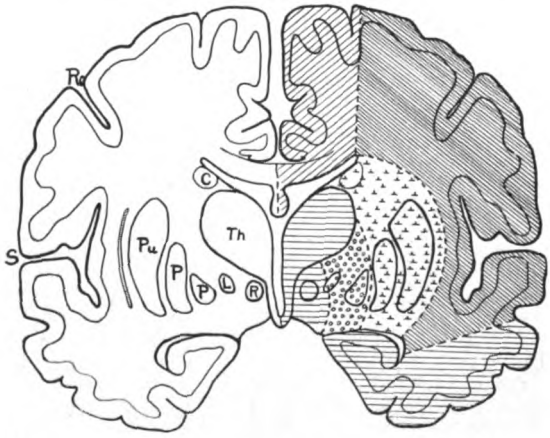


FIG. 65. DIAGRAM OF FRONTAL SECTION THROUGH BRAIN ILLUSTRATING DISTRIBUTION OF CEREBRAL ARTERIES

S = lateral cerebral fissure (fissure of Sylvius). Ro = central sulcus (fissure of Rolando). C = caudate nucleus. L = nucleus hypothalamicus (corpus Luysii). P = globus pallidus. Pu = putamen. R = red nucleus. Th = thalamus

anterior cerebral artery

anterior choroidal artery

superficial branch of middle cerebral artery

deep branch of middle cerebral artery

posterior cerebral artery

(After Foix and Schiff-Wertheimer: Rev. d'oto-neuro-opht. 4: 561, 1926. Courtesy Gaston Doin & Cie)

vessel wall may be affected from without by a rapidly growing tumor, by toxins circulating in the perivascular spaces, or by inflammatory processes.

Sudden and complete interruption of blood supply may be brought about by occlusion of a vessel by an embolus or thrombus. The former may arise from tissue of the inner wall or valves of a diseased heart or from the lungs. Thrombus formation may follow sudden coagulation of blood at a point where the lumen of an arteriosclerotic vessel abruptly becomes

narrower or where the inner surface has become roughened following disease of the intima (figs. 82, 139).

Vascular malformation is more frequently the reason for unusual clinical pictures of cerebral vascular damage than the average textbook description would lead one to expect. Figures 64 to 66 represent the average distribution of the more important cerebral vessels. But one should always have in mind the possible anatomic variations. The anterior cerebral

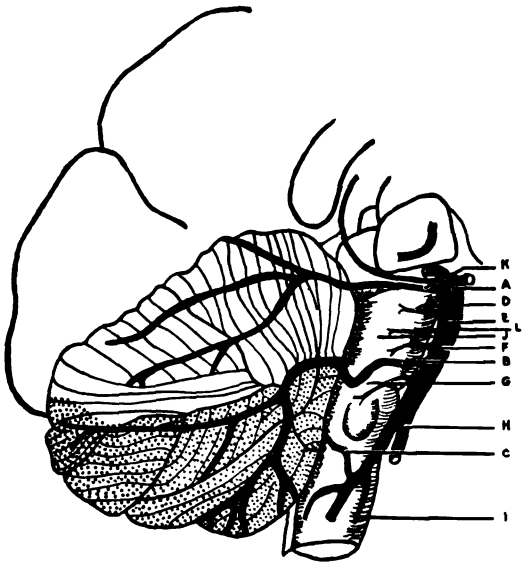


FIG. 66. ARTERIES OF CEREBELLUM, PONS, AND MEDULLA OBLONGATA

A = posterior cerebral artery. B = middle cerebellar artery. C = inferior cerebellar artery. D = transverse pontine artery. E and F = basilar artery (at E elevated to demonstrate paramedian artery behind it). G = lateral medullary artery. H = vertebral artery. I = medullary artery. J = pons. K = superior cerebellar artery

(*Foix, C., and Hillemand, P.: Rev. neurol., 1925. Courtesy Masson & Cie*)

artery usually arises from the internal carotid artery, but in exceptional cases it may arise from the middle cerebral artery or the anterior choroid artery. The posterior cerebral artery in 25 per cent of all cases branches off from the internal carotid artery. The anterior choroidal artery may be composed of two branches, one arising from the cranial division of the internal carotid artery to supply the paleostriatum and pyriform cortex, the other from the caudal division to supply the remainder of the choroidal field (Abbie).

The middle cerebral artery is more frequently the site of embolism than the posterior cerebral or the vertebral artery. The anterior cerebral

artery is least involved. Figures 64 to 66 indicate the area in which softening will follow occlusion of a given artery.

In the modern literature, sudden spasm of the smooth muscles of cerebral vessels has been held responsible for certain types of widespread, multiple softening, or, in milder, transitory forms without histologic changes, for the cortical stimulation in the convulsive states. Its anatomic basis is the nervous regulation of the cerebral vessels, a fact that has been generally acknowledged. The destruction of these vasomotor nerves in certain intoxications (carbon monoxide) explains the circulatory disturbances following weeks or months after the original damage.

Anemic Softening of the Brain

It is evident that the damage and repair following interruption of blood supply will depend upon different factors—the duration of the interruption, the size and the histologic structure of the area involved, and the presence of disease simultaneously affecting the vitality of the surrounding tissue. Furthermore, there will be a difference in reaction in cases in which the interference with blood supply has been produced by complete occlusion of a vessel without hemorrhage (anemic softening), by softening of the cortex combined with multiple small hemorrhages (hemorrhagic softening), by massive hemorrhages, or by diffuse lesions of the capillary endothelium (brain purpura).

First, the anatomic and histologic picture of an extreme case of complete and sudden interruption of a cerebral artery may be described. When death occurs within twenty-four hours it may sometimes be impossible to delineate the affected area. Larger foci within the white matter appear somewhat jelly-like, differentiated from the surrounding region by a light yellowish color and softer consistency. After the first day the tissue undergoes more definite changes. Though it may be difficult to recognize grossly an anemic area in a fresh brain, it may be distinguished after formalin fixation by its different shade of color and by its voluminous appearance. If several days have elapsed, the consistency of this area will be very soft, comparable to that of Camembert cheese. After three weeks the focus appears white, creamlike. A cystlike transformation of the anemic focus, containing fluid, points to an age of several months. Such cysts may exist for years, with partial absorption of the fluid and formation of a trabecular meshwork filling out the shrunken cavity.

Histologically the sequence of events will be as follows: As early as from 8 to 24 hours following the lesion, polymorphonuclear leukocytes may be seen in the affected area. They have erroneously been taken as indicating an infection, but careful studies have revealed cultural sterility in such areas. These leukocytes disappear very quickly (within from 3 to 6

days). A few hours after the interruption of blood supply, the nervous tissue of the anemic focus begins to disintegrate. Neurons and glia cells lose their staining qualities, the nuclei are pale, the cellular processes disappear (figs. 67–70). Neurons are more susceptible to anoxemia than the supportive tissue. Both are more resistant to infiltrative gliomas and to the plaque formation in disseminated sclerosis than are myelin sheaths.

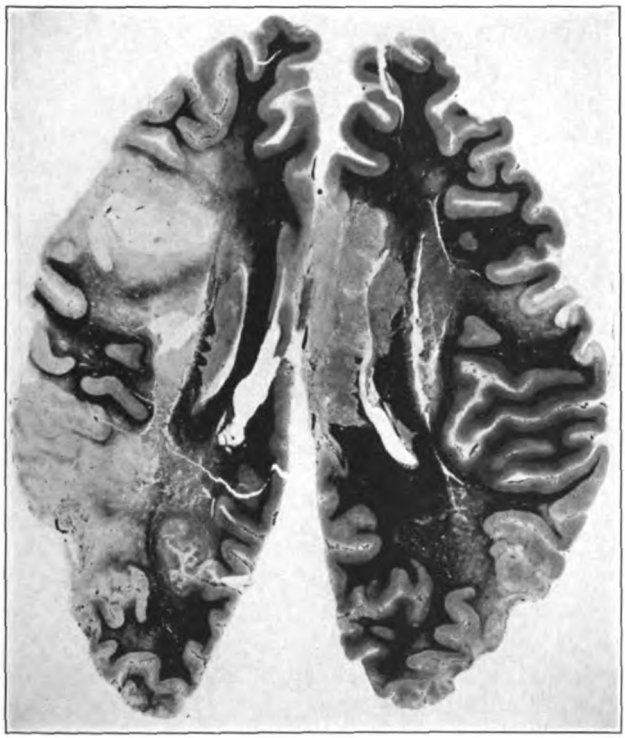


FIG. 67. MULTIPLE ANEMIC SOFTENING IN ARTERIOSCLEROSIS
Horizontal section. Weil stain. Thrombosis of left middle cerebral artery and multiple small areas of softening in right cortex

The following data, in addition to the data on neuronal changes that have been cited above, may give an approximate idea of the time necessary to produce various histopathologic changes in anemia of the human brain.

In the *glia*, first signs of disintegration appear in 3 hours. Increase in the number of nuclei is seen in from 14 to 15 hours. Gitter cells first appear in from 32 to 48 hours. Large basophilic astrocytes in tangential layers

are found in from 24 to 40 hours. New formation of glia fibers occurs in 3 days.

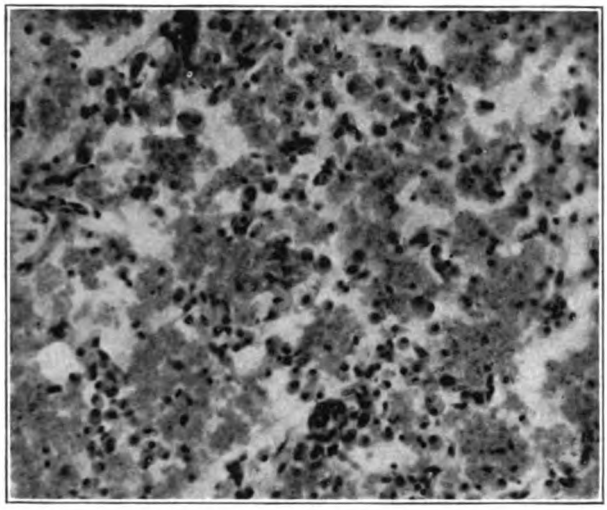


FIG. 68. ANEMIC SOFTENING FOLLOWING THROMBOSIS OF MIDDLE CEREBRAL ARTERY
Gray matter of cerebral cortex. Hematoxylin-eosin stain. Compound granular corpuscles appear in necrotic area

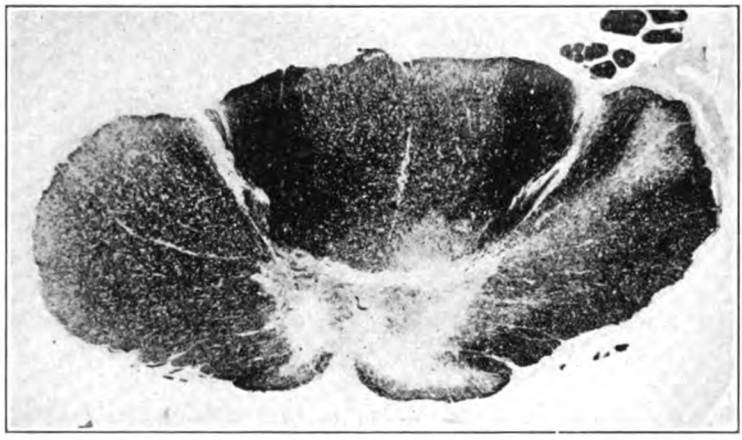


FIG. 69. ANEMIC SOFTENING FOLLOWING THROMBOSIS OF ANTERIOR SPINAL ARTERY
Dorsal segment of spinal cord. Weil stain. Anterior horns and part of lateral columns are necrotic

In the *mesenchyme*, widening of capillaries takes place in 15 minutes. Circular hemorrhages appear in carbon monoxide poisoning after from 3

to 7 hours. Metachromatic staining of endothelial cells is seen after 15 hours. Swelling of the intima and media is found in 2 days. Formation of mitotic figures takes between 1 and 2 days. Sprouting of capillaries occurs after 48 hours.

In the *axis-cylinders*, swelling and nodule formation appear in 24 hours; disintegration, and tendency to droplet formation and thickening, in 6 days.

In the *myelin sheaths*, change in staining is seen after 24 hours.

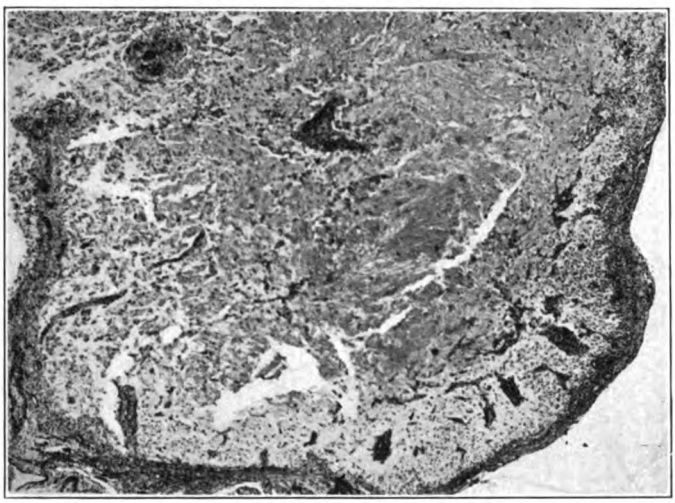


FIG. 70. HIGHER MAGNIFICATION OF ANTERIOR HORN SHOWN IN FIG. 69

Accumulation of compound granular corpuscles and increase in capillaries and connective tissue fibers in periphery of anemic focus. Hematoxylin-eosin stain

The mesenchyme of the anemic area may be more resistant and may survive. From the remaining capillaries and from the periphery, fibroblasts and capillary sprouts are seen invading the necrotic area on the second day. At the same time large round cells with small, half-moon-like, peripherally located nucleus appear (gitter cells) (fig. 40). As early as two days following the lesion, they may be seen in large numbers breaking up and digesting the necrotic tissue.

In the early stages fragments of myelin sheaths and axis-cylinders may be recognized along with red blood cells or parts of neurons. The myelin debris stains early by the Marchi method; later it is transformed into substances staining with sudan III.

Laden with fat droplets, the gitter cells wander toward the perivascular

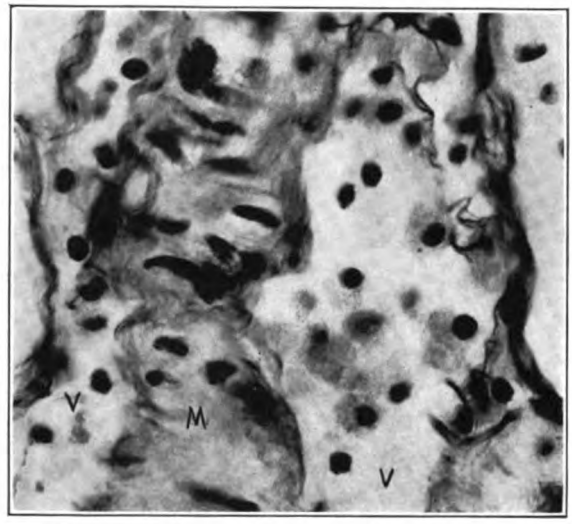


FIG. 71. PERIVASCULAR LYMPHATICS (VIRCHOW-ROBIN SPACES)

Environment of focus of anemic softening. Klarfeld-Achucárro stain. Cortical artery cut tangentially. In center, media is cut longitudinally, and perivascular lymphatics filled with compound granular corpuscles are seen on both sides. M = media. V = Virchow-Robin spaces

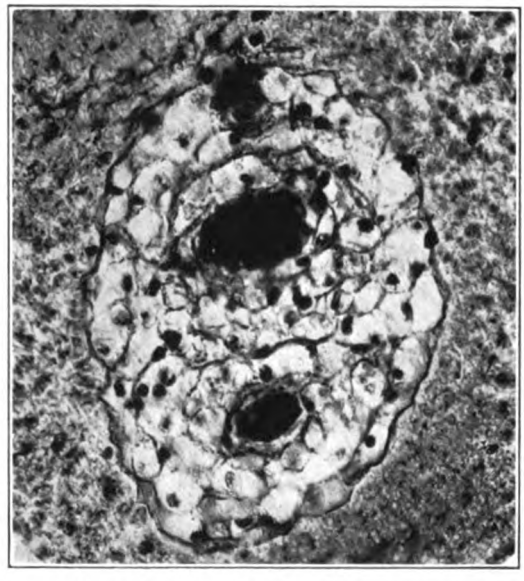


FIG. 72. PERIVASCULAR LYMPHATICS

Organized myelopathy of spinal cord. Klarfeld-Achucárro stain. Compound granular corpuscles caught in meshes of perivascular spaces

spaces of the arteries in the surrounding normal tissue, where they either disintegrate or remain in shrunken forms for many months or even years (figs. 71, 72). Not all of them can escape; many of them are caught in the meshwork of the fine connective tissue fibers that encircle the anemic area. After this first emergency wall formation of the mesenchyme, the fibrous glia surrounding the wall begins to proliferate. Gradually, coarse glia fibers intermingle with the connective tissue and partly replace it. They penetrate into the focus itself and after some time form a dense glial scar replacing the original brain tissue of smaller foci (figs. 73, 74).

The process of repair following interruption of blood supply is not the same in the brain of an adult and in that of a newborn child. In the young brain an anemic focus is not repaired by mesenchymal and glial scars. Here the debris becomes liquefied and cysts or cavities remain; these probably are responsible for porencephalia in young children.

In old, arteriosclerotic brains, in cachexia, or in chronic disease, the vitality of mesenchyme and glia may be impaired to such a degree that organization may be retarded. Instead of proliferating blood vessels and glia fibers, there will be found a homogeneous, sometimes caseous mass devoid of nuclei. Large areas of softening, involving for example a whole frontal lobe, may remain in this condition or may undergo cystic degeneration with fluid formation (fig. 75). Coagulation necrosis is found only in older people, in whom the necrotic tissue cannot be digested and removed as in younger persons. It has been found mostly in the neighborhood of foci of anemic softening and near the ventricular wall.

Between this complete and lasting interruption of blood supply and mild, temporary interruption through spasm of the blood vessels, lasting for only a few seconds, many transitional stages occur. The blood supply may be only partly diminished by narrowing of a vessel following arteriosclerosis or endarteritis, by pressure of a tumor, or by infiltration of the perivascular spaces with products of disintegration, with tumor cells, growing yeast cells (Torula), etc.

A transitory anemia may produce death of neurons only while the glia cells remain intact. The threshold of stimulation in such a case does not seem to be high enough to lead to the formation of compound granular corpuscles. The structure of the area involved remains intact. In cresyl violet–stained sections one may find pale-staining areas within the cortex in which the neurons have disappeared or are degenerated, while glia nuclei only are seen. There is, however, no glia proliferation or fiber formation in such areas.

It is not clear whether the edematous area around blood vessels in arteriosclerotic brains, with mild demyelinization and mild proliferation of fibrous glia in the environment, is due to sclerosis of the vessel wall interfering

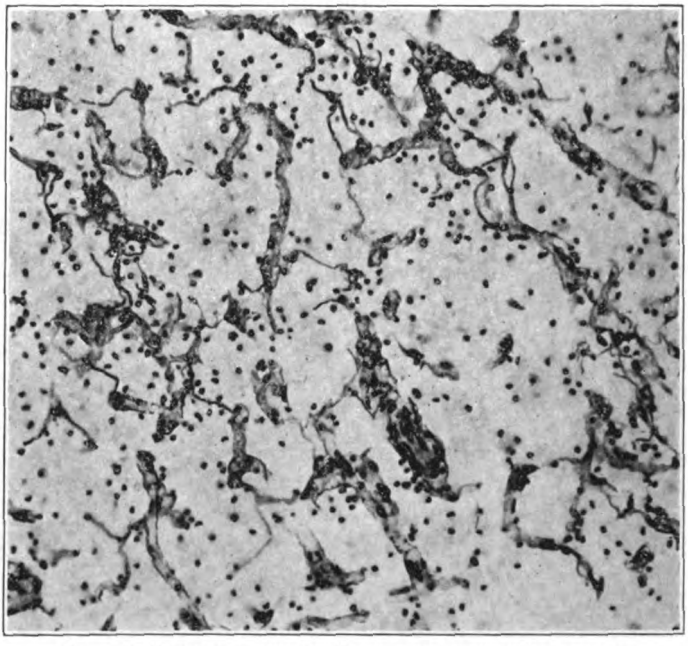


FIG. 73. ORGANIZATION OF FOCUS OF ANEMIC SOFTENING
Klarfeld-Achucárro stain. Sprouting of newly formed capillaries into inner part of focus

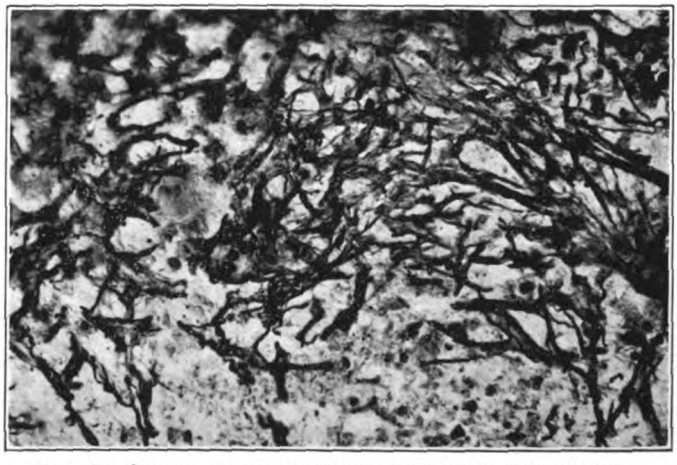


FIG. 74. ORGANIZATION OF FOCUS OF ANEMIC SOFTENING
Same section as in fig. 73. New formation of mesenchymal fibers in outer wall of anemic focus

with diffusion of oxygen, plasma, and tissue fluids, or whether it represents a toxic process due to the elimination of metabolic products retained in the blood following kidney and liver disease.

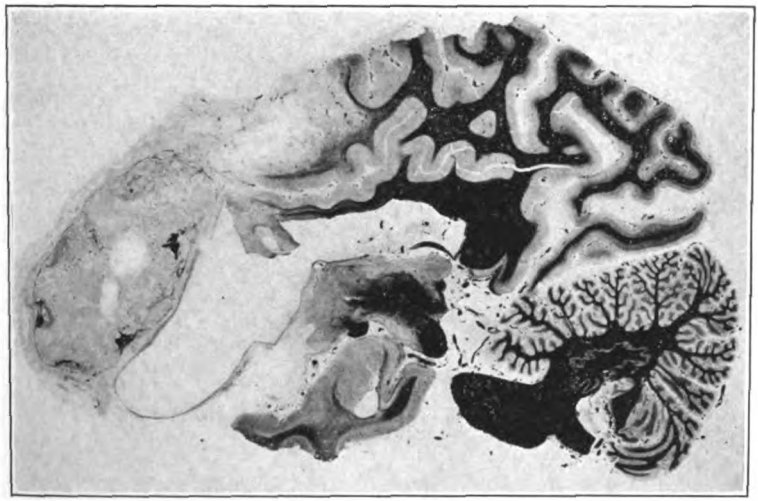


FIG. 75. THROMBOSIS OF ANTERIOR CEREBRAL ARTERY
Anemic softening of frontal lobe. Sagittal section through brain. Weil stain. Formation of cysts without organization

HEMORRHAGIC SOFTENING OF THE BRAIN

The sequence of events in hemorrhagic softening and necrosis following hemorrhage is not much different from that in the anemic type. It becomes more complicated in hemorrhages by reason of the destruction of tissue in the environment of the original hemorrhagic focus under the influence of the suddenly increased pressure of the blood ejected from the ruptured vessel. Furthermore, if the hemorrhage breaks through the outer layer of the cortex into the subarachnoidal spaces or into the ventricles, with invasion of the basal cisterns through the foramina of Magendie and of Luschka, the organization of these meningeal hemorrhages will require additional effort of repair on the part of the piarachnoid. The red blood cells that overflow into the nervous tissue retain their original form for several days and therefore are a reliable indication of recent hemorrhage. Later on they disintegrate, are taken up by phagocytic cells that break down the hemoglobin into its components, protein and pigment or hemosiderin (pigmented compound granular cells) (fig. 76). The hemoglobin loses its iron and in this form, hematoidin, may be differentiated from the blue-

staining hemosiderin by its crystalline forms (platelets of yellow or brownish red color) and by the absence of blue staining with potassium ferrocyanide and hydrochloric acid (prussian blue formation). The hemosiderin appears in granular form first in phagocytic cells. These phagocytic cells break down after the digestive process has been completed and free blood pigment may then be seen in the original hemorrhagic area. Other cells take up this free pigment and carry it to the perivascular spaces in the neighboring region. As in anemic softening, many of the pigment-containing scavenger cells are caught in the meshwork of the newly formed wall (figs. 77, 78). The latter is not different in its histologic make-up from the wall around a focus of anemic softening; only the presence of pigment, free

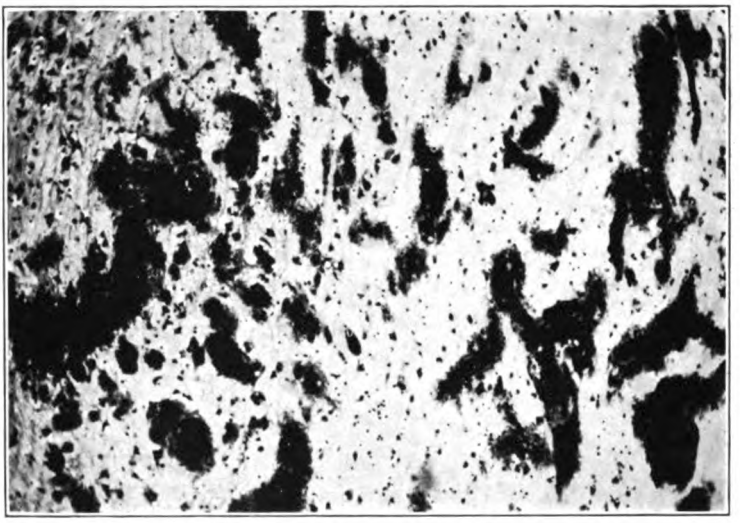


FIG. 76. DIFFUSE PERIVASCULAR HEMORRHAGES
Case of scarlatina in boy aged 5 years. Frontal cortex. Cresyl violet stain. Hemolysis in outer zone of hemorrhages

or inclosed in cells, will tell, after a period of a month, of the original insult. It may be valuable sometimes, especially for medicolegal purposes, to state the approximate age of an area of organized hemorrhage. Table 10, derived from experimental data pertaining to animals, may be a guide.

In summary it may be said that the presence of round red blood cells staining yellowish green in cresyl violet preparations indicates an age of not more than five days, free pigment outside of cells an age of approximately three weeks. It should be added that the red blood cells may disappear without formation of pigments. Isolated intact red blood cells may be encountered after several weeks.

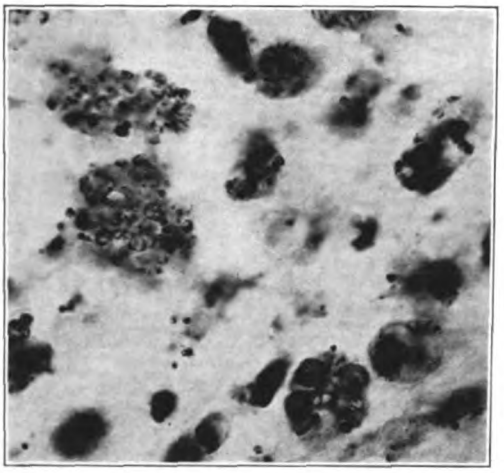


FIG. 77. SCAVENGER CELLS IN HEMORRHAGIC SOFTENING

Cerebral cortex. End of second week following hemorrhage. Cresyl violet stain. Scavenger cells laden with debris of red blood cells and coarse granules of hemosiderin

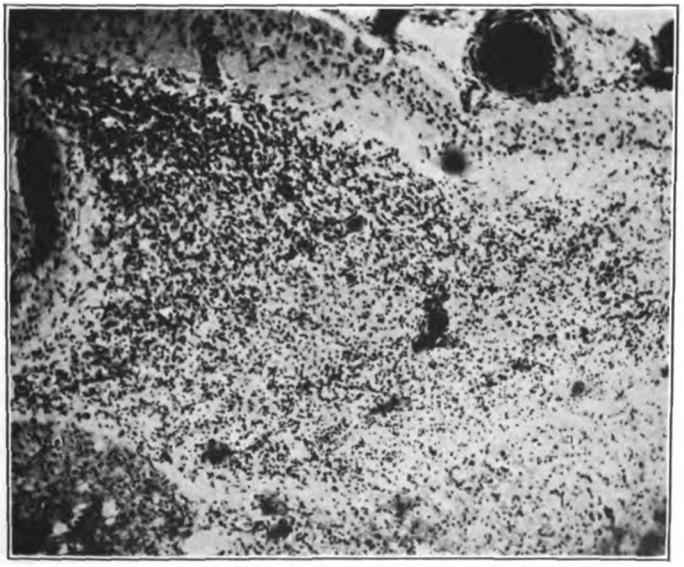


FIG. 78. ORGANIZED HEMORRHAGIC SOFTENING

Occipital cortex, 6 months after cerebral hemorrhage following tryparsamide treatment. Van Gieson stain. Proliferated neuroglia intermingled with newly formed capillaries and connective tissue fibers forming scar

Frequently the blackish granular pigment found in normal red blood cells or within the areas of recent hemorrhages has been taken to be hemosiderin. It is not generally known that such pigments arise under the influence of formalin fixation and do not indicate a beginning decomposition of hemoglobin intra vitam. Such a differentiation is very important from the medicolegal point of view. In doubtful cases the prussian blue test for hemosiderin or the golden brown color of hematoidin should easily decide the differential problem.

Brain Purpura

The passive necrosis of nervous tissue following total occlusion of larger blood vessels (softening) is different histologically from the necrosis of nervous tissue produced by multiple thrombosis of precapillaries or capil-

Table 10.—*Decomposition of Red Blood Cells*

No. days	Type of Change
2	swelling and decolorization of red blood cells
3	appearance of phagocytes containing red blood cells
4	shrinkage of red blood cells
5	first appearance of hemosiderin (positive reaction with potassium ferrocyanide and hydrochloric acid)
10	hemosiderin diffusely distributed in scavenger cells
12	granulation of hemosiderin
18	presence of free pigment outside of cells
25	decomposition of pigment containing corpuscles into very fine granules; formation of hematoidin
45	only iron-free pigment found in tissues: cells that contained this pigment have disappeared
After 6 wk. (approx.)	hemorrhage liquefied and surrounded by membrane stained yellow or golden brown

laries. Such foci of small ringlike necrotic areas, which are frequently surrounded by hemorrhage (brain purpura), have been described in different infectious diseases—pneumonia, scarlatina, malaria—or as following intoxication by poisonous war gases, or occurring after severe burns, and also in pernicious anemia. In the older literature such multiple petechial hemorrhages have been described as "encephalitis haemorrhagica." However, the absence of mesenchymal reaction or of migration of white blood cells excludes assumption of an inflammatory process. Histologically, one finds the center of such a focus formed by a thrombosed precapillary or capillary. The endothelium of the vessel is destroyed, perhaps through the action of toxins circulating in the blood; thrombosis follows this lesion of the wall. Around these small vessels a necrotic area devoid of nuclei

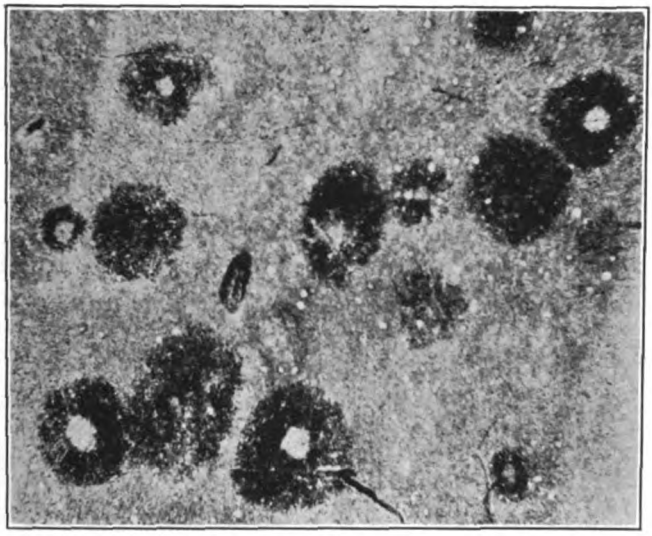


FIG. 79

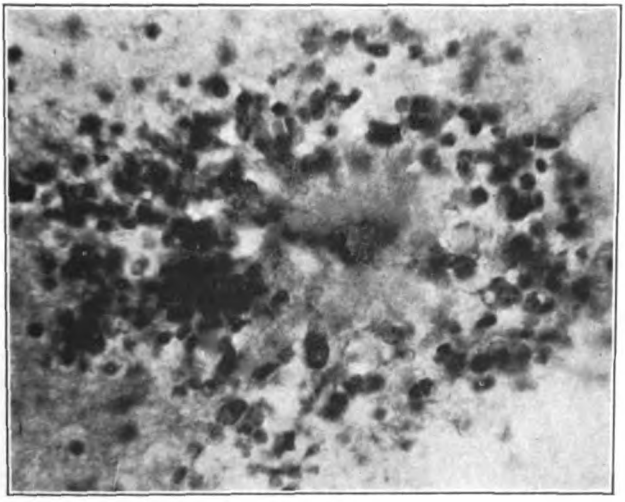


FIG. 80

FIGS. 79, 80. BRAIN PURPURA IN CASE OF INFLUENZA

Fig. 79. White matter of cerebral cortex. Ringlike hemorrhages around thrombosed and necrotic vessels. Hematoxylin-eosin stain.

Fig. 80. Ringlike arrangement of glia cells around necrotic perivascular area. Cresyl violet stain

is seen; the latter have perhaps been destroyed by the same toxin that acted upon the endothelial cells. Then follows a zone of proliferated glia cells forming a wall around the necrotic area. Outside of this wall an infiltration of red blood cells is seen extending diffusely into the brain tissue. Within the focus of necrosis the myelin sheaths can no longer be stained, and in silver-impregnated material a destruction of the axis-cylinders is seen (figs. 79, 80). The hemorrhage originates centrally from the thrombus, where the pressure of the blood, encountering resistance, bulges the thin wall of the capillary or precapillary. If rupture occurs at this point, the blood will flow alongside the thrombosed vessel and surround the necrotic area, provided that time enough has elapsed to allow formation of a glia wall.

VI

ARTERIOSCLEROSIS

Vascular Disease in Arteriosclerosis

The term "arteriosclerosis of the brain" embraces different vascular diseases that may exist as separate entities or in various combinations. They are *atherosclerosis*, *arteriolosclerosis*, *arteriocapillary fibrosis*, and *calcification of the media*.

Atherosclerosis

The diagnosis of an atherosclerosis of a larger cerebral artery may often easily be made with the naked eye. Yellowish or grayish plaques irregularly spread in the vessel wall are the more common sign. The artery is hard and brittle, its wall is thickened, and the lumen narrow. Most frequently the basilar artery is involved, next the middle cerebral arteries, and the process can be followed into the finer ramifications of these vessels.

Our conception concerning the etiology of this process has undergone considerable changes during the last decade. Formerly it was thought that the primary process consisted in fatty degeneration and necrosis of the intima and media, followed by infiltration with lipoids and formation of a reactive connective tissue scar. On the basis of experimental evidence (Leary), we now assume that the cholesterol found within the plaques of the atheromatous vessel wall is a primary deposit followed by reactive phenomena. It originates within the Kupffer cells of the liver, where cholesterol is esterified. These cells become detached, crowd the lymphatics, circulate in the blood stream, and finally, in contact with the arterial wall, penetrate into the subendothelial layer.

In young persons this incursion of globular lipophages into the subendothelial tissue of the intima is followed by production of young fibroblastic tissue, and the young fibroblasts surround and metabolize the lipoids without leaving a final connective tissue scar. This minimal scarring is due to the fact that young fibroblasts do not form collagen. In middle age, scar formation surrounding such foci of cholesterol-containing foam cells will interfere with nutrition, and necrosis occurs, with formation of secondary atheromatous abscesses. In old age, when there is no longer any formation of young fibroblastic tissue that will metabolize

the cholesterol esters, globular lipophages accumulate in masses. The inadequate nutrition is the reason for necrosis of these plaques and formation of a primary atheromatous abscess. Calcification may arise in connection with the necrosis or after the necrosis has developed.

The affinity of the cholesterol-laden cells for the intima of blood vessels has been explained as "chemotaxis." Lesions of the intima following trauma, infections, or intoxications will enhance such an attraction. Saturation of plasma with cholesterol may lead to formation of macromolecular colloidal films covering the endothelial lining and interfering with the nutrition of the vessel walls. This may be followed by swelling and proliferation of the endothelial cells, which engulf the colloid and are thus transformed into foam cells (Hueper).

This pathologic process begins after the fortieth year. It is produced earlier or accelerated by intoxication with alcohol or lead, in gout, or following various chronic infections. Contributing to the primary etiology are mechanical factors (abnormal blood pressure, disuse with increasing age), chemical factors (high blood content of lipoids, cholesterol, or endotoxins), and vasomotor disturbances. The destruction of the elastic membrane and later of the media is followed by a loss of elasticity and of adaptability to the ever changing blood pressure. The narrowing of the lumen following the intima proliferation results in a diminished blood supply; this can be only partially overcome by the increased blood pressure. The predilection of the intima as regards the degenerative process, as is seen in the larger cerebral vessels, is for the type of atherosclerosis found in the aorta, while in the vessels of the extremities and the larger arteries of the abdomen, the media is first diseased as a rule.

ARTERIOLOSCLEROSIS

The histologic changes of the smaller arterioles and precapillaries of the cerebral hemispheres and the nuclei of the brain in arteriosclerosis are different from the atheroma formation and intima proliferation of the larger vessels. Here we find the picture of hyaline degeneration of the vessel wall (arteriolosclerosis). In sections stained by van Gieson's method, the wall of such a vessel stains brilliant red; with eosin it stains bright red or to rose color. The structure is homogeneous and the design of the finer collagenous fibers has been lost. Most authors explain this process as caused by the diffusion of plasma into the widened meshes of the subendothelial tissue, with ensuing swelling that leads to degeneration and hyalinization of the intima. Others assume that the degeneration of the intima, with liberation of proteins, leads to formation of antibodies that react again with the degenerated mesenchymal fibers, the product of this immunoreaction being the hyalin.

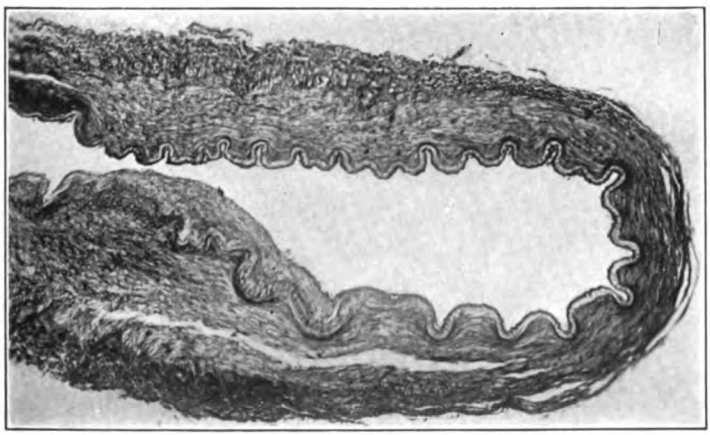
The hyalin may undergo fatty degeneration, with subsequent destruction of the vessel wall. The endothelial lining may remain intact or may only

FIG. 81 (*left*). ATHEROSCLEROSIS OF BASILAR AND VERTEBRAL ARTERIES

Combined with arteriolosclerosis of spinal cord in man aged 23 who was suffering from ganglioneuroma of suprarenal glands and hypertension

FIG. 82 (*below*). ATHEROSCLEROSIS OF BASILAR ARTERY

Proliferation of intima with thickening of elastica interna.
Hematoxylin-eosin stain



be swollen. The whole process finally leads to a narrowing or complete obliteration of the lumen (fig. 84).

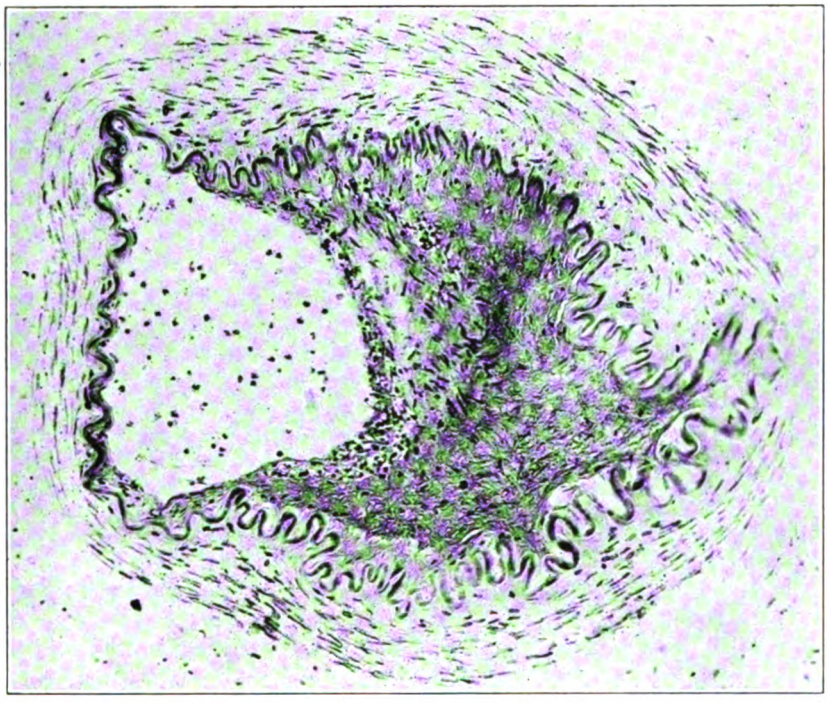


FIG. 83. ARTERIOSCLEROSIS OF BRAIN: PROLIFERATION OF INTIMA OF MIDDLE CEREBRAL ARTERY

Proliferation of both endothelium and subendothelial fibroblasts. Elastica interna is broader and edematous. Van Gieson stain

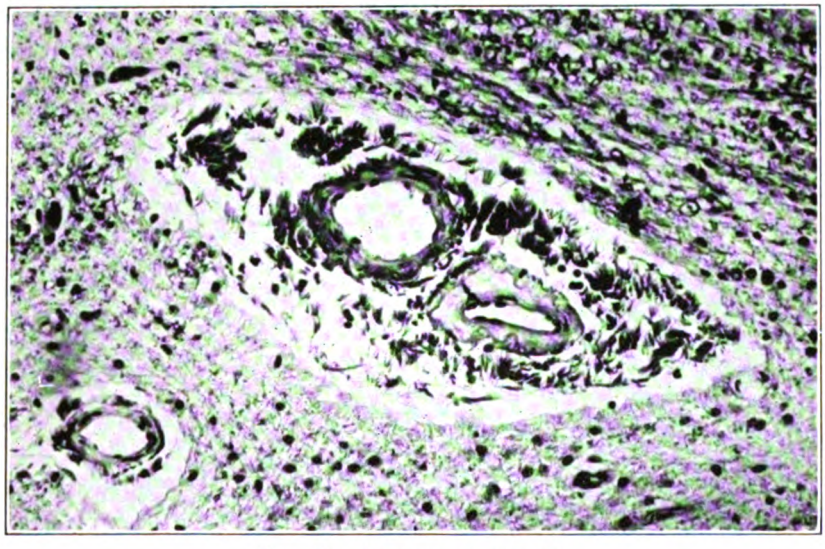


FIG. 84.—ARTERIOLOSCLEROSIS

Central small arteries of spinal cord in case of syphilis of spinal cord. Van Gieson stain. Hyaline degeneration of vessel wall

CALCIFICATION OF THE MEDIA

Calcification of the media, a process that occurs independently in the larger arteries of the extremities (arteria radialis, femoralis), has been described as occurring occasionally in the larger arteries of the basal ganglia, especially in the globus pallidus. But most authors do not consider this process an important factor in the etiology of arteriolosclerosis of the brain.

Occasionally one may find within and in the neighborhood of foci of softening a generalized calcification of the vessel walls, with absence of atherosclerosis or arteriolosclerosis in other parts of the brain. Penfield

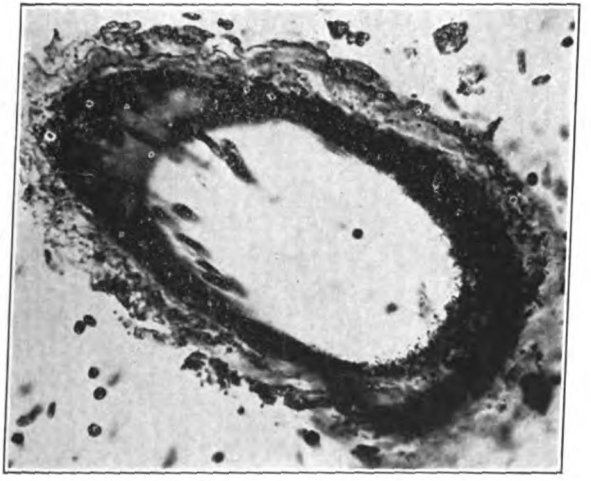


FIG. 85. CALCIFICATION OF MEDIA
Case of arteriosclerosis of brain with arteriolosclerotic kidneys and uremia. Cresyl violet stain

has described such a generalized calcification of the smaller cerebral vessels as a familiar occurrence. Among our own material was found a case of anemic softening of the midbrain with calcification of the wall of the surrounding vessels. It remains open to discussion whether this calcification was primary, an expression of disturbed metabolism, or secondary to the softening (fig. 85).

ARTERIOCAPILLARY FIBROSIS

Arteriocapillary fibrosis may occur independently of the other forms of arteriosclerosis in senile brains, but frequently it is associated with arteriolosclerosis and atherosclerosis. In order to demonstrate the process, it

is necessary to apply special staining methods, preferably the Klarfeld-Achucárro tannin-silver method or the Bielschowsky method. Stern's method for glia also will bring out the fine fibers. In the outer layers of the cerebral cortex or in the white matter, one finds a dense meshwork of very fine fibrils encapsulating the capillaries. These "silver fibers" cannot be stained by the van Gieson method for collagenous fibers. They may also be found around larger vessels. With increasing number they compress the fine capillaries, narrowing their lumens and interfering with circulation. The nuclei of the endothelium finally degenerate and stain dark bluish in cresyl violet–stained preparations (fig. 86).

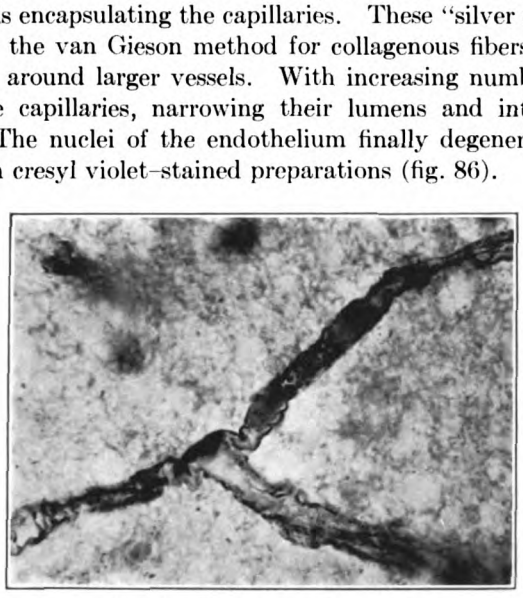


FIG. 86. CAPILLARY FIBROSIS

Frontal cortex in case of arteriosclerosis of brain. Klarfeld-Achucárro stain. Capillary surrounded by meshwork of argyrophile fibers

PATHOLOGY OF THE BRAIN

If we remember the sensitiveness of the nervous parenchyma to diminution or interruption of blood supply, it will be evident that these different diseases of the cerebral vessels must be followed by profound and diffuse changes in the brain itself. The sequence of events following interference with blood supply has been described above. In the following sections certain types of arteriosclerosis of the brain will be instanced.

APOPLEXY

The massive hemorrhages of the apoplectic attack have been subdivided into those occurring (1) in the claustrum and putamen, (2) in the upper half of the white matter of the hemispheres, and (3) in the pons (Schwartz and Goldstein). Besides arising in these regions, they may originate in different parts of the cortex. Frequently hemorrhages into the basal ganglia are combined with atherosclerosis of the larger vessels at the base

of the brain, while the latter may be found normal in cases of hemorrhage into the white matter. At autopsy a large smooth-walled cavity filled with coagulated blood is found. If the hemorrhage penetrated into a ventricle, the whole ventricular system and the subarachnoidal spaces at the base are filled with blood. Besides the massive hemorrhages into the hemispheres, multiple smaller ones are found in the surrounding region and, in about one-fourth of all cases, in the pons. What is most impressive is the massive loss of cerebral substance in cavities that may measure 5 cm. and more in diameter (fig. 88).

Many theories have been advanced to explain such sudden and massive hemorrhage. The classic theory of the formation of miliary aneurysms of the cerebral vessels that suddenly burst no longer satisfies the modern investigator. It is known that aneurysm formation and atherosclerosis

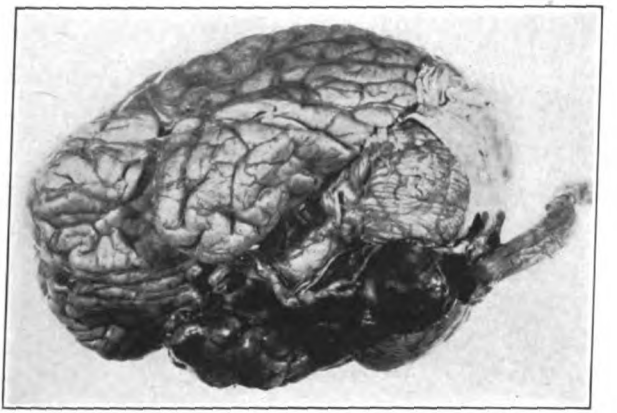


FIG. 87. ANEURYSM OF BASILAR ARTERY

may be absent, while only arteriolosclerosis is found. Besides, the hemorrhages do not seem to originate in one vessel only, but are multiple in type and are found in regions remote from the larger cerebral focus (pons). Some authors assume therefore that two different factors are combined in the production of the apoplectic hemorrhage. The first is an anemic softening that develops in the region of the diseased vessels within the brain or that may be produced by occlusion or spasm of larger vessels outside the brain. Within this focus, which does not necessarily become completely necrotic but may show only a mild edema with swelling or demyelinization of the surrounding nerve fibers, degeneration of the vessel wall gradually develops, followed by hemorrhage, by diapedesis, and, finally, when the blood pressure is suddenly increased, by the bursting of a larger vessel. Other authors assume that functional disturbances of the

is necessary to apply special staining methods, preferably the Klarfeld-Achucárro tannin-silver method or the Bielschowsky method. Stern's method for glia also will bring out the fine fibers. In the outer layers of the cerebral cortex or in the white matter, one finds a dense meshwork of very fine fibrils encapsulating the capillaries. These "silver fibers" cannot be stained by the van Gieson method for collagenous fibers. They may also be found around larger vessels. With increasing number they compress the fine capillaries, narrowing their lumens and interfering with circulation. The nuclei of the endothelium finally degenerate and stain dark bluish in cresyl violet–stained preparations (fig. 86).

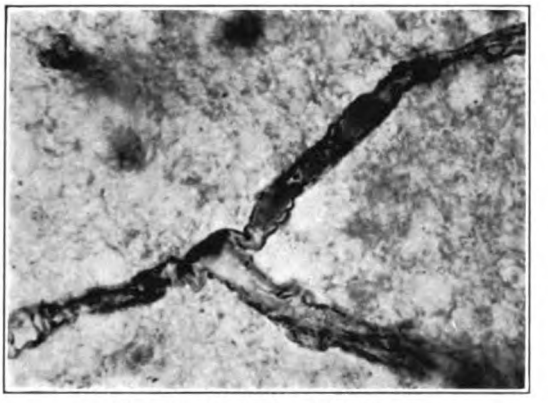


FIG. 86. CAPILLARY FIBROSIS

Frontal cortex in case of arteriosclerosis of brain. Klarfeld-Achucárro stain. Capillary surrounded by meshwork of argyrophile fibers

PATHOLOGY OF THE BRAIN

If we remember the sensitiveness of the nervous parenchyma to diminution or interruption of blood supply, it will be evident that these different diseases of the cerebral vessels must be followed by profound and diffuse changes in the brain itself. The sequence of events following interference with blood supply has been described above. In the following sections certain types of arteriosclerosis of the brain will be instanced.

APOPLEXY

The massive hemorrhages of the apoplectic attack have been subdivided into those occurring (1) in the claustrum and putamen, (2) in the upper half of the white matter of the hemispheres, and (3) in the pons (Schwartz and Goldstein). Besides arising in these regions, they may originate in different parts of the cortex. Frequently hemorrhages into the basal ganglia are combined with atherosclerosis of the larger vessels at the base

of the brain, while the latter may be found normal in cases of hemorrhage into the white matter. At autopsy a large smooth-walled cavity filled with coagulated blood is found. If the hemorrhage penetrated into a ventricle, the whole ventricular system and the subarachnoidal spaces at the base are filled with blood. Besides the massive hemorrhages into the hemispheres, multiple smaller ones are found in the surrounding region and, in about one-fourth of all cases, in the pons. What is most impressive is the massive loss of cerebral substance in cavities that may measure 5 cm. and more in diameter (fig. 88).

Many theories have been advanced to explain such sudden and massive hemorrhage. The classic theory of the formation of miliary aneurysms of the cerebral vessels that suddenly burst no longer satisfies the modern investigator. It is known that aneurysm formation and atherosclerosis

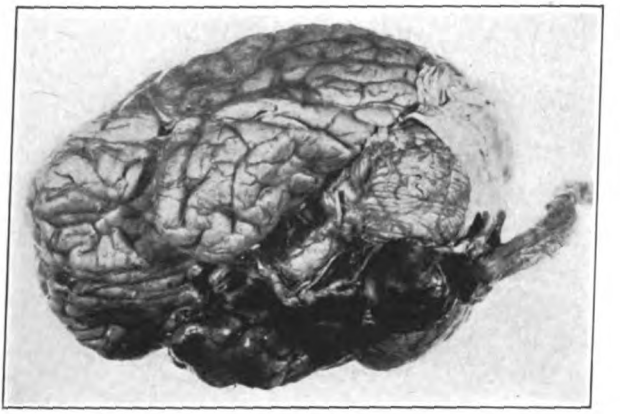


FIG. 87. ANEURYSM OF BASILAR ARTERY

may be absent, while only arteriolosclerosis is found. Besides, the hemorrhages do not seem to originate in one vessel only, but are multiple in type and are found in regions remote from the larger cerebral focus (pons). Some authors assume therefore that two different factors are combined in the production of the apoplectic hemorrhage. The first is an anemic softening that develops in the region of the diseased vessels within the brain or that may be produced by occlusion or spasm of larger vessels outside the brain. Within this focus, which does not necessarily become completely necrotic but may show only a mild edema with swelling or demyelinization of the surrounding nerve fibers, degeneration of the vessel wall gradually develops, followed by hemorrhage, by diapedesis, and, finally, when the blood pressure is suddenly increased, by the bursting of a larger vessel. Other authors assume that functional disturbances of the

vasomotor regulation of cerebral circulation are the primary factor. In hypertonia a sudden spasm produces anemia, or a paralysis of vasomotor nerves with dilatation produces stasis, both followed by softening. Capillary hemorrhages into this focus contribute to general dissolution of brain tissue and the final massive hemorrhage.

In evaluating these different theories, it seems that the solution of the problem will not be found in generalizations. Various possible causes

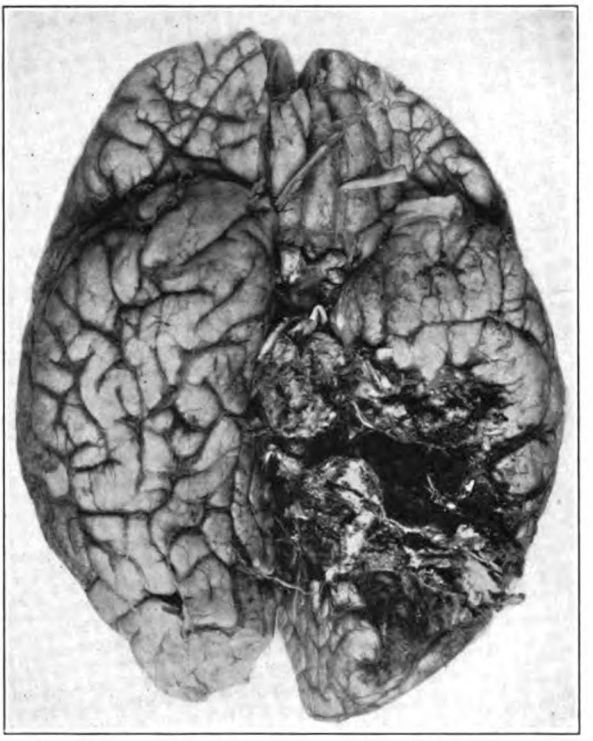


FIG. 88. APOPLECTIFORM CEREBRAL HEMORRHAGE
Hemorrhage into occipital lobe

may exist—i. e., primary vascular disease or primary functional disturbance of vasomotor regulation.

THE ARTERIOSCLEROTIC BRAIN

The arteriosclerotic brain is usually somewhat atrophic. The leptomeninges show milky discoloration and are thickened and adherent to the underlying cortex. In vertical sections a widening of the ventricular system may be found, owing to shrinkage of the cortex (hydrocephalus

internus ex vacuo). The perivascular spaces may appear widened even to the naked eye. An accumulation of these spaces is called état criblé ("sievelike state"). This should be differentiated from état lacunaire, in which the small cysts are the residue of multiple foci of softening and are not arranged perivascularly. These conditions are frequently found in the basal ganglia, especially in the striatum. It should be remembered, however, that even in the normal brain wide, fluid-filled spaces around blood vessels may be seen at the base of the putamen and globus pallidus (figs. 89, 90).

Instead of formation of one large focus or multiple smaller foci of softening, there may be softening of the cortex as a whole. In such a case there will be found, extending over one or more gyri, a complete softening of the gray matter, which is separated from the piarachnoid only by a small

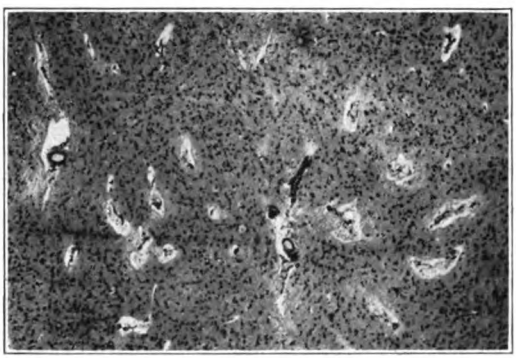


FIG. 89. ETAT CRIBLÉ
Striatum in arteriosclerosis of brain

margin of glia tissue, and is rather sharply demarcated from the white matter.

The scars forming after cortical softening produce many bizarre pictures. The cortex may show formation of holes, imitating a worm-eaten state (état vermoulu), or there may be deep fissures (fig. 92).

It is not always possible to determine from old scar formations whether the preceding softening was anemic or hemorrhagic. After periods of many months or years, the residue of the blood pigments may have completely disappeared. In more recent foci of hemorrhagic softening, features similar to those of anemic softening may be recognized—localization of the hemorrhages in the cortical gray, multiple perivascular hemorrhagic foci in the white matter and the basal ganglia.

The conditions that have been described are the end stages of total

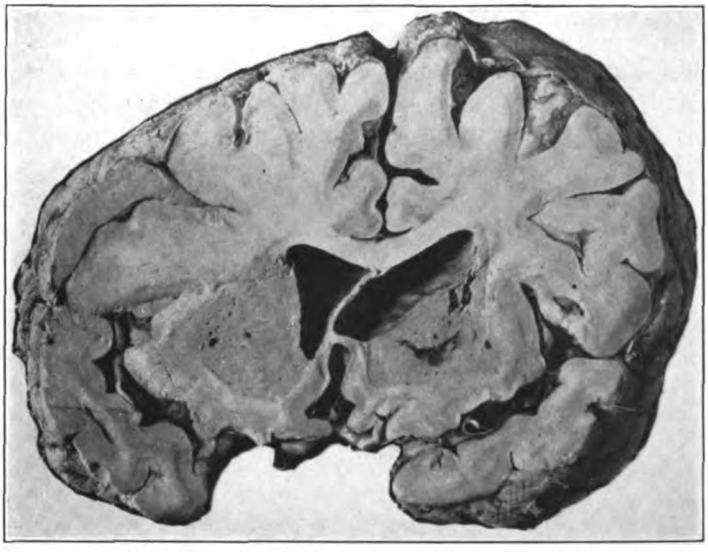


FIG. 90. CYST FORMATION IN NEOSTRIATUM

Parkinsonian syndrome in case of arteriosclerosis of brain. Other cysts were found in substantia nigra

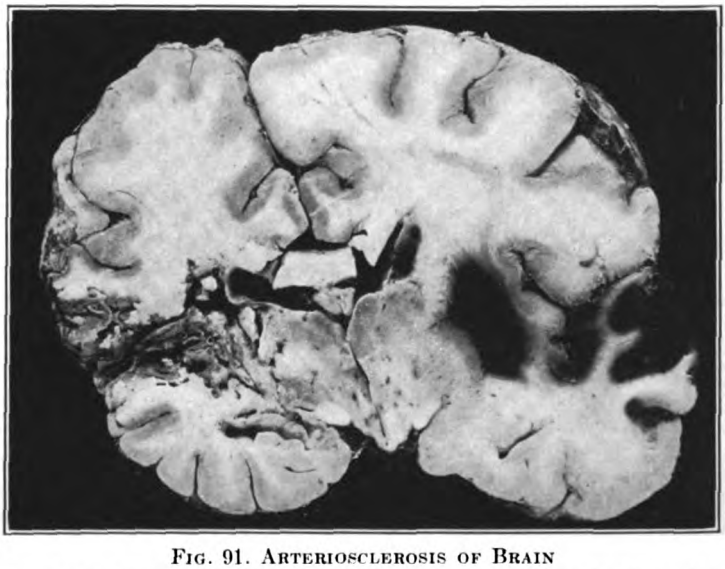


FIG. 91. ARTERIOSCLEROSIS OF BRAIN

Anemic softening in left hemisphere and hemorrhagic softening in right, involving approximately symmetric regions

interruption of blood supply, with subsequent death of nervous tissue. Besides these extremes, milder transitional forms are known, in which merely temporary spasm or stasis of the circulating blood produces death of the more sensitive neurons but leaves the glia intact. Histologically, such foci in the cortical gray impress one by their paler staining with cresyl violet, and by the absence of neurons with preserved glia nuclei; the latter sometimes are increased in number, corresponding to an increase in fibrous glia in Holzer-stained sections.

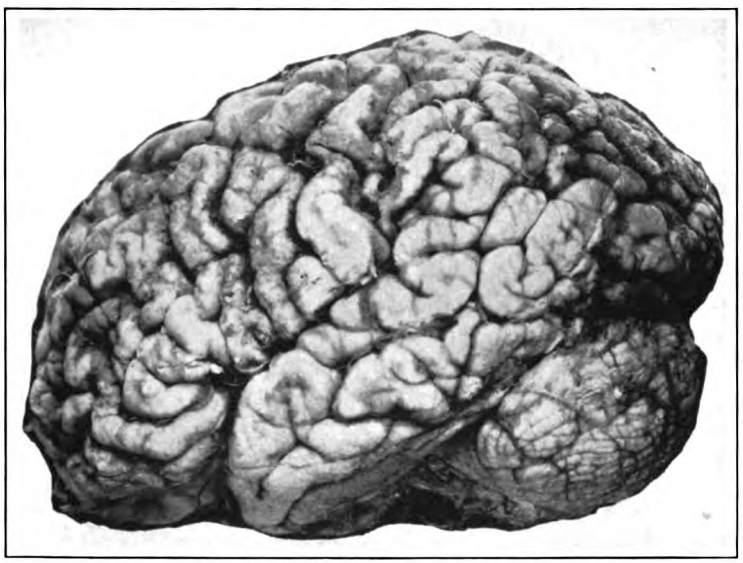


FIG. 92. ARTERIOSCLEROSIS OF BRAIN

Cortical changes: verrucose appearance of middle frontal and anterior central gyrus with operculum; état vermoulu in upper part of supramarginal gyrus

Other vascular generalized diseases leading to a narrowing of the lumens of blood vessels or interference with nutrition following disease of the vessel wall may also produce more or less advanced and extended necrosis of cerebral tissue. Examples may be found in the literature among cases of thrombo-angiitis obliterans or periarteritis nodosa. Massive necrosis of the brain involving both ectodermal and mesodermal tissues has been described in other forms of angiitis of unknown origin (N. A. Levy).

It is evident that all the different forms of vascular disease described in relation to arteriosclerosis of the brain may occur in manifold variations within the same brain, and every attempt to establish certain types

of arteriosclerotic disease characterized by typical histologic pictures meets with difficulties. The different types of apoplexy in combination with different forms of vascular disease have been mentioned above.

TABLE 11.—*Pathologic Changes in Senile and Presenile Types of Arteriosclerosis*

Type of Change	Percentage	
	Senile Type	Hypertonic Type
Hypertrophy of heart	10	100
Arteriosclerotic contracted kidney	60	60
Arteriosclerosis of aorta	90	30
Arteriosclerosis of coronary arteries	20	30
Atherosclerosis of basilar artery	80	60
Hyaline degeneration	70	100
Apoplexy	5	40
Hemorrhagic softening	20	40
Anemic softening	100	40

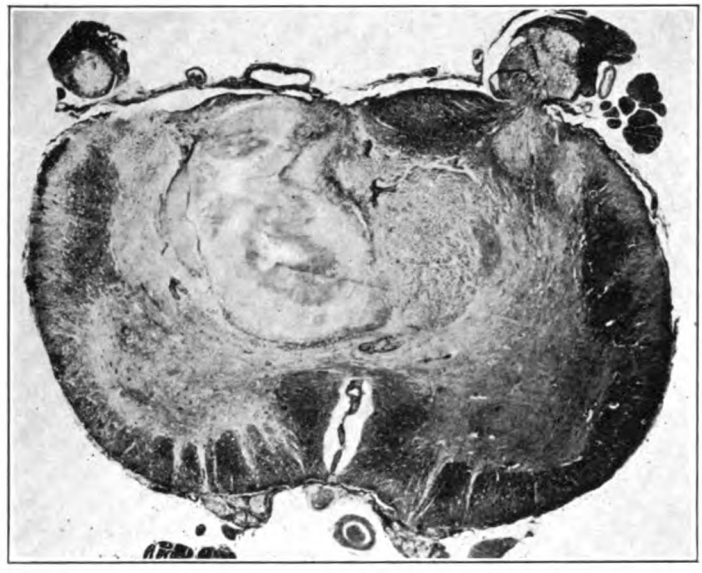


FIG. 93. ARTERIOSCLEROSIS OF SPINAL CORD
Hemorrhagic softening in posterior columns. Van Gieson stain. Organization of 4 weeks' duration

The theory that certain constitutional types (as the "pyknic" type of Kretschmer, the "typus digestivus" of Chaillou and MacAuliffe) have a predisposition to arteriosclerosis, has been disproved by statistics.

Neubürger differentiates a senile from a presenile type with hypertension. He gives an interesting tabulation that contrasts the different pathologic organic changes in these two types (table 11).

Arteriosclerosis of the Spinal Cord

The changes that have been described as regards the cerebral vessels also affect the blood vessels of the spinal cord. In older persons, there is found rather constantly a hyaline transformation of the walls of the central arteries, with mild perivascular edema. The atherosclerosis of the anterior spinal artery may sometimes be detected with the naked eye by reason of the thickening and the convoluted appearance of the vessel. Isolated foci of demyelinization, with a mild increase of fibrous glia, are the residue of foci of softening. Sometimes larger foci of triangular form, with their bases at the periphery of the spinal cord section, are found. An analogy to the massive anemic softening or the apoplectic hemorrhage in the brain is only very rarely found in the spinal cord, in the form of a myelomalacia involving the whole or a great part of the segment. Anterior horn cell degeneration in the form of pigment increase or other degenerations of the neurons is frequently found in arteriosclerosis of the spinal cord. It is, however, present also in senile brains without marked vascular disease (fig. 93).

VII

INFLAMMATION

Definition

The conception of inflammation was first created by the clinician, and to the pathologist was left the task of finding the histologic phenomena corresponding to the four syndromes of "rubor," "tumor," "calor," and "dolor." The definition of inflammation has been and still is the subject of an ardent discussion in the literature. We may define it in two different ways. Either we look for the causes that produce the phenomenon and study in a utilitarian way the reaction of the body to the damage, in which case inflammation is defined as "a protective reaction of the body against the agent attacking the tissues"; or we study as histologists the changes occurring in an organ that during life showed the phenomenon of inflammation, describe the histopathologic changes that are found, and then define inflammation as "primary alteration of the tissue with secondary reaction of the vascular mesenchymal tissue in the form of cellular exudation and proliferation." The causative agent may either invade the organism from without (exogenously) or may be produced by changes of the body or its parts (endogenously). In the first case we may differentiate between infectious causes (micro-organisms) and noninfectious causes (chemical, thermic, mechanical, and anaphylactic).

The direct application to the brain of observations pertaining to other organs of the body is responsible for many controversies regarding the conception of encephalitis. It was often forgotten that besides the mesenchymal structures the ectodermal glia plays an important part in the defense reaction of the central nervous system. If we adhere to the first definition, that inflammation is a reaction of defense against tissue damage, then the formation of a fibrous glia wall surrounding an invading tumor, the proliferation of glia around a necrotic area in endogenous intoxication, the neuronophagia of cells destroyed by bacterial toxins, are inflammatory reactions, or encephalitis. If we adhere to the thesis that primary alteration followed by exudation and proliferation of the mesenchymal derivatives is the essential histologic feature of encephalitis, then the perivascular leukocytic infiltration in the neighborhood of large foci of anemic softening, together with the sprouting of capillaries and fibroblasts, is an encephalitis.

The subject has become more complicated through the attempt that has been made to draw conclusions from a certain type of inflammatory reaction

regarding an etiologic agent common to the type. Inflammation was thought to be synonymous with infection. If the type of perivascular plasma cell infiltration that is peculiar to general paresis was found, it was argued that one was dealing with a chronic type of infection, possibly produced by a spirochete. If mesenchymal cellular exudation was minimal, mesenchymal proliferation absent, and the progressive glia reaction dominant, in the presence of intense necrosis of myelin sheaths and axis-cylinders, as in leuko-encephalitis, it was assumed that the same filtrable virus was responsible for these lesions as found in various diseases. On the other hand, the combination of necrosis of tissue with active proliferation of the surrounding glia, with mild mesenchymal exudation, and sometimes with pronounced mesenchymal vascular proliferation, as seen for example in pseudosclerosis, is classified as a toxic-degenerative process.

Spielmeyer has pointed out similar discrepancies. He prefers to restrict the designation "-itis" to the syndrome of "alteration, exudation, and proliferation," if it can be proved that this process is independent of other brain lesions such as tumors, softening, etc. In the latter case he speaks of "symptomatic or reparative encephalitis" (fig. 105). He also warns against forming any conclusion as to the agent in a case of unknown etiology from the histologic picture alone. The bacteriologist and the experimental research worker should have precedence over the histologist when it comes to investigation of the unknown etiology of a given disease.

There should be no questioning of the principle that the pathologist should have the last word in the anatomic diagnosis of a case. It is, however, a matter of personal feeling whether one should compromise with the clinician and apply the term encephalitis to the histologic picture one sees in the white matter of the brain of a child that suffered from chickenpox and showed a neurologic syndrome called "encephalitis" by the clinician, or whether one should call it an "encephalopathy of probably toxic origin." It is important that both clinician and pathologist be aware of the peculiarity of histologic reaction in this specific disease and that they refrain from any conclusions as to the factor causing the lesion until the problem has been cleared up in experimental research. On the other hand, an exact nomenclature is essential for mutual understanding. Therefore, it will be best at present to restrict "-itis" (as in the terms encephalitis, myelitis, neuritis) to a process in which primary lesion of nervous tissue produced by the toxins of micro-organisms, or other toxic substances, is connected with perivascular infiltration of round cells of mesenchymal origin and proliferation of fibroblastic or neuroglial elements. If the lesion of nervous tissue is not connected with any defense reaction of glial or mesenchymal elements, we shall designate it by the suffix "-pathy" (encephalopathy, myelopathy, neuropathy). "Malacia" (encephalomalacia, myelomalacia) is synonymous with softening. It is understood that the

suffix "-itis" means "inflammatory" in the sense that it applies to a defense reaction of the nervous tissue to a noxious agent. The presence of glia differentiates this process in the brain from inflammation in other organs of the body. The nature and concentration of the noxious agent may possibly decide the relative parts that ectodermal and mesodermal derivatives take in this reaction of simultaneous defense and repair.

Consequently, inflammations of the nervous system may be classified into three groups: (1) predominantly mesenchymal reaction, e.g., purulent encephalitis and meningitis in pyemia, syphilis, tuberculosis; (2) predominantly glial reaction, e.g., encephalitis following measles, vaccination, smallpox, and typhus, encephalitis of endotoxic origin, brain purpura; (3) mixed type reaction, e.g., lethargic encephalitis, acute poliomyelitis.

In the descriptions in the following sections, the etiology of an inflammatory reaction will decide the classification of a given disease process. Consequently we shall differentiate between infectious and noninfectious diseases and subdivide the latter as toxic (endo- and exotoxic) and traumatic diseases.

The Hemato-encephalic Barrier

The central nervous system is well protected against invasion by toxins and micro-organisms through various membranes that are generally called the "hemato-encephalic barrier." To be exact, three different sets of membranes must be assumed: (1) the blood-liquor barrier, formed by the endothelial lining of the vessels of the choroid plexus and its ependymal cells and by the walls of the pial vessels; (2) the liquor-brain barrier, formed by the ependymal lining of the ventricles and the pia-glia membranes covering the surfaces of the brain and spinal cord and forming the outer wall of the perivascular lymphatics (Virchow-Robin spaces) (fig. 94); (3) the blood-brain barrier, represented by the walls of the capillaries.

These three different types of membranes show differences in permeability in relation to colloidal substances, to substances in molecular solution, and to electrolytes. It seems that the electrical charge plays an important role in determining the permeability of a substance. According to Friedemann, positive charge or absence of charge allows toxins to pass the cerebral capillaries at the *p*H of the blood. The latter may be impermeable to substances carrying a negative charge. This may explain the greater toxicity of cobra venom and of the toxin of lamb dysentery, which carry a positive charge, as compared with the slow action of the tetanus, diptheria, and botulinus toxins, which carry a negative charge. The blood-liquor barrier is semipermeable. Colloids are normally not found in the cerebrospinal fluid, but substances in molecular solution, like glucose, may pass. The latter is found in from 45 to 62 per cent of the amount of the blood sugar. A similar relation between the concentrations

in blood and liquor respectively exists in the case of urea and creatin and of certain drugs such as alcohol, acetone, chloroform, and urotropin.

The fact that in relation to electrolytes an equilibrium is easily established was utilized for demonstration of changes in permeability of the hemato-encephalic barrier under various pathologic conditions. The bromide method (Walter), which is based on determination of the relative amounts of bromides in blood and spinal fluid following several days' feeding of potassium bromide, is frequently used. Normally the amount of bromides

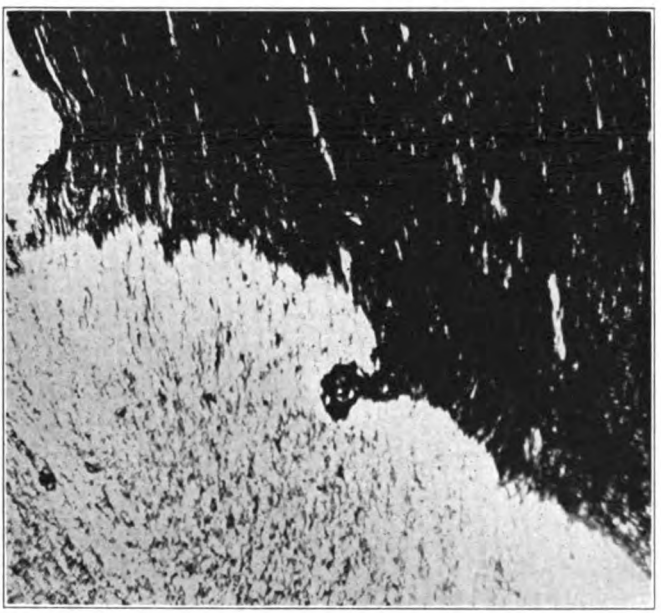


FIG. 94. PIA-GLIA MEMBRANE

Eighth nerve at its exit. Van Gieson stain. Connective tissue endoneurium is stained dark black, while glia endoneurium is very lightly stained

in the blood is from 2.9 to 3.5 times that in the spinal fluid. These figures become smaller, i.e., the permeability to bromides is increased in different types of meningitis (from 1.3 to 2.4 in acute meningitis, from 1.7 to 2.4 in tuberculosis, and from 2 to 2.7 in experimental aseptic meningitis) and in the different syphilitic manifestations (normal and higher values after malaria treatment of general paralysis). However, the original enthusiasm for this method has considerably decreased since it has been found that the original method of Walter for determination of bromide gave wide variations (Fremont-Smith et al.).

Together with electrolytes, larger colloidal particles may pass the barrier under such pathologic conditions. This fact explains the appearance of hemolytic amboceptors in the spinal fluid in general paralysis (Weil-Kafka reaction) and of isohemagglutinins or of ferments in certain infections and intoxications. The demonstration of an increased permeability during the agonal state will help to explain many generalized pathologic changes that are encountered during the final stages of infectious diseases.

Goldmann devised a classic experiment for the demonstration of these different types of membranes. If trypan blue is injected intravenously, the different organs of the body and the dura mater are vitally stained, but the brain substance itself remains unstained. If, however, the trypan blue is injected into the subarachnoidal spaces, the dye penetrates into the brain and its neurons, while the dura mater and the other organs of the body remain unstained. In the first case the injected animal does not show any cerebral symptoms; in the second case severe convulsions and paralysis are observed. These experiments prove that the blood-liquor and blood-brain barriers are impermeable to trypan blue, but the liquor-brain barrier is not. Later experiments have demonstrated that these facts cannot be applied generally to all colloidal dyes. It was found that colloids with small particles, of high dispersity, like fluorescein, may penetrate into the brain after intravenous injections, and that basic dyes easily penetrate into the brain substance but not into the liquor. The capacity of dyes to permeate depends on their electrical charge, a positive charge favoring, a negative charge reducing permeability. Basic dyes (safranine excepted) appear in the brain following intravenous injection. Some acid dyes, like acid fuchsin, do not stain at all; others, like eosin, stain only after injection of concentrated solutions. In all these cases of vital staining, the gray matter was more intensively stained than the white matter, a fact that Spatz tried to explain as due to the larger number of capillaries in the gray (cf. chap. v).

Injection of hypophysin, adrenalin, or thyroxin in relatively high concentration increases by as much as five times the permeability of the blood-brain barrier to cobra toxin, strychnine, alcohol, urethane, and paraldehyde (Friedemann and Elkeles); low concentrations of such hormones decrease the permeability (Gellhorn). Damage of the endothelial lining of the blood vessels makes them permeable to vital stains that normally would not penetrate. Such damage may be produced experimentally by injections of ether or chloroform. It plays an important role under pathologic conditions, when toxins circulating in the blood affect the endothelial lining of the intima.

The permeability of the membranes in the brain of the newborn child and of the senile differs from that of the normal adult brain. In the first case, substances that do not appear in the adult brain may be demon-

strated—such as bile pigments in cases of icterus in newborn children. In icterus in adults, only the dura mater is stained yellow, like the other organs of the body, while the brain and spinal cord remain colorless. In icterus neonatorum parts of the brain, the basal ganglia by predilection, are intensively stained. We must assume that this increased permeability of the vessels of the striate body persists throughout life. This will explain the selectivity of diffusion of toxic metabolites in liver disease (Wilson's disease). Experimental proof for the changes of permeability of blood vessels with increasing age is the fact that intravenous injection of acid fuchsin in very young rats produces convulsion, while it is harmless in adult rats. However, concomitant injection of theophylline increases the permeability to such a degree that in adult rats likewise a dose of .25 mg. per gram of weight will produce convulsions (Fröhlich and Mirsky). Injections of bile intraperitoneally produce convulsions in young rats only up to the age of 10 days, while intracerebral injection will also produce convulsions in adult rats (Senne). The same applies to permeability to virus with increasing age. Fifteen-day-old mice are 100 per cent susceptible to intramuscular or intra-abdominal inoculation with the virus of the eastern type of equine encephalomyelitis, while at the age of 1 month from 40 to 50 per cent are already resistant, and beyond the age of 3 months this resistance rises to 95 per cent (Sabin and Olitzky).

At present our knowledge concerning the fundamentals of these different types of permeability of cerebral vessels and membranes is still very limited. The examples above have been cited in order to point out the importance that this recently acquired knowledge may have in the future for a better understanding of the etiology of intoxications and infections of the central nervous system.

The following chapters contain examples demonstrating the affinity of certain types of infections for certain regions of the nervous system, or the selectivity of response of certain groups of neurons or glial elements to the effects of certain toxins. The conception of "pathoclisis" created by C. and O. Vogt assumed a definite chemical affinity between the affected tissue and the noxious agent. While a chemicophysical affinity may play a role in the effect of certain narcotics that are lipoid-soluble, or of myelolytic toxins, many cases of "local vulnerability" (Spielmeyer) cannot be explained merely on the basis of such an affinity between tissue and toxin. From the examples of membrane selectivity cited above, it seems likely that the dispersity of a colloidal toxin or minute virus, its acid or basic nature, the permeability of the blood vessels of a given region, and the normal or pathologic conditions of the vascular endothelium or of the ependymal cells, will be of no lesser importance in determining the localization of an intoxication or infection.

VIII

INFECTIONS

The Mode of Invasion of Micro-organisms

Micro-organisms may invade the central nervous system in different ways. They may enter by way of the blood, if, following an infection elsewhere in the body, micro-organisms are circulating in the blood. Of 294 cases of diptheria treated with antitoxin, 4.4 per cent showed involvement of the central nervous system; of 137 cases of transverse myelitis, 5.1 per cent were secondary to known infections; of 422 cases of meningitis, 5.7 per cent followed infections of the head (Foster Kennedy). The micro-organisms form thrombi in the smaller vessels and capillaries, and their toxins produce necrosis of the vessel wall, which breaks down and allows an overflow of micro-organisms into the surrounding region. Around such a small focus of infection a small abscess is formed. Polymorphonuclear leukocytes act as phagocytes and their debris—fragmented nuclei—testifies to the struggle with the invader. Often such multiple abscess formation in the cortex ends very soon with death, and no time is left for a protective reaction of the glia or connective tissue. The neurons in the neighborhood of such a miliary abscess show severe degeneration (fig. 111). However, experimental injections of bacteria into the carotid artery or aorta rarely produce encephalitis and then only in brains that have been injured in one way or another A greater frequency of encephalitis was observed where small emboli-producing granules were injected together with the bacteria, producing multiple areas of softening.

In cresyl violet–stained sections, colonies of micrococci may easily be recognized by their dark blue staining. Such metastatic abscess formation may follow an endocarditis or pneumonia. It occurs when, following an infected skull fracture or infected trauma of the brain (operation), micro-organisms gain access to a larger vessel.

Infection of the meninges may follow a primary abscess formation in the brain itself, or it may occur simultaneously with encephalitis in trauma or blood infection. Generalized primary leptomeningitis without encephalitis may also develop in blood infections that lead to different types of meningitis, which will be described later.

The lymph spaces that accompany the adventitia of the vessels and the perineurium of nerves entering the skull and the spinal canal are another

important means of entrance of micro-organisms into the central nervous system. In the brain two roads seem to be of special importance. One is the connection along the olfactory bulbs through the lamina cribrosa with the lymphatics of the nasal mucous membranes and from there indirectly with the lining of the maxillary sinus. The second is the direct connection along the eighth nerve with the perilymphatic spaces of the cochlea of the inner ear through the canaliculus cochleae. The connection with the lymphatics of the orbit is established along the route of the optic nerve into the perichoroidal spaces. Infections of the nasal cavity (sinuses), of the inner ear, or of the orbita may thus lead to a migration of micro-organisms via these perineural lymphatics into the subarachnoidal space. From there they have access to the brain substance along the pia sheaths that accompany the vessels and that together with the adventitia of the vessels form the lymphatics of the Virchow-Robin space (fig. 71).

As to the spinal cord, it is important to remember that the subarachnoidal spaces of the cervical, thoracic, and lumbar segments are connected along the lymphatics of the spinal nerves with the extensive lymphatics of the mediastinum, the retroperitoneal region, and the abdominal cavity.

Experimentally it can be domonstrated by injection of india ink at different levels of the subarachnoidal spaces that certain direct connections with the lymphatic system of the body exist. The intensiveness of staining of the lymph vessels and lymph nodes depends upon the site of the injection (Galkin). Injections into the caudal part of the spinal subarachnoidal spaces produce an intense black staining of the retroperitoneal, lumbar, and mesenteric lymph nodes, the nodes at the hilus of the spleen, the follicles of the large intestine, and some of Peyer's patches. Injections into the suboccipital spaces stain the nasal mucous membranes, the deep and superficial lymph nodes of the neck, and the lymph nodes along the trachea. After ligation of the spinal cord at the level of the second cervical vertebra, injections below the ligation produce an intensive staining of the lymph nodes of the mediastinum, but those of the neck are not stained. In man it was found that inflammatory lesions of the leg were followed by inflammation of the lumbar spinal cord, while arm infections produced cellular infiltration in the cervical spinal cord.

The epidural lymph spaces seem to be more independent. Infectious processes invading the cranial cavity or the spinal canal through lesions of the skull or vertebrae are usually localized on the outer surface of the dura mater, which reacts with an intense connective tissue proliferation in an attempt to encapsulate the infectious focus. The invasion of the subarachnoidal spaces, however, leads to an extensive inflammatory reaction, eptomeningitis, followed by encephalitis or myelitis.

Extradural infection may spread to the brain and cerebellum along

perivascular and perineural lymphatics without producing a diffuse leptomeningitis. A common combination is that of extradural and cerebellar abscess formation following suppurative labyrinthitis.

There seems to be a predilection in certain types of infections for different parts of the central nervous system. If the inflammatory process is localized in the gray matter, we add the prefix "polio-," meaning "gray" (polio-encephalitis, poliomyelitis); if it is localized in the white matter, we add "leuko-." If the meningitis affects mostly the lower surface of the brain, we speak of "basilar" meningitis. Spatz has tried to arrange the different types of encephalitis in the following six groups, according to their localization.

Classification of Infections

1. meningo-encephalitis

The micro-organisms either invade the subarachnoidal space from the lymphatics mentioned above and spread along the base of the brain through the foramina of Luschka and of Magendie into the fourth ventricle, or they are eliminated from the choroid plexus (arteria chorioidea). From the subarachnoidal spaces the infection spreads along the blood vessels into the brain substance.

2. metastatic or embolic disseminated encephalitis

Colonies of micro-organisms floating in the blood form thrombi in the capillaries of the brain. Surrounding each small thrombus, an area of inflammation develops. These foci may be spread all over the brain. Sometimes there is a predilection for the gray matter or, if the deep branch of the middle cerebral artery is invaded, they may be found in the white matter of the hemispheres and the basal ganglia.

3. diffuse polio-encephalitis

The most important representative of this group is general paresis. The infection spreads continuously over the gray matter of the cortex and the striatum. Plasma cells form the main part of the cellular perivascular infiltration.

4. disseminated polio-encephalitis

This is represented by the different types of epidemic encephalitis, a "nonpurulent" encephalitis, i.e., characterized by the absence of polymorphonuclear leukocytes in larger numbers. It has a preference for certain parts of the brain stem, especially the midbrain. The substantia nigra is involved in nearly all cases. Spatz classifies acute anterior poliomyelitis (*Heine-Medin'sche Krankheit*) and rabies with this group.

5. DISSEMINATED ENCEPHALITIS WITH DEMYELINIZATION

Acute disseminated sclerosis and acute disseminated encephalomyelitis are representatives of this classification, indicating a spread in large, well circumscribed foci that have no relationship to the vessels. There are two places of predilection—the angles of the lateral ventricles ("weather corner" of Steiner) and the optic nerves.

6. DIFFUSE PERIVENOUS FOCAL ENCEPHALITIS

The sixth type is represented by encephalitis following measles and encephalitis post vaccinationem. These diseases of the brain spread through the gray and the white matter, with a predilection for the latter. They are characterized by foci of demyelinization and destruction of axis-cylinders around veins. In some cases perivascular cellular infiltration may be absent; in others it consists in only a proliferation of glia, chiefly of microglia. Despite frequent absence of the mesenchymal reaction, the process is classified as an "-itis," by some authors as a "leuko-encephalitis."

This classification may give a good working basis for the grouping of forms of encephalitis. However, one should always be conscious of the fact that it does not indicate anything about the etiologic factor and that one should abstain from diagnosing a certain type of infection merely from the type of distribution of the inflammatory foci.

Furthermore, each brain seems to have its individual type of reaction against infection. It was observed during the St. Louis epidemic of encephalitis that one brain would show the classic combination of perivascular mesenchymal cellular infiltration together with formation of glial foci, while in another brain the mesenchymal reaction was minimal and the glia reaction predominant, or vice versa.

The mode of invasion will depend to a certain degree upon the resistance to infection of different parts of the central nervous system tissue. There is a predisposition for growth of micro-organisms in areas of softening, which in cases of septicemia easily become infected, acting as "bacterial traps." The intoxication of the brain following an overflow of endotoxins into the blood (e.g., after liver damage) may lower its resistance to invading micro-organisms, and the theory has been advanced that saprophytic bacteria or virus may be stimulated under such conditions to become virulent and produce an encephalitis. Weakening of the resistance of the hemato-encephalic barrier following fever, intoxication, etc., may also favor the immigration of micro-organisms into the brain. The mesenchymal and glial defense reaction may be diminished under such conditions, as it is following inanition and in the arteriosclerosis of old age.

Experimentally it has been demonstrated that intravenous injections

of pathogenic micro-organisms produce meningitis in cats after drainage of cerebrospinal fluid or after diminution of its pressure by injections of hypertonic salt solutions (Weed, Wegeforth, Ayer, and Felton).

The brain itself does not seem to produce immune bodies and therefore is dependent upon the antitoxin production in other organs. Immune substances and specific antibodies have been demonstrated in the cerebrospinal fluid of both actively and passively immunized animals, indicating a passage through the hemato-encephalic barrier. Hemolysins that are present in the human serum in certain diseases may be demonstrated in the cerebrospinal fluid (Weil-Kafka test), indicating meningitis and an increased permeability of the membranes. The number of immune bodies, however, is very small as compared with those in the blood. This relation of antibodies was 0.3:100.0 after immunization of rabbits against typhoid bacilli (Freund). Diphtheria toxin injected intracerebrally acts differently than it does on intravenous or subcutaneous injection. Subcutaneous injection of antitoxin protects against the effects of intracerebral injection of the toxin. It is possible to obtain an active immunization of the central nervous system against tetanus, with production of large numbers of antibodies, following subarachnoidal inoculation of anatoxin (Doerr and Kon).

The degree of damage produced by the bacterial toxins determines the degree of the defense reaction. Repair following the necrosis with multiple hemorrhages in Streptococcus haemolyticus invasion is difficult on account of the destroyed glia and mesenchyme within the necrotic focus. It is easily accomplished if the toxin seems to stimulate glia proliferation while at the same time destroying the neurons, as in encephalitis lethargica.

Tissue Alterations Following Infection

The lesions of nervous tissue are always largest at the place of invasion of the micro-organisms or their toxins. In septicemia, the intima of the vessels suffers first. It shows signs of swelling and disintegration, with subsequent narrowing of the lumens, favoring formation of infected thrombi in smaller arteries or capillaries. From there the micro-organisms penetrate into the environment of the blood vessels. Under the influence of the toxins, the surrounding glial elements and nerve fibers swell and disintegrate, producing an edematous, loose appearance of the perivascular tissues. Neurons in this region, being more sensitive than other nervous elements, suffer most, showing swelling, necrosis, vacuolation, and shrinkage. The neuronal disease may be spread diffusely throughout the whole central nervous system in certain infections, in the manner of the "severe ganglion cell disease" or the "acute swelling" that occur in typhoid

fever or anthrax. The invasion of micro-organisms is favored by the anoxemia, resulting in softening that follows thrombus formation.

The farther away they are from the focus of infection, the more diluted the toxins become, and the milder their destructive effect. It seems that at a certain dilution they may at the same time destroy neurons and stimulate proliferation of glia.

Many types of fungus cells do not seem to produce very toxic substances. In Cryptococcus hominis infection, for example, no marked nerve cell disease is found in the neighborhood of very large cortical foci, and the mesenchymal reaction is only mild.

In certain types of infection the micro-organism seems to have a predilection for particular nervous structures, a fact that has previously been brought out in connection with the scheme of Spatz. At present we are unable to explain the preference of the virus of encephalitis lethargica for certain parts of the central gray matter, with the almost constant destruction of the pigmented cells of the substantia nigra, or the severe disease of anterior horn cells in acute poliomyelitis. We can merely register the fact, without explanation, that the Negri bodies in rabies are found in neurons, most frequently in the large pyramidal cells of the cornu Ammonis. Schizotrypanum cruzi (Chagas' disease) may be found within astrocytes and microglia, sometimes inside of neurons.

The myelin sheaths succumb early to the toxins of micro-organisms. In the peripheral zones of the spinal cord in purulent meningitis, the myelin sheaths are swollen, disintegrated, and stain pale in sections stained for myelin sheaths. A similar small zone of myelin destruction may be seen around the perivascular and cellular infiltrations of different kinds of encephalitis. The severe destruction around the abscess formations in the embolic type may, however, be due partly to the anoxemia. The demyelinization seen in the encephalitis following vaccination or measles is accompanied by a severe destruction of the axis-cylinders.

After micro-organisms invade the subarachnoidal spaces, their toxins tend to destroy the cellular lining of the arachnoidal membrane and the ependymal cells of the ventricular walls and of the choroid plexus. The connective tissue reacts by swelling, seemingly without undergoing destruction. Penetrating from the subarachnoidal and ventricular spaces into the brain substance, the toxic effect in this meningo-encephalitis is most marked in the subependymal tissue and in the outer layers of the cortex.

Exudation and Proliferation

The mobile cells found in a focus of infection during the primary phase of inflammation are either of hematogenous origin or else arise from the small lymphocytes and histiocytes along the blood vessels or in the meshes

of the piarachnoid. The histiocyte, which plays such an important role in inflammatory processes of other organs, seems to be present in small numbers only in the meninges, the choroid plexus, and the pial and adventitial sheaths of the larger vessels. It seems that the type of cellular exudation depends upon the nature and virulence of the micro-organisms and the duration of the disease. The first hematogenous cells that appear at the place of invasion have been described as polymorphonuclear leukocytes (granulocytes), mostly neutrophils, with fewer eosinophilic or basophilic types. In many infections of the central nervous system, however, they seem to disintegrate very quickly, and are replaced by small

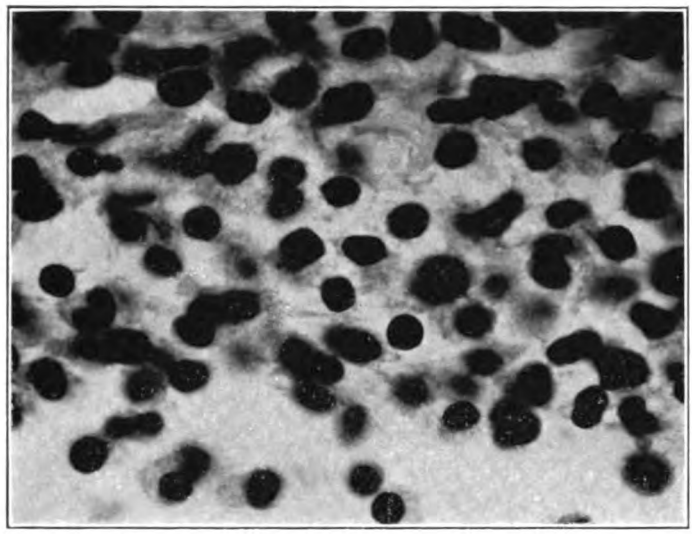


FIG. 95. CELLULAR EXUDATE IN MENINGITIS

Epidemic meningitis of 4 days' duration. Cresyl violet stain. Higher magnification of cellular exudate shown in fig. 101. Exudate consists of mononuclear cells (polyblasts) mainly; polymorphonuclear leukocytes are absent

lymphocytes (polyblasts) and large monocytes, or do not occur at all. In the early stage of meningitis, e.g., epidemic meningitis, one may see many polymorphonuclear leukocytes, characterized by the oxydase reaction, in the cellular exudate of the piarachnoid and the cerebrospinal fluid. After three days their number is relatively small as compared to the number of small and large mononuclear cells, polyblasts, histiocytes, and fibroblasts. The same is true in the case of tuberculous meningitis and many types of encephalitis (figs. 95, 96).

Under the influence of certain toxins, the lymphocytes undergo transformation into plasma cells. These are regularly found in large numbers

in the wall of a cerebellar abscess; they are found in other more chronic processes, in tuberculosis and syphilis. In general paresis they form the typical element of the perivascular infiltrations (fig. 97). Under the influence of fever therapy they disappear and are replaced by small lymphocytes. The plasma cell received its name from the affinity of the cytoplasm for acid dyes. In cresyl violet–stained sections it stains purple. The wheel-like nucleus gives the cell another characteristic. It is usually situated peripherally and surrounded by a pale halo. The form of the plasma cells may be elongated, oval, as in abscess walls or general paresis,

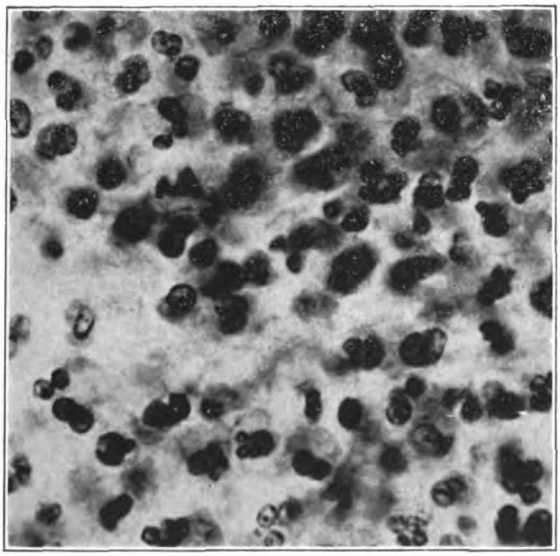


FIG. 96. CELLULAR EXUDATE IN MENINGITIS

Epidemic meningitis of 8 days' duration. Unna-Pappenheim stain. Many of polyblast nuclei show fragmentation. Isolated plasma cells are seen

or more round in meningeal infiltrations. A derivative of the plasma cell is the Russell body, a large round cell with a lattice-like structure, staining bluish with cresyl violet and yellowish red in van Gieson preparations. Its staining reaction and the form and position of the nucleus differentiate it from the gitter cell (fig. 98). Large mononuclear cells (macrophages) with eccentric nucleus and basophilic peripheral cytoplasm are frequently found in meningitis. They are phagocytic cells, containing the remains of granulocytes or lymphocytes and micro-organisms. It seems likely that they are derivatives of the histiocytes that can be demonstrated in the mesenchymal structures of the central nervous system (fig. 99). Their

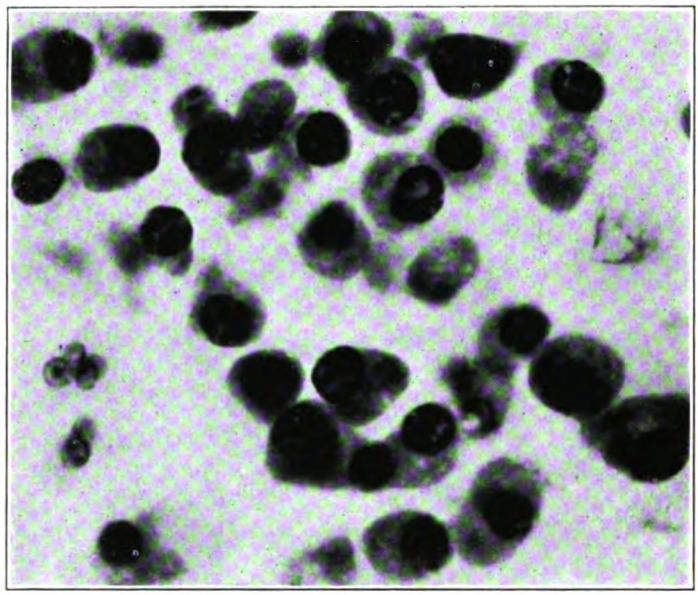


FIG. 97. PLASMA CELLS

Wall of cerebellar abscess. Cresyl violet stain. Cytoplasm stained purple. Unstained zone around nucleus, which is eccentric, with its chromatin arranged in form of wheel ("clock-faced")

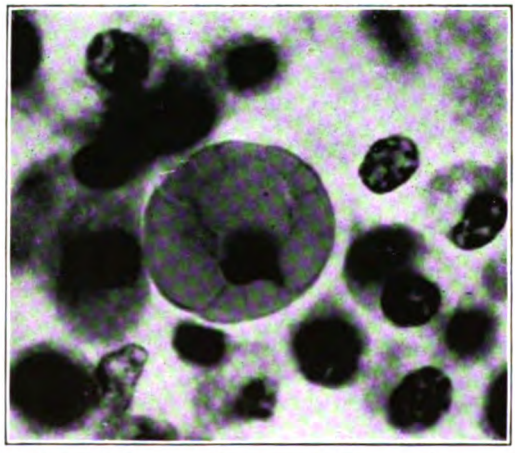


FIG. 98. LARGE, COLLOIDAL PLASMA CELL

Wall of cerebellar abscess. Cell shows fenestration of cytoplasm, and is surrounded by smaller plasma cells. Van Gieson stain. (Suggestive of Russell body)

meshlike structure sometimes recalls gliogenous gitter cells. They are, however, larger.

According to the presence or absence of pus, in the form of either abscess formations or diffuse infiltration with pus cells—mainly polymorphonuclear leukocytes and their debris—one may differentiate between purulent and nonpurulent (suppurative and nonsuppurative) encephalitis (meningitis). From the observations on the variation of the cellular exudate it is evident, however, that these subdivisions do not relate to the etiologic factor.

The mobile cells that have been described are the first line of defense in an inflammation of infectious origin. It seems that the fixed glial elements

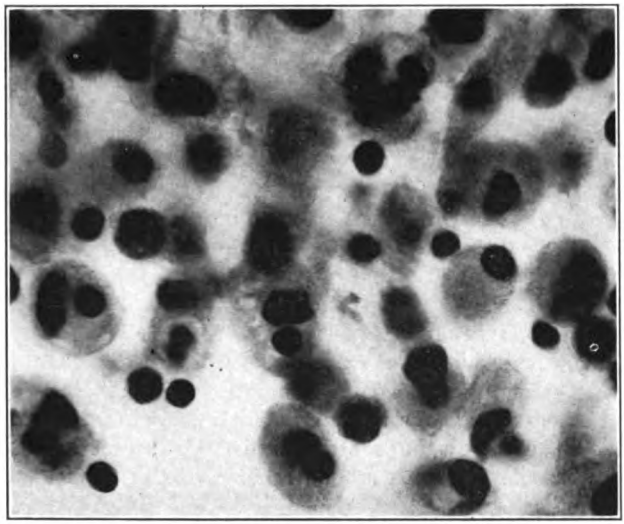


FIG. 99. MACROPHAGE CELLS IN TUBERCULOUS MENINGITIS
Large round cells resembling compound granular corpuscles and containing inclusions (lymphocyte nuclei). Van Gieson stain

and fibroblasts take over the role of localizing the infectious focus. In some cases of meningitis there appears, as early as the third day, a marked increase in collagenous connective tissue fibers, which form a network about the cellular elements. They persist after the acute stage of the infection has passed and the cellular exudate has disappeared. Instead of the loose meshwork of the arachnoidal membrane, one then finds dense layers of coarse connective tissue fibers that form adhesions between the arachnoidal lining and the cerebral surface. Around infectious foci of the brain and spinal cord, astrocytes increase in number at an early stage, forming a fibrous meshwork around the focus, which, in larger areas, is

intermingled with connective tissue fibers and capillary sprouts. The center of the infectious focus may become cystic or may later come to be completely replaced by a glia scar. It may be transformed into a cavity filled with white blood cells and their debris—in which case an abscess develops. A detailed description of the development and organization of different types of infections will be given later.

The progressive proliferation of the glia may occur independently of the mesenchymal infiltration. In encephalitis following rheumatic endocarditis, or in infections with staphylococci, in typhus, or in trichinosis of the brain, nodules of glia cells not containing lymphocytes or polymorphonuclear leukocytes have been described around blood vessels or colonies of micro-organisms. In certain types of infections the mesenchymal proliferation may be minimal or entirely absent and replaced by perivascular infiltration with glial elements (in measles and following vaccination).

In the outer molecular zone of the cortex or the subependymal tissue, an active proliferation of fibrous astrocytes accompanies leptomeningitis. After the disease has subsided, a dense meshwork of fibrous glia remains.

It seems that gitter cells appear on the scene only as scavenger cells to remove tissue debris and that they have no function of protection against invading micro-organisms. Staphylococci, however, have been found in astrocytes and microglia of glia nodules.

Certain infections produce a typical tissue reaction that is the same in the brain as in other organs of the body. Such granulomas are found in tuberculosis (tuberculoma), syphilis (gumma), tularemia, and actinomycosis. In others the colonies of the invading organism form typical structures that make the diagnosis easy, as in Cryptococcus hominis infection. The capsule formation around echinococcus or cysticercus is the same as in other organs.

Under the influence of gas-forming bacteria, e.g., Bacillus welchii (Frankel), the brain may assume the appearance of Swiss cheese. In most of these cases one is seemingly dealing with a postmortem invasion and not with a primary infection (fig. 3).

In other forms the pus of an abscess formation becomes putrified through the fermentative action of the micro-organism. It seems that such putrid abscess formation occurs frequently in infections with the Plaut-Vincent spironema (and the symbiotic fusiform bacillus).

Meningitis

Acute Leptomeningitis

Inspection of the outer surface of the brain is sufficient in most instances for making the diagnosis of a leptomeningitis with the naked eye. Instead

of the transparent piarachnoid there is seen a milky coloration, with pus infiltration or even formation of thick tissue layers adherent to the underlying cortex. It should be borne in mind that in old arteriosclerotic brains, milky discoloration of the meninges covering the convexities is a "normal" picture, and one should not be led to mistake small white nodules of calcification along the meningeal vessels for tubercles, nor should any significance be attributed to small or large calcified platelets in the piarachnoid of the dorsal spinal cord. The extradural fat is more prominent at these levels and creates a protective buffer in the narrows of the spinal canal.

The basal part of the leptomeninges, overlapping the space between the infundibulum and the pons, is frequently the seat of inflammation. Tuberculous and syphilitic processes are found here, but pneumococcic and epidemic meningitis may also show their most intensive cellular exudation at this level. From here the infection may spread along the larger vessels and the subarachnoidal reservoirs to the cisterna pontis and upward to the hemispheres. The latter are sometimes more severely affected in certain types of purulent meningitis. In the spinal cord the lower dorsal segments are a site of predilection for meningitis, usually the syphilitic inflammation, which rarely is found in the cervical segments. The sheaths of the peripheral nerves are affected by inflammatory processes of the surrounding tissues; these may spread into the interior of the nerves, and peri- and endoneuritis will follow as a sequela of meningitis.

The dura mater is resistant to infections of the piarachnoid. Usually the cellular infiltration is confined to the latter and only a mild hyperemia may be present in the dura. Infectious processes on the outer surfaces of the dura mater, however, produce a pachymeningitis, with formation of granulation tissue and adhesions to the bony cavities. In some instances such an inflammation gains access to the subarachnoidal spaces, e.g., in caries of the skull and vertebrae, and in otitis media, while in others, such as lymphogranulomatosis, it is mostly confined to the outer dura.

In most cases of acute leptomeningitis it is impossible to draw any conclusions from the histologic picture as to the infectious agent. This applies especially to the virus-induced types of acute lymphocytic meningitis or lymphocytic choriomeningitis, first described by Armstrong and Lillie in 1934. At present four different types of virus have been identified as being responsible for this type of nonpurulent meningitis, which is characterized by monocytic infiltration of both piarachnoid and choroid plexus. The virus has been transmitted by intracerebral injections into mice; in these it disappears during an incubation period of approximately six days, reappearing then and causing death after from seven to nine days.

In more advanced cases of syphilis and tuberculosis, the granulomas

may help to determine the diagnosis; in Sporotrichum, Coccidioides, or Torula infections the fungus cells cannot be overlooked, and in acute stages of epidemic meningitis the diplococcus may be found within the leukocytes, easily recognized in cresyl violet–stained sections, but negative in Gram's stain.

It is not correct to call the edema of the piarachnoid, with accumulation of fluid in the subarachnoidal spaces, a "serous" meningitis, because all the other criteria of an "-itis" are absent. Such conditions may be found as the preliminary stage of an infection, as in infectious mononucleosis, in generalized infectious diseases of the body, in uremia, and in alcoholism. The accumulation of fluid may also occur over atrophic gyri following softening or arteriosclerosis. It may be present in "arachnitis adhaesiva circumscripta et cystica" (Pette), which starts as a pachymeningitis, with proliferation of the dural endothelium, and finally involves the arachnoidal membrane, leading to formation of fibrous precipitates. There are many transition stages from this "hydrocephalus externus" to true *serous* meningitis if the cellular exudate and the fibroblastic reaction increase (fig. 179).

An *aseptic* meningitis, with edema and mild cellular infiltration of the piarachnoid, may easily be produced under experimental conditions after subdural injections of serum or salt solutions, or hemorrhage following spinal puncture. Purulent meningitis does not necessarily indicate the invasion of the subarachnoidal spaces by micro-organisms. It may be seen as an allergic reaction to bacterial toxins. Injections of old tuberculin into the cistern in guinea pigs, from three to six weeks after tubercle bacillus infection, produced severe leptomeningitis with massive infiltration of polymorphonuclear leukocytes (Burn and Finley.)

CHRONIC LEPTOMENINGITIS

Like the serous meningitis described above, which represents the acute stage of a mild infection or intoxication, the end stages of such mild inflammatory reactions are often diagnosed as "chronic" leptomeningitis. A true type of chronic meningitis is the tuberculous or syphilitic leptomeningitis, in which constant irritation by the toxins of the multiplying micro-organisms produces new foci of infection before the old ones have had a chance to heal. But besides these conditions, which will be described later, one often finds marked thickening of the piarachnoid, with mild scattered infiltration of a few lymphocytes, plasma cells, and large mononuclear cells, which is diagnosed as a "chronic" leptomeningitis. It is common to find such pictures in old arteriosclerotic brains, in chronic alcoholism, or in renal disease of long standing. It is almost impossible to determine the etiology of such conditions, i.e., whether they are of an infectious nature or produced by endotoxins circulating in the cerebrospinal

fluid. Proliferation of the mesothelial cellular lining of the arachnoid is often found in association with an increase in connective tissue (fig. 208).

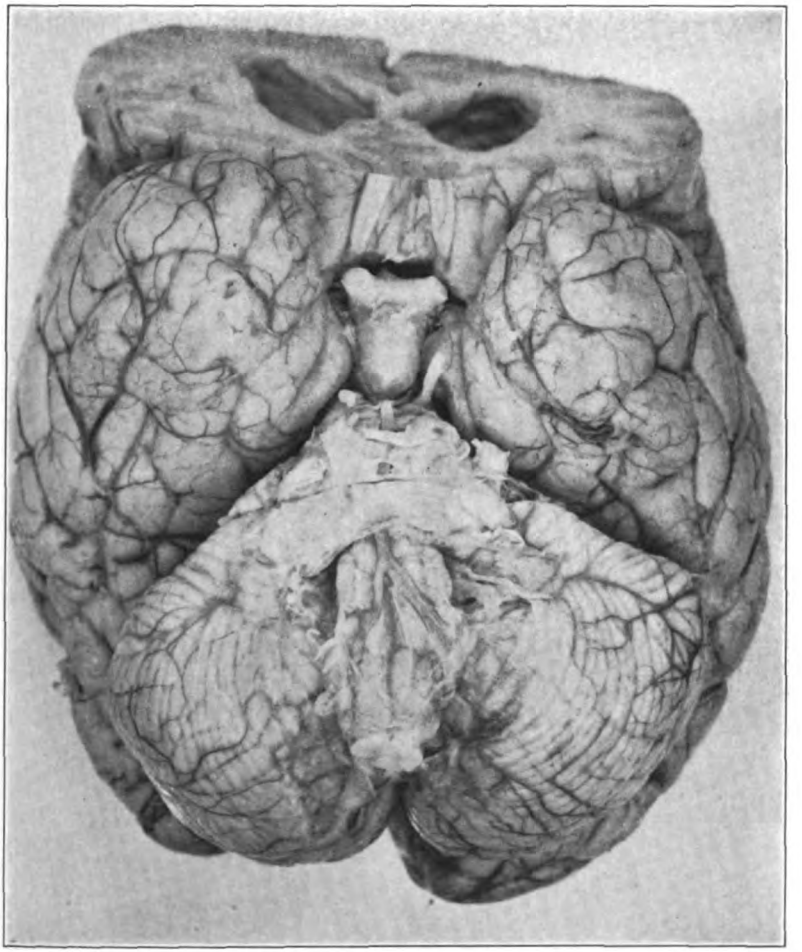


FIG. 100. PURULENT LEPTOMENINGITIS

Base of brain. Piarachnoid between optic chiasm and pons is filled with pus. Occlusion of foramina of Magendie and of Luschka has led to internal hydrocephalus. Widening of lateral ventricles is visible at cut frontal poles

At the same time similar changes may be found in the choroid plexus in the form of an increase of the connective tissue, with atrophy of the ependymal cellular lining and calcification of the blood vessels. The formation of small cysts in the choroid plexus should not be given too much

importance, because they are often found in the brains of older persons without neurologic disease.

EPENDYMITIS

The factors that produce inflammation of the meninges will at the same time irritate the ventricular linings. This may result in swelling and breaking down of the latter, or in intense proliferation, with formation of papilla-like protrusions, and an intense reaction of the fibrous glia in the subependymal tissue. Such "ependymitis granulosa" has been described as occurring in general paresis, but it may also be found in tuberculous meningitis, to a milder degree in arteriosclerotic brains, and single papillae may be found accidentally in otherwise normal brains.

In the more malignant types of leptomeningitis, the breaking down of the protective ependymal lining of the ventricles opens the surrounding brain tissue to the invasion of the infectious micro-organism.

Judging from experimental work on meningitis, there seems to be some reason to assume that micro-organisms injected into the blood may produce inflammatory reactions, first in the subependymal tissue surrounding the lateral ventricle. This region is a site of predilection in disseminated sclerosis; in experimental liver damage, it seems to show predisposition for the destructive action of endotoxins; in many chronic infections and in arteriosclerosis, amyloid bodies are found here in large numbers, together with an intense glia proliferation. The last-named fact may indicate that a current of cerebral fluid flows toward the ventricles and is dammed up here by the ependymal linings, which perhaps act selectively in the transmission of water and soluble substances to the ventricles. This leads to an accumulation of toxins and metabolic products.

Epidemic Meningitis

Synonyms: German, *epidemische cerebrospinale Meningitis, Genickstarre;* French, *méningite cérébro-spinale.*

Meningococcus intracellularis (Weichselbaum) is found in the earlier stages of the disease as a diplococcus within leukocytes. It can be differentiated from the penumococcus by the failure of the meningococcus to stain under Gram's method. It can easily be detected in smears stained with cresyl violet and may also be seen in early stages in colony form in sections of the brain stained by the same method.

The histologic pictures vary with the age of the disease. At a very early stage, in cases in which death has occurred within from twenty-four to forty-eight hours, the piarachnoid may appear somewhat hyperemic, containing a small amount of serous fluid. Microscopically the cellular infiltration may be confined at this stage to the subarachnoid space around

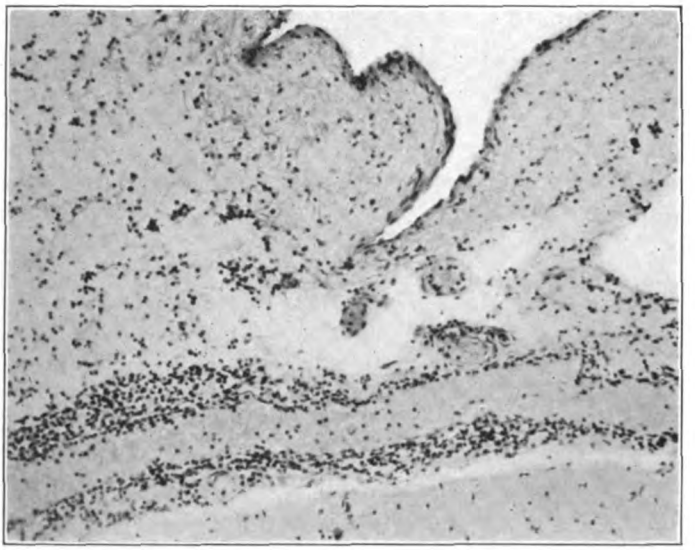


FIG. 101. EPIDEMIC MENINGITIS

Condition of 4 days' duration. Piarachnoid covering parietal cortex. Cellular exudate is confined to perivascular spaces of vein cut longitudinally next to cortex. Rest of arachnoid is edematous, nuclei are slightly increased in number, outer lining of mesothelial cells is well preserved. Cresyl violet stain

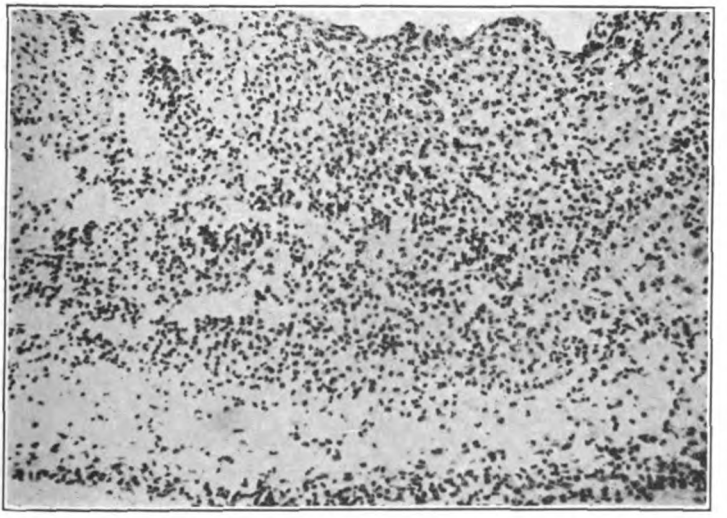


FIG. 102. EPIDEMIC MENINGITIS

Same brain as in fig. 101. Piarachnoid covering pons. Cellular exudate is denser here than in leptomeninges covering convexities. It consists of polyblasts mainly. Cresyl violet stain

the chiasma and to the outside of the hypophysis. After several days' duration of the disease the leptomeninges are very hemorrhagic; along the larger veins may be seen stripes of pus. Later the yellowish pus is accumulated mostly at the base of the brain and along the meninges of the spinal cord, with preference for the dorsal surface. Here usually the infiltration of pus is not evenly distributed; it may be localized in the lumbar segments and the cauda equina. In other cases it may be most pronounced over both convexities of the brain, while the pons and medulla oblongata are spared. The dura mater may also be affected, showing a pachymeningitis haemorrhagica interna. Inspection of the inner surface of the dura mater will reveal fine blood-infiltrated membranes that can be removed or, in older cases, thick adherent layers. Microscopically these consist of a granulation tissue with multiple hemorrhages in process of organization. Histiocytes are intermingled with leukocytes and fibroblasts, forming fine fibrillae of connective tissue. These microscopic pictures, so common in the past, may soon become rareties, however, owing to the success of the sulfa drugs in curing epidemic meningitis.

The character of the cellular infiltration of the piarachnoid changes with the duration of the disease. In the first days it may consist of scattered small polymorphonuclear leucocytes and histiocytes with well staining nuclei intermingled with red blood cells and fibrin; they cluster around larger veins and are found in the walls of the vessels. At a later stage, the cellular infiltration is much denser; the picture is dominated by mononuclear cells intermingled with fragmented nuclei of degenerated cells; they are also found in the lateral ventricles, covering the choroid plexus and the ependyma (figs. 101, 102).

If the epidemic meningitis is overcome by the defense reactions of the body or by chemotherapy, a gradual decomposition and absorption of the cellular infiltration, together with a proliferation of fibroblasts, sets in. This leads finally to a thickening of the piarachnoid, with adhesions to the brain surface. The arteries show at these end stages thickening of the intima, i.e., endarteritis. The occlusion of the foramina of Magendie and of Luschka may lead to a retention of cerebral fluid in the ventricles and to internal hydrocephalus.

As in other types of infection of the meninges, the inflammatory process spreads along the pia sheaths into the brain and spinal cord. Multiple abscess formations are found; these may reach a diameter of 1 cm. Severe lesions of the vessel walls, and infiltration with inflammatory cells, lead in other cases to multiple small hemorrhages that may be detected macroscopically as small red petechial foci in the white matter; these contain clusters of small round cells besides the red blood cells (encephalitis haemorrhagica). Similar foci are seen in the gray and the white matter of the

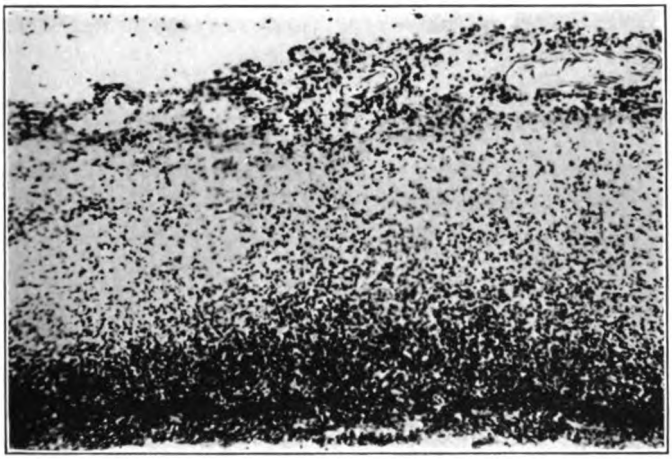


FIG. 103. ACUTE PURULENT LEPTOMENINGITIS (STAPHYLOCOCCUS)

Frontal pole. Cresyl violet stain. Cellular exudation is most pronounced at outer zone of piarachnoid; here most of colonies of streptococci are seen

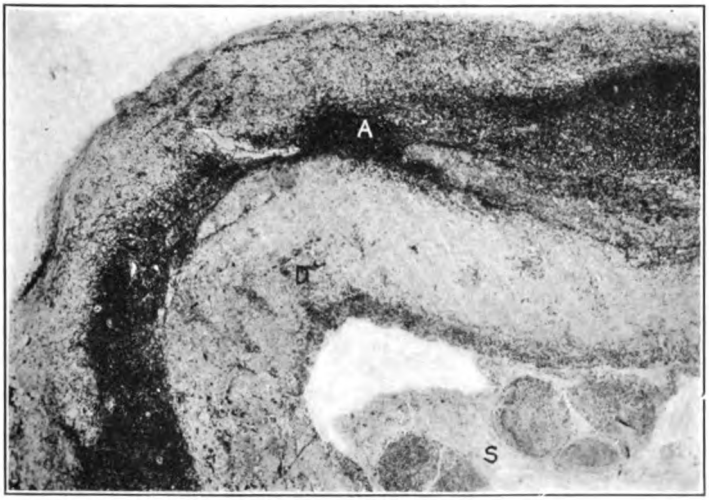


FIG. 104. EPIDURAL ABSCESS

Following infection after epidural injections. Transverse section through lumbar segment of spinal cord. Van Gieson stain. S = subarachnoidal spaces with posterior roots. D = dura mater. A = abscess formation between dura mater and periosteum of vertebra

spinal cord, where the lesions may produce ascending and descending secondary (wallerian) degeneration. Infiltration of the peri- and endoneurium with inflammatory cells may be found in the cranial and spinal nerves, with predilection for the optic and acoustic nerves. In healed epidemic meningitis the residues of these inflammatory processes may produce degeneration of the nerves involved or destruction of the anterior horn cells in the spinal cord may lead to an amyotrophy.

Nonepidemic Forms of Purulent Meningitis

Purulent meningitis may also be produced by many other micro-organisms. The histologic picture does not differ essentially from that in epidemic meningitis, with a few exceptions to be described later. From the macroscopic appearance of the piarachnoid or from the localization and the amount of cellular infiltration, no conclusions can be drawn as to the etiologic factor. Examination of the cerebrospinal fluid in smears and cultures must help to detect the micro-organism if the clinical history did not give any clue.

Infection of laboratory animals with the different micro-organisms isolated in human cases of purulent meningitis seems to be difficult. On injection into the subarachnoidal spaces, only relatively very large amounts of the culture of the original strain produce a leptomeningitis. After several animal passages by agency of intrameningeal injections, however, the virulence of some micro-organisms was markedly increased, in some instances several thousand times. The intrameningeal injection proved to be at least five hundred times more pathogenic than intravenous injections. Bacillus lactis aerogenes seemed to be an ideal micro-organism for production of an acute, fatal leptomeningitis in cats and rabbits (Felton) (cf. table 12).

The following micro-organisms have been found in purulent meningitis (the common names are added in parenthesis): Bacillus anthracis, Borrelia vincenti (Spironema vincenti), Brucella melitensis (Bacillus melitensis), Clostridium welchii (Bacillus welchii), Diplococcus pneumoniae (Pneumococcus), Eberthella typhi (Bacillus typhi), Escherichia coli (Bacillus coli), Haemophilus influenzae (Bacillus influenzae), Leptospira icterohaemorrhagiae, Neisseria gonorrhoeae (Gonococcus), Pasteurella pestis (Bacillus pestis), Staphylococcus albus, aureus, and citreus, Streptococcus haemolyticus and pyogenes.

Infectious Encephalitis and Myelitis

In a preceding chapter we have discussed the histologic criteria that justify the diagnosis of encephalitis. It has been emphasized that the cellular infiltration is not always significant as a reaction of the nervous tissues

against direct invasion of a micro-organism or a toxin. It was pointed out that "symptomatic" encephalitis could follow damage of the brain tissue by vascular insults or trauma. Spielmeyer emphasized this difference

TABLE 12.—*Different Degrees of Pathogenicity of Different Kinds of Bacteria for Rabbits**

Bacterium	Injections	
	Subcutaneous, Intravenous, Intraperitoneal	Suboccipital
Pneumococcus, type 1	nearly nonpathogenic	very markedly pathogenic: 0.1 cc. of 1:1000 dilution, + after 20–30 hr., in exceptional cases after 11 days
Streptococcus	very mildly pathogenic	Markedly pathogenic: 0.05 cc., + after 24–60 hr. Single animals survive
Staphylococcus pyogenes aureus	very pathogenic	Still more pathogenic: 0.1 cc. of 1:10 dilution, + after 30 hr.
Bacillus suipestifer	very pathogenic: intravenous injection of 0.1 cc. of culture, + after 48 hr.	very pathogenic: even 1 cc. of 1:10,000 dilution, + after 20 hr.
Bacillus tuberculosis bovinus	pathogenic: intravenous injection of 1 cc. of 1:10,000 dilution produces progressive tuberculosis	less pathogenic: 1 cc. of 1:10,000 dilution, + in 9–29 days
Bacillus tuberculosis hominis	mildly pathogenic	markedly pathogenic: 1 cc. of 1:10,000 dilution, + in 6–50 days. Some animals survive
Order of pathogenicity	subcutaneous, etc., injections	Pneumococcus, type 1; Streptococcus; B. tuberculosis hominis; B. tuberculosis bovinus; Staph. pyogenes aureus; B. suipestifer
	suboccipital injections	Streptococcus; Staph. pyogenes; Pneumococcus, type 1; B. tuberculosis hominis; B. tuberculosis bovinus; B. suipestifer

* From Cohn, H.: Experimental infection of the central nervous system. Zentralbl. f. d. ges. Neurol. u. Psychiat. *65:* 454, 1932.

between the "encephalitic symptom complex" and encephalitis. Encephalitis is the *independent* appearance of the encephalitic symptom complex and is a defense reaction. Sometimes it is impossible to prove the independence of the inflammatory reaction, especially if hemorrhages,

softening, and thrombi are intermingled with the encephalitic symptom complex in encephalitis. That cellular infiltration of lymphocytes and plasma cells is not always indicative of an infectious process, but may point to presence of a toxic encephalitis, should be learned from the reaction of the brain tissue following invasion by certain cancer metastases.

Earlier in our discussion, "encephalitis neonatorum" has been mentioned as an example of the fact that round cell accumulation does not always mean inflammatory reaction. It is found more frequently in premature

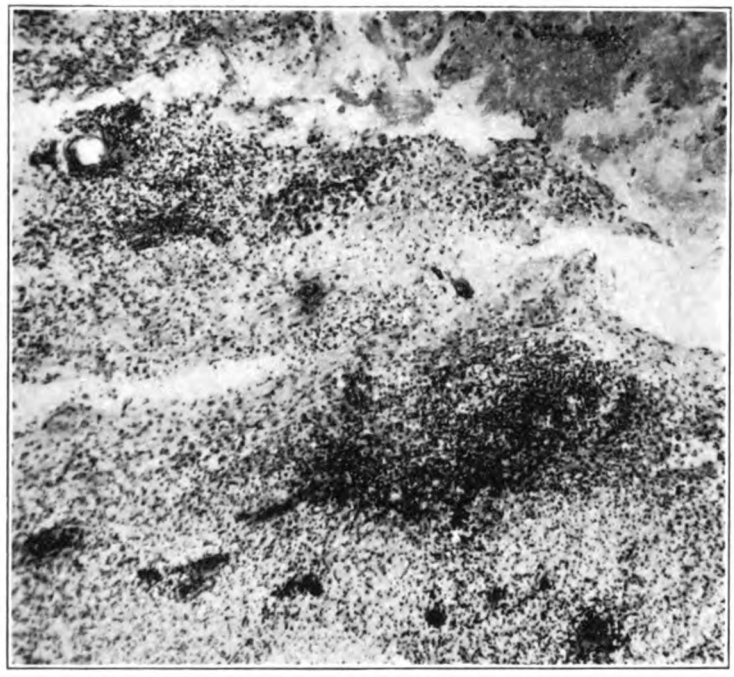


FIG. 105. REPARATIVE ENCEPHALITIS

Environment of focus of anemic softening. Cresyl violet stain. Dense perivascular infiltration with small mononuclear round cells

births, with predilection for the basal ganglia, most pronounced with respect to the angle between the caudate nucleus and thalamus.

The classification of the types of infectious encephalitis according to the histologic picture does not have any bearing as regards the etiologic agent. Purulent and nonpurulent forms may be produced by the same micro-organism. A focal process may become disseminated. One and the same micro-organism may produce either an acute, fulminant encephalitis or a more slowly progressing, chronic type. Hemorrhagic

encephalitis is not a characteristic manifestation of a given micro-organism, but only of its virulence and toxicity.

There is, however, a propensity of certain types of micro-organisms to production of a given type of encephalitis. Examples are the nonpurulent type of encephalitis lethargica, the predominance of the hemorrhagic type in influenza, rabies, scarlatina, anthrax, and typhoid fever (fig. 124), and of the purulent type in infections due to Streptococcus and Staphylococcus pyogenes, albus and aureus.

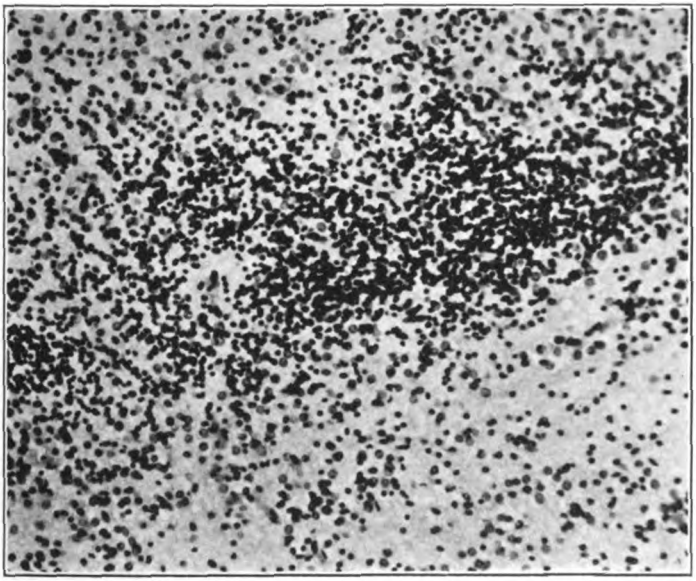


FIG. 106. ENCEPHALITIS NEONATORUM

White matter of cortex of newborn child. Van Gieson stain. Dense accumulation of glia nuclei staining intensively with iron hematoxylin, and intermingled with compound granular corpuscles, simulates formation of focus of inflammatory reaction

Encephalitis may follow most of the infectious diseases of the body—typhoid fever, influenza, diphtheria, measles, scarlatina, chickenpox, rheumatism, anthrax, glanders, typhus, rabies. It may occur as secondary to an infectious meningitis or an infected wound of the skull.

That an encephalitis following an infectious disease is not always directly related to the infectious agent should be learned from the findings in the encephalitis following measles, smallpox vaccination, and antirabies treatment. That an infection of the brain is not necessarily indicated by the encephalitic symptom complex may be learned from the examples of very acute and pernicious cases of lethargic encephalitis. Spielmeyer has

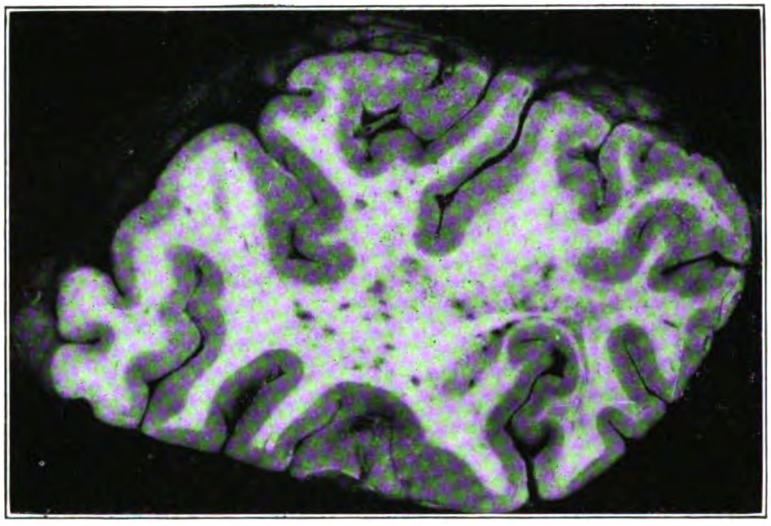


FIG. 107

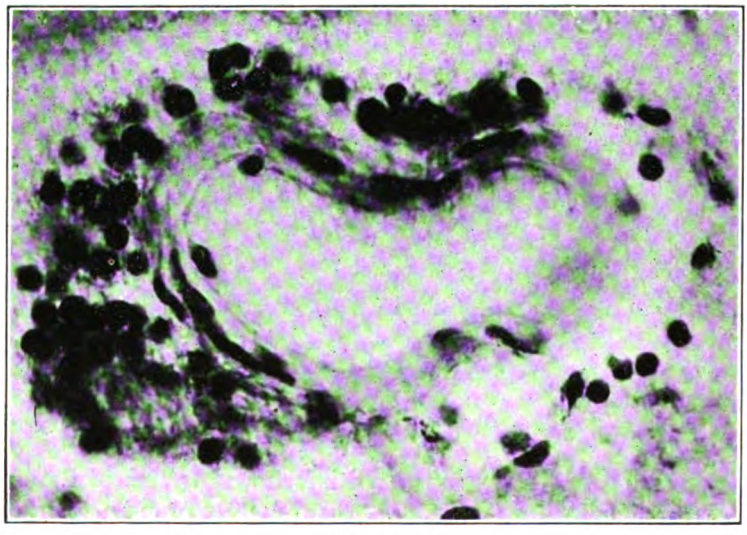


FIG. 108

FIGS. 107, 108. ACUTE NONPURULENT ENCEPHALITIS (BACILLUS COLI COMMUNIS)

Fig. 107. Coronal section through cerebral hemisphere. Petechial hemorrhages in white matter

Fig. 108. Perivascular cellular exudate. Van Gieson stain

emphasized repeatedly that infection with a given micro-organism may produce, separately and independently, alteration of the neurons and glia cells, vascular disturbances, or the inflammatory reaction.

Everything that has been said about the etiology and histologic manifestations of infectious encephalitis may also be applied to infectious myelitis. The micro-organisms may be carried to the spinal cord either by way of the blood in pyemia or abscess formation in other organs, by way of the lymphatics along the spinal nerves in infections of the thoracic, abdominal, or pelvic cavity, or, in meningitis or infections of the vertebrae, along the pial sheaths accompanying the blood vessels.

The anatomic peculiarity of the spinal cord easily allows a spread of the infection upward and downward along the nerve fibers and the longitudinal glia fibers. Therefore the term "transverse myelitis" implies rather the

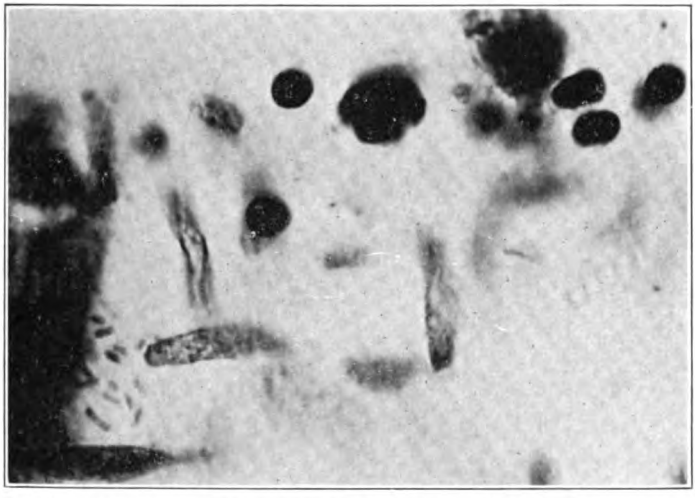


FIG. 109. ACUTE NONPURULENT ENCEPHALITIS (B. COLI COMMUNIS)
Same case as in figs. 107, 108. Thrombosed vessel with emigrating bacilli and mild cellular exudate. Cresyl violet stain

clinical conception of a complete interruption of the fiber tracts at a given level than an anatomic localization in one segment of the spinal cord. In more than 50 per cent of cases of sepsis of the spinal cord, one may find hemorrhages at the borderline of the gray and the white matter, with perivascular infiltration and myelin sheath degeneration in the spinal roots. The intervertebral ganglia may also be affected. Furthermore, the degenerative and vascular changes taking their origin from a focus of infection may dominate the histologic picture, and sometimes only a careful investigation of longitudinal sections extending over different segments will disclose this focus.

Purulent Encephalitis and Brain Abscess

Following infectious diseases of the lungs (pneumonia, bronchitis, empyema), or of the heart (endocarditis), small particles of tissue may be carried by the blood stream into the internal carotid artery and from there into vessels of the hemispheres. These emboli close the lumens of smaller vessels and form a favorable culture medium for the micro-organisms carried away with them. After destruction of the vessel wall and necrosis of the surrounding tissue, the infection of the brain tissue is followed by an

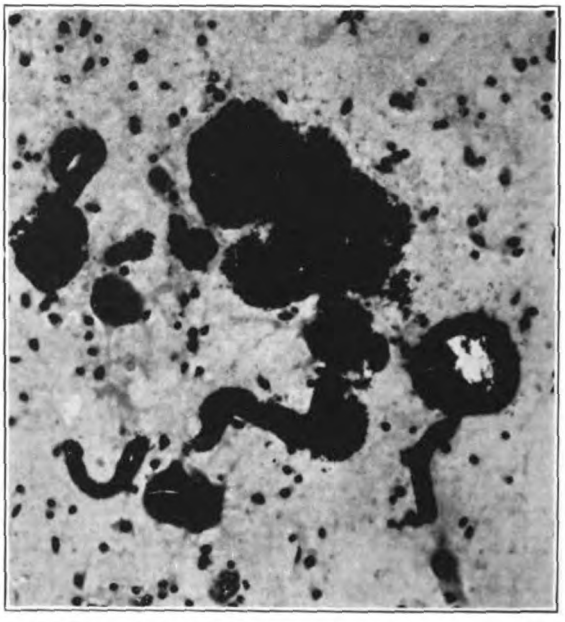


Fig. 110. Colonies of Cocci Forming Thrombi in Cortical Vessels

Absence of any inflammatory reaction indicates agonal or postmortem process. Cresyl violet stain

intense exudation of serum and of leukocytes. These gradually disintegrate, and a small abscess is formed (fig. 111). Such multiple miliary abscess formation may also follow thrombus formation by colonies of micro-organisms in the different infectious diseases mentioned above, or micro-organisms may become detached from purulent foci elsewhere in the body (liver abscess, phlegmon, etc.). In most cases such types of hematogenous purulent encephalitis followed by purulent meningitis or breaking through into a ventricle are lethal. If, however, the virulence of the invading micro-organism is not very pronounced, the infection may progress slowly.

The small miliary abscesses enlarge, become confluent with others, and finally are surrounded by a capsule of mesenchymal and glial fibers: an abscess has been formed. Four stages may be differentiated in the formation of a cerebral abscess: (1) focal necrosis with hyperemia and microglial proliferation; (2) fibrosis of meso- and astroglia, appearance of compound granular corpuscles; (3) intensification of fibrosis, with formation of a glial wall; (4) repair, and proliferation of new vessels without perivascular infiltration (Carmichael, Kernohan, and Adson).

Metastatic invasion of the brain by pus-forming micro-organisms follows infections of the middle ear—with relatively high frequency in approximately 83 per cent of cases, as compared with an incidence of 9 per cent in

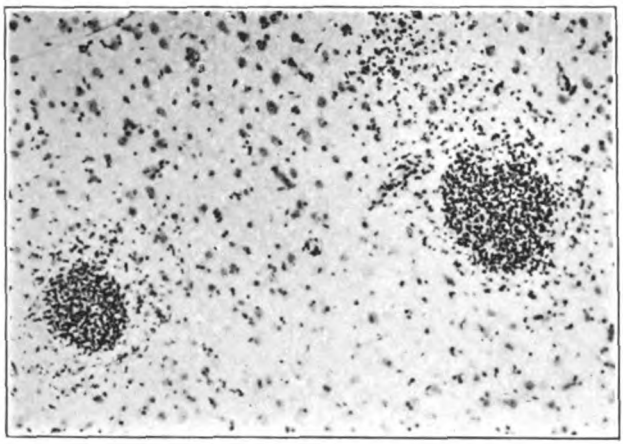


FIG. 111. MILIARY ABSCESS FORMATION
In case of purulent meningo-encephalitis following brain injury. Cresyl violet stain

cases of sinus infection and 8 per cent in infections of other metastatic origin (J. E. King). Abscess formation frequently follows fracture of the skull with or without a primary purulent pachymeningitis or sinus phlebitis. It may develop in connection with caries of the ethmoid bone or empyema of the maxillary sinus. Such an abscess is frequently not visible from the surface but is covered by a necrotic layer of cortex. The inner part is filled with pus of creamy or soft consistency, of yellow or greenish color. It is surrounded by a capsule of dense tissue; in some cases it is separated entirely from the surrounding tissues (fig. 114). In microscopic sections it consists of different layers. In its innermost part, the debris of brain tissue is intermingled with newly formed capillaries and a loose stroma of argyrophile fibers that encircle the cavity of the abscess (zone of granula-

tion). In the next layer these fibers appear coarser and are arranged perpendicular to the inner circle. They seem to be formed by spindle-shaped fibroblasts. Numerous blood vessels with thickened, homogeneously staining walls are seen in this layer (zone of demarcation). Frequently a marked infiltration of plasma cells gives this area, under low power lenses, the appearance of a tumor-like growth. Toward the periphery, fibers and plasma cells become less numerous, and there is a gradual transition to edematous necrotic brain tissue (zone of irritation). This,

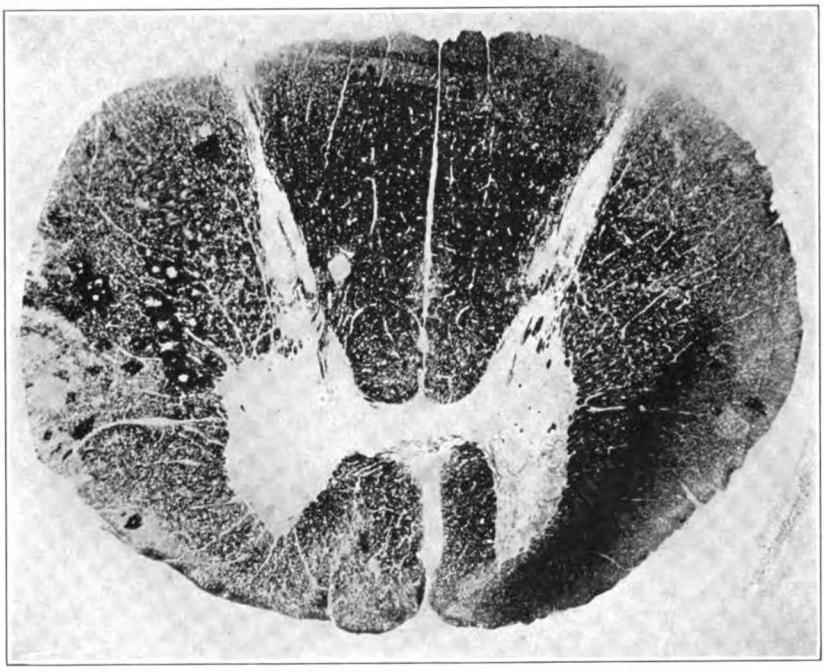


FIG. 112. SEPTICEMIA (STREPTOCOCCUS) WITH MULTIPLE FOCI OF VASCULAR THROMBOSIS

Spinal cord with multiple foci of vascular thrombi surrounded by area of necrosis that in turn is followed by circular hemorrhage. Van Gieson stain

finally, is surrounded by a dense layer of fibrous glia. From experimental evidence one may conclude that such a capsule formation indicates an age of the abscess of a least two weeks (fig. 115).

There are many deviations from this scheme. The abscess may gradually infiltrate the surrounding nervous tissue without being localized by the formation of a capsule, only mild fibrous glial proliferation indicating an attempted defense reaction. In other cases the outer wall may be transformed into a thick, homogeneously staining, hyaline-like structure.

FIG. 113. SEPTICEMIA (STREPTOCOCCUS) WITH MULTIPLE FOCI OF CAPILLARY THROMBOSIS

Same case as in fig. 112. Two thrombosed small arteries surrounded by area of edema that is followed by cellular infiltration. Van Gieson stain

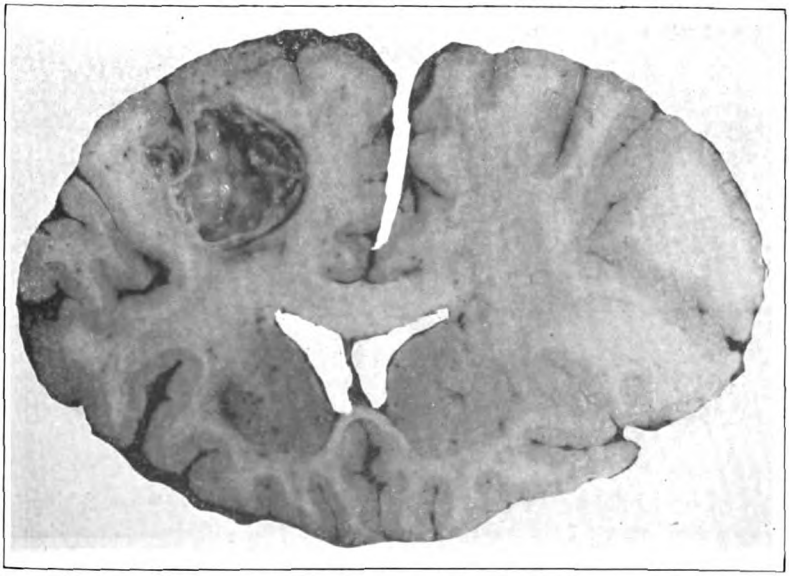


FIG. 114. METASTATIC ABSCESS IN FRONTAL LOBE FOLLOWING LUNG ABSCESS

It has been stated that infections of Bacillus coli communis lead to chronic encapsulated abscesses, those of Pneumococcus to acute abscesses (Lund).

The contents of the abscess may completely disintegrate with no nuclei or stainable fragments remaining. The center may become incrusted with calcium salts and even transformation into bonelike structures has been described. There has been discussion of the possibility that the connective tissue capsule may after years be replaced by fibrous glia. Despite encapsulation of an abscess, the possibility remains that the wall may become

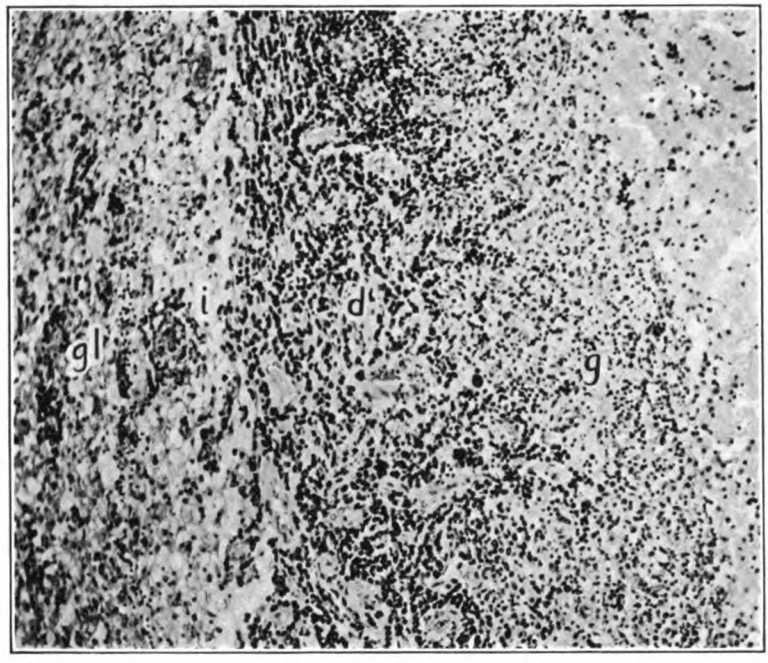


FIG. 115. CEREBELLAR ABSCESS FOLLOWING OTITIS MEDIA

Section through capsule. Hematoxylin-eosin stain. g = zone of granulation. d = zone of demarcation. i = zone of edema (zone of irritation). gl = zone of glia proliferation

necrotic after some time or become involved in the abscess formation itself. The ensuing perforation will then give origin to a new purulent encephalitis in the neighborhood.

PURULENT MYELITIS

The macroscopic appearance of the spinal cord in infectious myelitis does not offer many characteristic features. The soft consistency of the segments involved, and their edematous and swollen appearance, may also

be found in anemic softening or myelopathies of different etiology. In transverse sections the gray and the white can hardly be differentiated; they may be interspersed with multiple small hemorrhages. When the meninges are torn during autopsy, it may happen that the soft spinal cord tissue will protrude tumor-like over the surface.

The microscopic examination shows perivascular infiltration with polymorphonuclear leukocytes, lymphocytes, and in less acute cases with plasma cells and mast cells. Red blood cells may be intermingled with them in foci of petechial hemorrhages. In the region surrounding these infiltrated vessels, the tissue is edematous, showing wide meshes, swollen

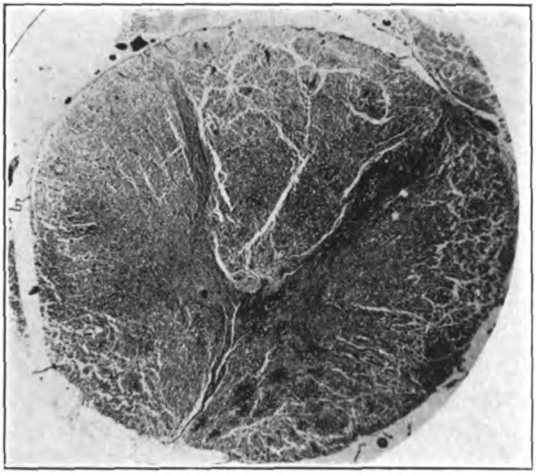


FIG. 116. HEMORRHAGIC MYELITIS

In case of pleuritis and retropharyngeal abscess. Transverse section through dorsal spinal cord. Weil stain. Spinal cord edematous. Multiple perivascular hemorrhages

and disintegrated neuroglia cells, fragmented myelin sheaths, and swollen axis-cylinders. If thrombosis of blood vessels is added as a complicating factor, areas of softening filled with compound granular corpuscles are seen. If the infectious process invades the gray matter, rapid degeneration of the neurons occurs. To make the histologic picture still more diffuse, ascending and descending fiber tract degeneration follows the destruction of nerve fibers in the infected foci (fig. 116).

The process of repair is started by the scavenger action of the gitter cells removing the tissue debris; this is followed by proliferation of capillaries and fibrous glia, which forms the final scar. In its final stage such a sclerotic scar formation is not different from repair following softening in

anemia, hemorrhage, or compression. The only criteria we have for the diagnosis of an advanced infectious myelitis, in addition to the clinical history, are the perivascular infiltration described above and the demonstration of the micro-organism by staining or by culture. Even these two criteria may be absent. Examples of infection without hematogenous cellular infiltration will be given later in connection with myelitis following measles. Micro-organisms seem to disappear from nervous tissue—sometimes rapidly—after the beginning of the cellular infiltration.

Abscess formation in the spinal cord is rare. It may follow hematogenous infection in bronchiectasis, pulmonary gangrene, purulent thrombophlebitis, or other forms of pyemia. It may develop in connection with a focal caries of the vertebrae or purulent meningitis. The wall formation is similar to that described above. The edema and necrosis of the surrounding tissue, however, seem to be more marked and spread into both upper and lower segments.

Acute Epidemic Encephalitis

Synonyms: encephalitis lethargica; von Economo's disease; French, *encéphalite léthargique.*

Both before and after von Economo described the outbreaks of epidemic encephalitis in Vienna, more or less widespread epidemics of this type occurred in Europe and on the American continent as well. The virus responsible for these epidemics occurs in different variations, which may be distinguished immunologically. Of more recent times in the United States, an epidemic was observed in St. Louis in 1933, followed by another outbreak in 1937. Shortly thereafter, there appeared along the Atlantic and Pacific seacoasts other types of epidemic encephalitis that both pathologically and immunologically resembled the virus-borne encephalomyelitis in horses that had been endemic in those regions with sporadic epidemic outbreaks. A fourth focus developed in the Dakotas, extending into Montana and Nebraska. Immunologically this form of encephalitis was found to be identical with the western equine encephalomyelitis.

Many attempts have been made to differentiate the various types of epidemic, virus-borne encephalitis histopathologically. Common to all of them is the peculiar tissue reaction, consisting of a nonpurulent mesenchymal proliferation combined with an intensive reaction of all the three different types of glia by formation of more or less widespread foci of glia. This inflammatory process is more pronounced in the gray matter (polioencephalitis) than in the white. The site of predilection is the brain stem, and here again the midbrain is mostly involved (figs. 117–20). Table 13 shows the relative intensity of inflammatory reaction in the St. Louis epidemic of 1933 and in the North Dakota epidemic of 1941.

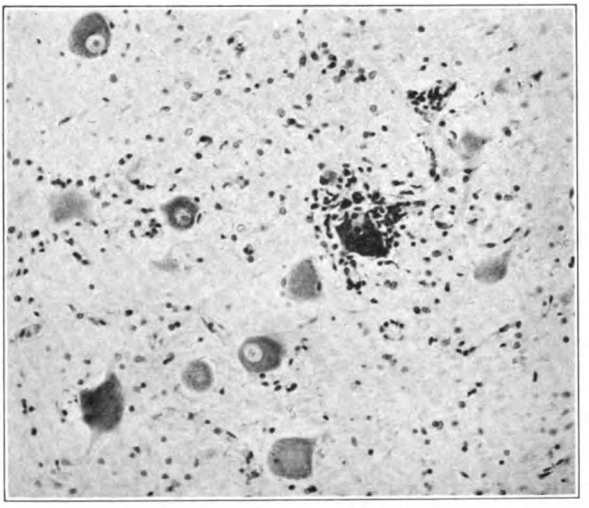


FIG. 117. EPIDEMIC ENCEPHALITIS (ST. LOUIS)

Anterior horn cells of spinal cord. Different stages of neuronal disease with neuronophagia of one anterior horn cell. Cresyl violet stain

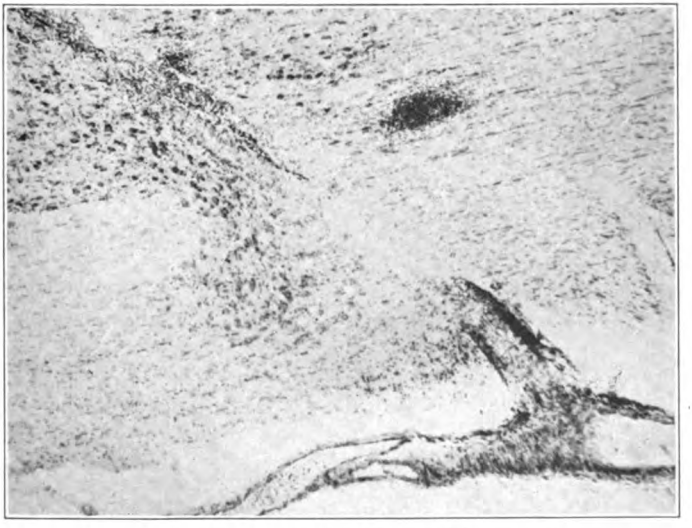


FIG. 118. EPIDEMIC ENCEPHALITIS (ST. LOUIS)

Same brain as in fig. 117. Base of pons. Mild perivascular infiltration of meningeal vessel, continuing along Virchow-Robin spaces into pons. Focus of proliferated glia at right of vessel

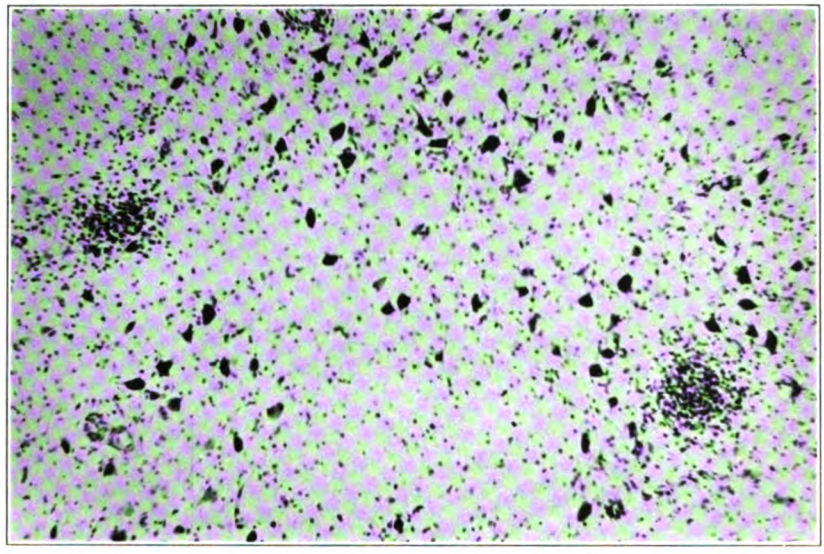


FIG. 119. EPIDEMIC ENCEPHALITIS (ST. LOUIS)
Midbrain; foci of glia proliferation. Cresyl violet stain

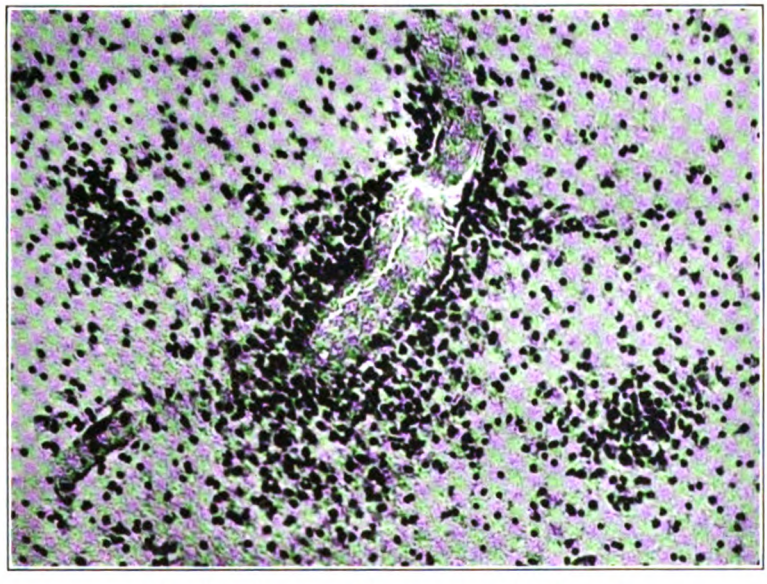


FIG. 120. EPIDEMIC ENCEPHALITIS (ST. LOUIS)
Same brain as in fig. 119. Cerebral cortex. Perivascular infiltration and foci of glia proliferation. Cresyl violet stain
(Figs. 117–20 courtesy Archives of Neurology and Psychiatry)

The intensity of inflammatory reaction within the different brains differed considerably. Besides, each brain seemed to have its peculiar type of reaction. Some developed a marked perivascular mesenchymal cellular proliferation; others responded with a more marked gliosis and only mild mesenchymal round cell infiltration, while in the majority of cases the two types of defense reaction were about equally developed.

The type of the North Dakota epidemic and the eastern equine type were differentiated from that of the St. Louis epidemic by the presence of foci of severe necrosis, especially in the white matter, which in early cases did not show any organization and which later were replaced by proliferated glia (figs. 121–23). In these areas both myelin sheaths and axis-cylinders were destroyed, and early attempts at encapsulation by proliferated astroglia forming a fibrous wall were seen. However, the glial proliferation was not confined to the environment of such foci of necrosis or inflammatory reaction; it was widespread and assumed proportions seen in experimental

TABLE 13.—*Relative Intensity of Encephalitis in Different Regions**

The intensity of the inflammatory reaction is somewhat arbitrarily graded from plus (+) to 3 plus (+++) and the mean values are calculated from observations on eight different brains

Epidemic	Cerebellum	Central Cortex	Striatum	Thalamus	Midbrain	Pons	Medulla Oblongata
St. Louis	1.3+	1.4+	1.5+	2.0+	2.4+	1.9+	1.8+
North Dakota	0.5+	0.2+	1.5+	1.7+	2.2+	0.8+	1.0+

* From Weil, A., and Breslich, P. J.: J. Neuropath. & Exper. Neurol. *1:* 49, 1942.

intoxications (metrazol, lead). The neurons were more severely diseased in the immediate environment of foci of inflammatory reaction. There were many variations, from mild swelling of cytoplasm and nucleus to a complete necrosis with transitory stages of disappearance of Nissl bodies, shrinkage, and hyperchromatosis of the nucleus. The neuronophagia was usually of a mild degree. The neuronal disease was most pronounced in the brain stem nuclei, but the spinal cord in many cases was also affected, as indicated clinically by the early symptoms of acute anterior poliomyelitis (fig. 117).

The meningeal changes were proportional to the intensity of inflammatory reaction of the underlying brain tissue. There was a mild edema with scanty distribution of small round cells within the piarachnoid, which assumed more intense proportions in the interpeduncular fossae, corresponding to the marked encephalitis of the midbrain.

Little can be said about the gross anatomic diagnosis. There was usually a marked hyperemia of the brain, with venous stasis seen within the white

matter, but hemorrhages, either macroscopically or microscopically discernible, were rare. Virus-borne hemorrhagic forms of meningo-encephalitis are more of the leuko-encephalitic type, as described for example in Russia by Margulis, Soloviev, and Shubladze, or as occurring in the influenza encephalitis (fig. 124). The pathologic feature in the Russian

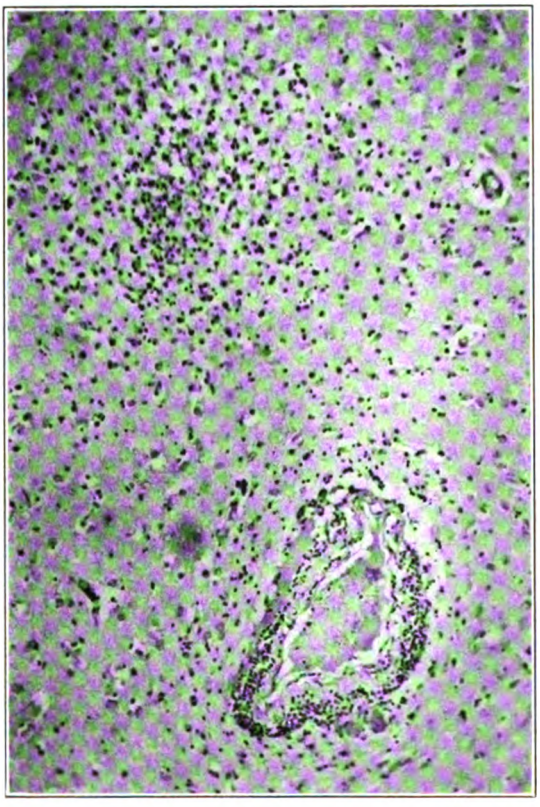


FIG. 121. EPIDEMIC ENCEPHALITIS (NORTH DAKOTA)
Disease of 1 week's duration. Striatum. Necrotic area filled with glia nuclei and mild perivascular round cell infiltration (cf. fig. 29)

epidemic was a primary endarteritis accompanied by perivascular cellular infiltration and secondary perivascular hemorrhages following necrosis of the vessel wall. Similar epidemics of hemorrhagic encephalitis of the leuko-encephalitis type and of the disseminated polio-encephalitis type have been described in the Japanese literature. Attempts to differentiate the latter from the von Economo types and the St. Louis epidemic type are

useless, owing to the great variety among individual cases in these epidemics (Flexner). Besides, it appears that different epidemics within the same group are differentiated with respect to the virulence of the specific virus. It should be pointed out that the encephalitis of the first North Dakota outbreak (1938) had a more stormy, acute character than that of the second (1941) epidemic; histopathologically the two were differen-

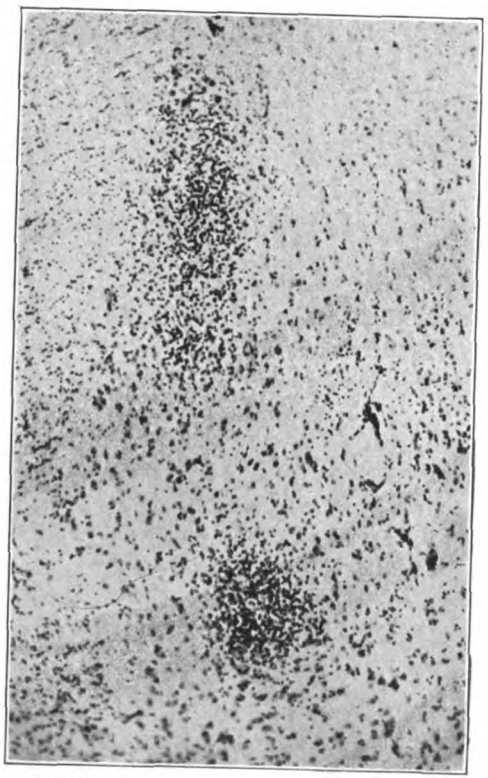


FIG. 122. EPIDEMIC ENCEPHALITIS (NORTH DAKOTA)
Same brain as in figs. 121, 123. Striatum. Two foci of proliferated glia

tiated by the presence of more necrotic foci in the brain in the cases of the first epidemic. Such a difference in the vitality of the virus, or in the development of an immunity, may also account for the fact that "post-encephalitic" or "chronic encephalitic" sequelae like parkinsonism, or postencephalitic amyotrophic lateral sclerosis, or postpoliomyelitic progressive spinal muscular atrophy, vary with the different epidemics. As

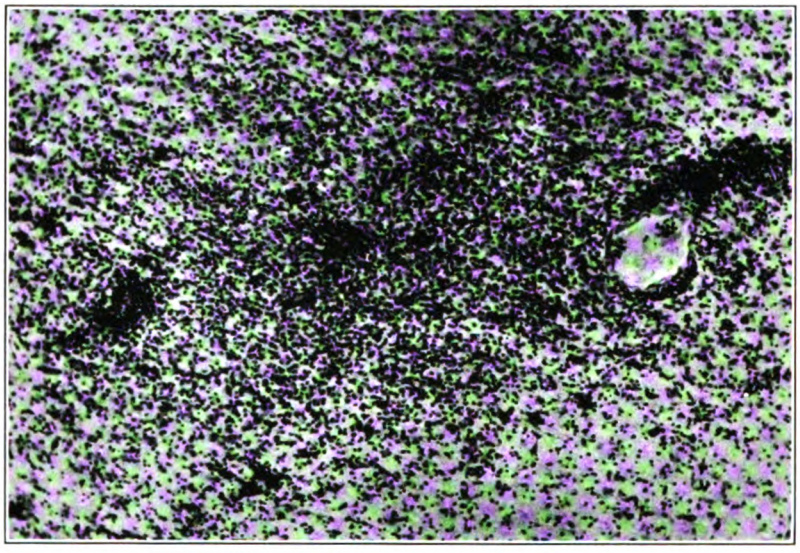


FIG. 123. EPIDEMIC ENCEPHALITIS (NORTH DAKOTA)
Same brain as in figs. 121, 122. Midbrain. Very intense inflammatory reaction

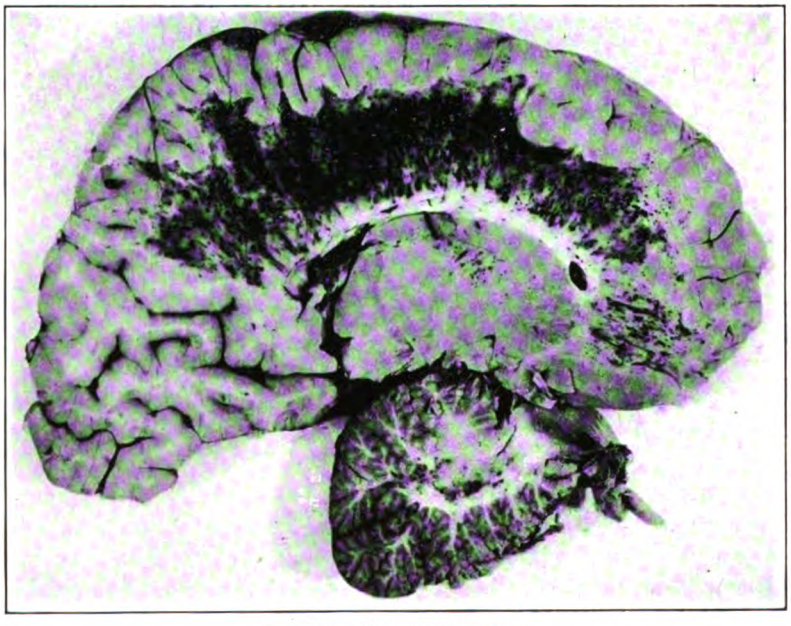


FIG. 124. BRAIN PURPURA
Case of influenza. White matter, sagittal section through brain
(Courtesy Dr. H. H. Dixon)

in the clinically healed forms of acute anterior poliomyelitis, we are compelled to assume that in the postencephalitic diseases likewise the virus survives, though in an attenuated form, and brings about the pathologic pictures we see, for example, in postencephalitic parkinsonism—i.e., foci of neuronophagia surrounding diseased neurons in the striatum and mesencephalon, scattered perivascular small round cells, and severe disease of the pigmented cells of the substantia nigra, with excessive gliosis (fig. 125). Experimental proof for such an assumption has been given by Bettina Warburg. By means of intracerebral injection of emulsions of spinal cords from monkeys that had survived experimental anterior poliomyelitis

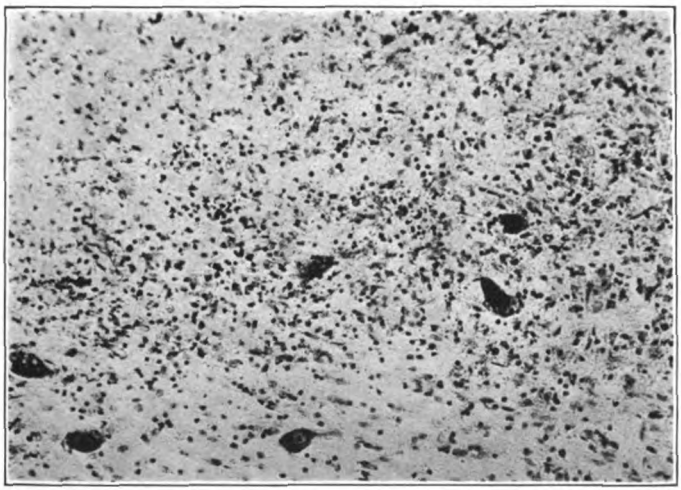


FIG. 125. POSTENCEPHALITIC PARKINSONISM
Substantia nigra. Cresyl violet stain. Disappearance of pigmented cells and proliferation of neuroglia

and had been clinically cured for several years, she succeeded in re-producing the acute disease in the injected animals.

Another nonepidemic type of virus infection in man is rabies. The inflammatory reaction is extremely mild, consisting of perivascular lymphocytic infiltration and formation of small, scattered glia foci. The cytoplasmic inclusions (Negri bodies) are of greater diagnostic importance. Similar inclusions in larger neurons have also been described in rare cases of encephalitis following infection with the herpes virus. The inflammatory reaction here is very similar to that described above in relation to epidemic encephalitis.

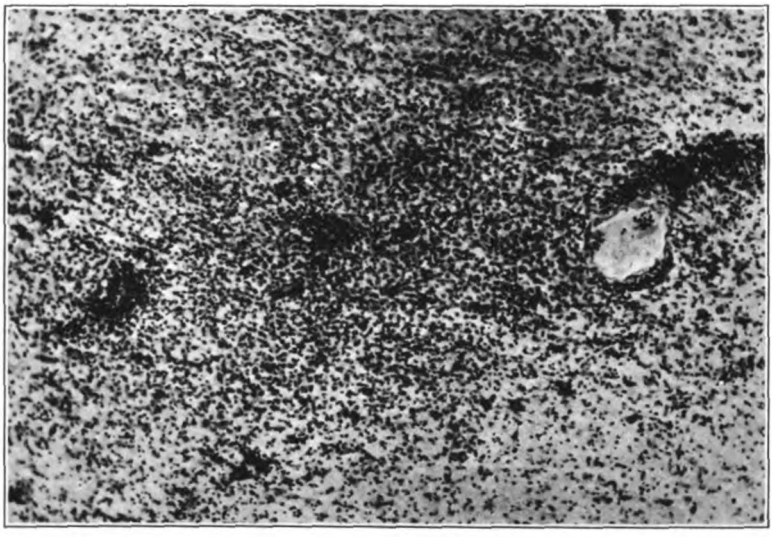


FIG. 123. EPIDEMIC ENCEPHALITIS (NORTH DAKOTA)
Same brain as in figs. 121, 122. Midbrain. Very intense inflammatory reaction

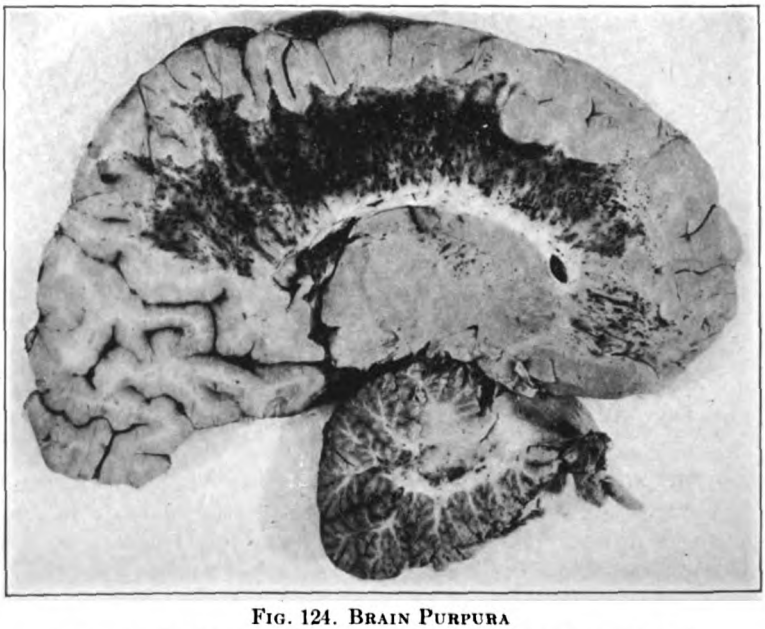


FIG. 124. BRAIN PURPURA
Case of influenza. White matter, sagittal section through brain
(*Courtesy Dr. H. H. Dixon*)

in the clinically healed forms of acute anterior poliomyelitis, we are compelled to assume that in the postencephalitic diseases likewise the virus survives, though in an attenuated form, and brings about the pathologic pictures we see, for example, in postencephalitic parkinsonism—i.e., foci of neuronophagia surrounding diseased neurons in the striatum and mesencephalon, scattered perivascular small round cells, and severe disease of the pigmented cells of the substantia nigra, with excessive gliosis (fig. 125). Experimental proof for such an assumption has been given by Bettina Warburg. By means of intracerebral injection of emulsions of spinal cords from monkeys that had survived experimental anterior poliomyelitis

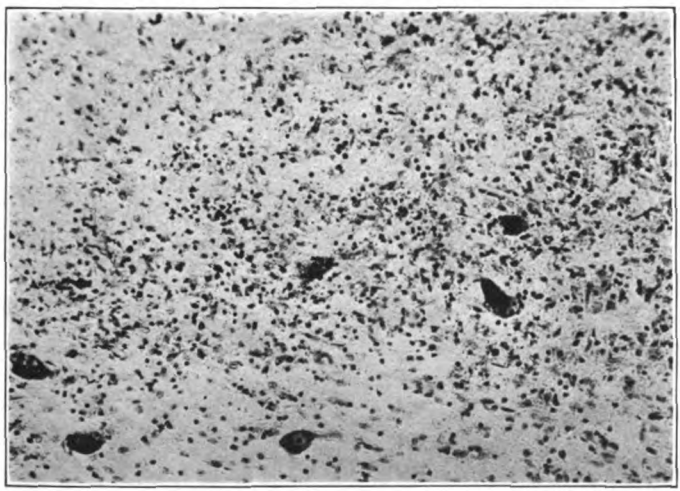


FIG. 125. POSTENCEPHALITIC PARKINSONISM
Substantia nigra. Cresyl violet stain. Disappearance of pigmented cells and proliferation of neuroglia

and had been clinically cured for several years, she succeeded in re-producing the acute disease in the injected animals.

Another nonepidemic type of virus infection in man is rabies. The inflammatory reaction is extremely mild, consisting of perivascular lymphocytic infiltration and formation of small, scattered glia foci. The cytoplasmic inclusions (Negri bodies) are of greater diagnostic importance. Similar inclusions in larger neurons have also been described in rare cases of encephalitis following infection with the herpes virus. The inflammatory reaction here is very similar to that described above in relation to epidemic encephalitis.

Acute Poliomyelitis

Synonyms: infantile paralysis; German, *Heine-Medin'sche Krankheit;* French, *maladie de Heine-Medin.*

The micro-organism producing acute poliomyelitis has been cultured and successfully transmitted to monkeys, but its morphology is still doubtful. Eberson described minute ovoid bodies, from 0.05 to 0.1 or 0.2 micron in size, "occurring in irregular clusters, in pairs, singly, very rarely in short chains and in densely packed masses." They could be cultured in mixtures of brain and broth.

The designation poliomyelitis ("polio-" for "gray") is not quite correct, because the inflammation is also found in the white matter of the spinal cord and brain, though to a much lesser extent than in the gray. Macroscopically the disease of the gray matter is revealed by edema, the presence of small hemorrhages, and protrusion of the gray matter over the cut surface. The piarachnoid is edematous, but transparent in early cases. Hyperemia and edema are also found in the meninges of the brain and sometimes in the brain itself. It is also not quite correct to speak in this instance of "myelitis," since the infection affects both brain stem and cortex, varying in intensity during the different epidemics. Since 1911 there has been a tendency of the virus to attack more adults, in both European and American epidemics.

The essential histologic feature in acute cases is an adventitial and perivascular cellular infiltration (of arteries and veins alike) with lymphocytes, polymorphonuclear leukocytes, and plasma cells, which spread diffusely into the environment. These are intermingled with proliferated glia cells. The neurons are severely diseased; during the first week they show swelling, and during the second week various degenerative stages such as fatty degeneration, vacuolization, shrinkage, loss of nuclei, and neuronophagia. In addition there is sometimes thrombosis of smaller vessels, with subsequent anemic softening of the surrounding regions and encapsulation of the latter by proliferated glia. The capillaries are widened and small hemorrhagic foci may be seen. The nerve fibers in the areas of inflammation are destroyed. The same perivascular infiltration is found in the meninges, with a mild extension into the arachnoidal spaces. The histologic picture of the brain stem and cortex is essentially the same, with the inflammation most marked in the hypothalamus and midbrain. The infection may spread from the spinal cord upward into the medulla oblongata and pons. The several structures may be diseased simultaneously or separately; polio-encephalitis, localized in the hemispheres, the cerebellum, or the brain stem, may occur in epidemics without poliomyelitis (figs. 127, 128). Its histopathology closely resembles that of the epidemic encephalitis of the St. Louis or von Economo type.

In the spinal cord the inflammation spreads very irregularly. One ventral horn may be diseased while that of the other side is spared. From an infected focus the inflammation spreads upward and downward on the same side, indicating a spread along the perivascular lymphatics.

After cessation of the infectious process, the debris of the destroyed nervous tissue is removed by compound granular corpuscles, and in the chronic stage ("infantile paralysis") a mild fibrous glia scar intermingled with epithelioid cells, a diminution in neurons, and sometimes cystic cavities testify to the previous presence of the disease. Macroscopically the anterior horns appear small and gelatinous, and the anterior roots are

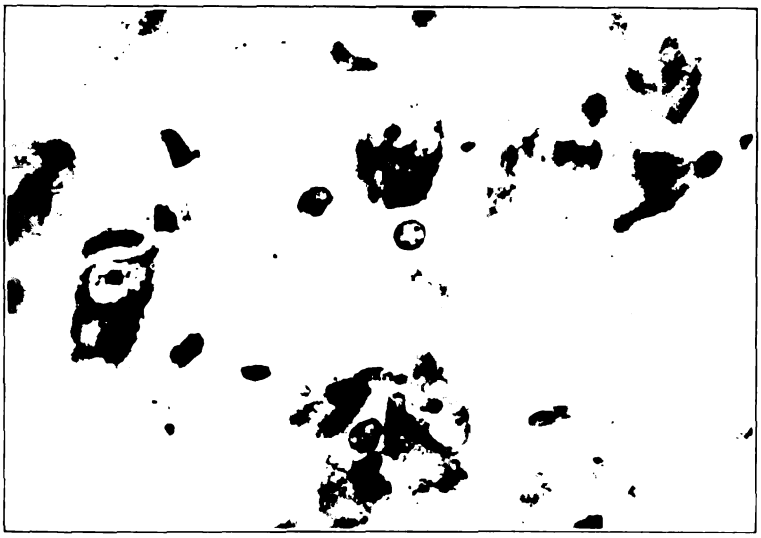


FIG. 126. RABIES

Dog brain. Cornu ammonis. Hematoxylin-fuchsin stain. Negri bodies, replacing part of cytoplasm, are stained black

atrophic. It seems that the virus may survive much longer than has been assumed until recently and may continue the inflammatory process even after functional recovery, as mentioned in connection with epidemic encephalitis.

TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM

TUBERCULOUS MENINGITIS

Next to epidemic meningitis, the tuberculous form is the most frequent type of inflammation of the meninges. About 16 per cent of the cases occur during the first year of life and 81 per cent in the first decade

(Macgregor and Green); the most frequent occurrence is in the age period between 2 and 6 years. In about 75 per cent of all cases the infection is caused by the typus humanus of the bacillus, the rest being produced by the typus bovinus. The tubercle bacillus may migrate into the meninges from a tuberculoma of the brain or from other tuberculous foci, as in the bones, middle ear, lungs, or mediastinal lymph glands. Hematogenous origin seems to be rare and seldom does a tuberculous meningitis occur together with acute miliary tuberculosis. The latter may lead to the forma-

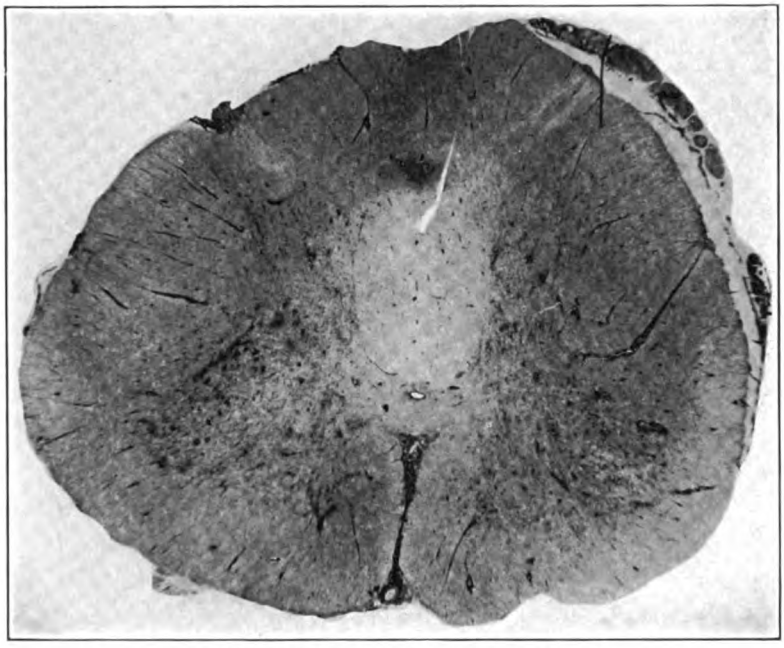


FIG. 127. ACUTE POLIOMYELITIS
Section through cervical spinal cord. Hematoxylin-eosin stain

tion of tubercles, which bring about a generalized tuberculous meningitis at the stage of caseation.

Gross inspection of the meninges may show the small grayish or, when caseated, more yellowish tubercles along the vessels of the sylvian fissure. In addition there may be a jelly-like cloudy exudate of a yellowish or greenish yellow color, most frequently filling the piarachnoid at the base of the brain. It may extend to the convexities or may cover the vermis of the cerebellum and the medulla oblongata. The cranial nerves may also be covered by such an exudate. In other cases, miliary tubercles along the sylvian fissures may be the only signs of the infection, and infiltration of the

piarachnoid may be entirely absent. The brain is very soft; the corpus callosum, the fornix, and the ventricular walls may be softened and macerated. The ventricles are widened and the choroid plexus may be covered with miliary tubercles.

Microscopically we can recognize two kinds of changes, which are also produced by the tubercle bacillus in other tissues of the body: (1) formation of a specific granuloma, the tubercle; (2) diffuse tuberculous inflammation. The tubercle arises from the wall of a vessel. Its center is formed by an accumulation of epithelioid cells, large cells of various shapes with

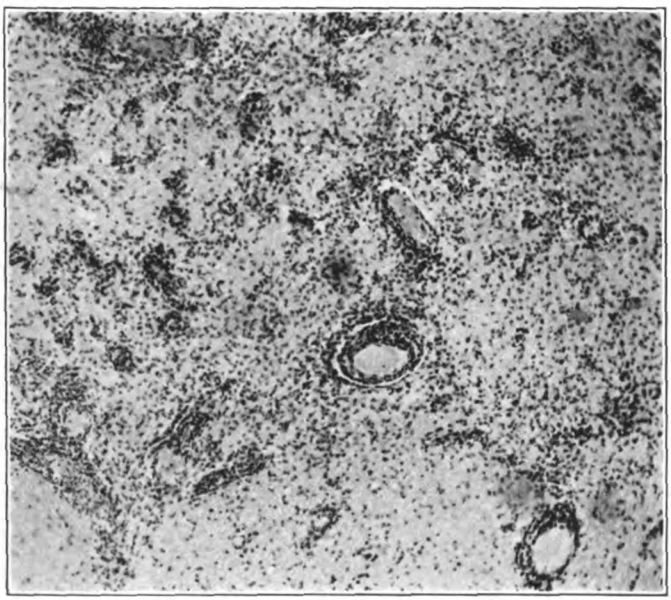


FIG. 128. ACUTE POLIOMYELITIS
Higher magnification of anterior horn shown in fig. 127

large, pale nuclei (derivatives of histiocytes). They may be intermingled with the giant cells of Langhans and are surrounded by a dense outer zone of lymphocytes, plasma cells, and macrophages. The center of this tubercle undergoes necrosis very soon, and a caseous mass is formed, containing the debris of nuclei and cells, but devoid of blood vessels and connective tissue. In tuberculous leptomeningitis the lymphoid cell tubercle is more frequently seen. Lymphocytes are more numerous and form densely packed centers that undergo necrosis.

Tubercle formation is mostly associated with a diffuse infiltration of the arachnoidal meshes with macrophages, lymphocytes, and polymorpho-

(Macgregor and Green); the most frequent occurrence is in the age period between 2 and 6 years. In about 75 per cent of all cases the infection is caused by the typus humanus of the bacillus, the rest being produced by the typus bovinus. The tubercle bacillus may migrate into the meninges from a tuberculoma of the brain or from other tuberculous foci, as in the bones, middle ear, lungs, or mediastinal lymph glands. Hematogenous origin seems to be rare and seldom does a tuberculous meningitis occur together with acute miliary tuberculosis. The latter may lead to the forma-

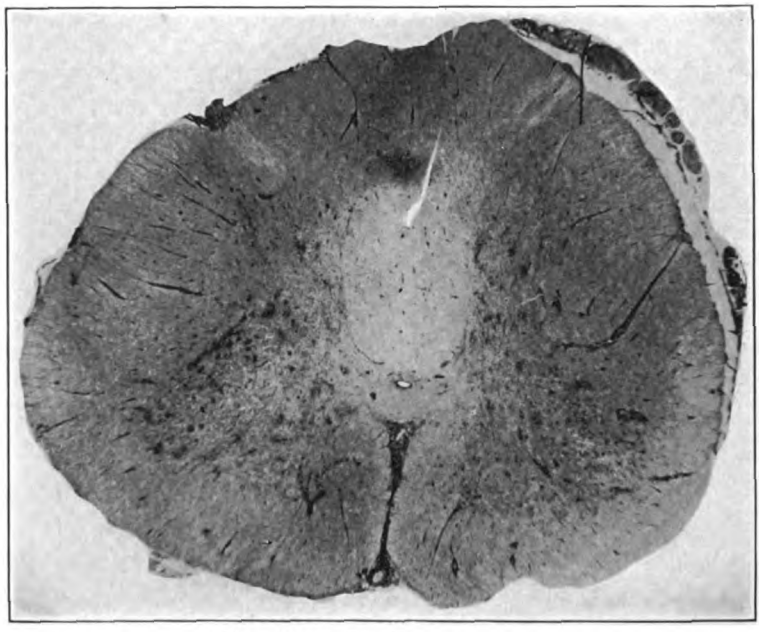


FIG. 127. ACUTE POLIOMYELITIS
Section through cervical spinal cord. Hematoxylin-eosin stain

tion of tubercles, which bring about a generalized tuberculous meningitis at the stage of caseation.

Gross inspection of the meninges may show the small grayish or, when caseated, more yellowish tubercles along the vessels of the sylvian fissure. In addition there may be a jelly-like cloudy exudate of a yellowish or greenish yellow color, most frequently filling the piarachnoid at the base of the brain. It may extend to the convexities or may cover the vermis of the cerebellum and the medulla oblongata. The cranial nerves may also be covered by such an exudate. In other cases, miliary tubercles along the sylvian fissures may be the only signs of the infection, and infiltration of the

piarachnoid may be entirely absent. The brain is very soft; the corpus callosum, the fornix, and the ventricular walls may be softened and macerated. The ventricles are widened and the choroid plexus may be covered with miliary tubercles.

Microscopically we can recognize two kinds of changes, which are also produced by the tubercle bacillus in other tissues of the body: (1) formation of a specific granuloma, the tubercle; (2) diffuse tuberculous inflammation. The tubercle arises from the wall of a vessel. Its center is formed by an accumulation of epithelioid cells, large cells of various shapes with

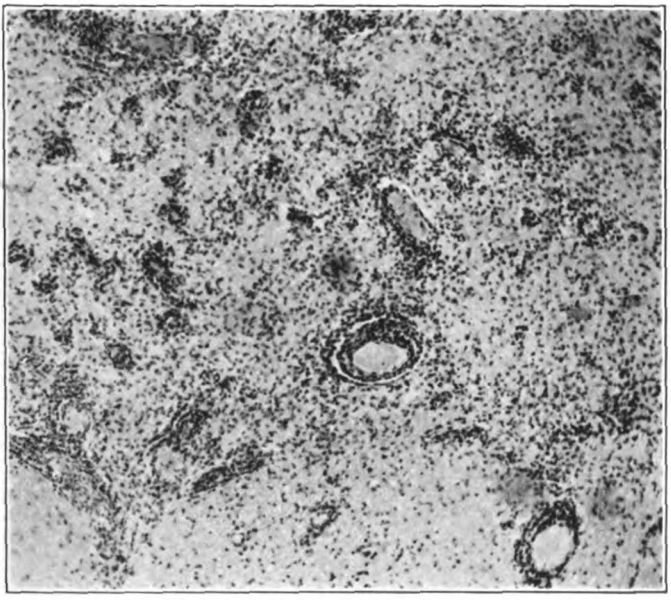


FIG. 128. ACUTE POLIOMYELITIS
Higher magnification of anterior horn shown in fig. 127

large, pale nuclei (derivatives of histiocytes). They may be intermingled with the giant cells of Langhans and are surrounded by a dense outer zone of lymphocytes, plasma cells, and macrophages. The center of this tubercle undergoes necrosis very soon, and a caseous mass is formed, containing the debris of nuclei and cells, but devoid of blood vessels and connective tissue. In tuberculous leptomeningitis the lymphoid cell tubercle is more frequently seen. Lymphocytes are more numerous and form densely packed centers that undergo necrosis.

Tubercle formation is mostly associated with a diffuse infiltration of the arachnoidal meshes with macrophages, lymphocytes, and polymorpho-

nuclear leukocytes. These cells too may be destroyed under the influence of toxins of the tubercle bacillus, and large zones devoid of nuclei are seen, indicating such necrotic areas. A very active connective tissue proliferation is added to this picture of tubercle formation, cellular exudation, and necrosis; this gives a characteristic appearance in many cases of tuberculous meningitis. The infection spreads also to the blood vessels of the meninges; these show dense cellular infiltration of their walls, all the different layers of which may be affected. Occlusion of the lumen may finally produce softening. The demonstration of tubercle bacilli by the Ziehl-Neelsen or by other methods is helpful in establishing the diagnosis (fig. 129).

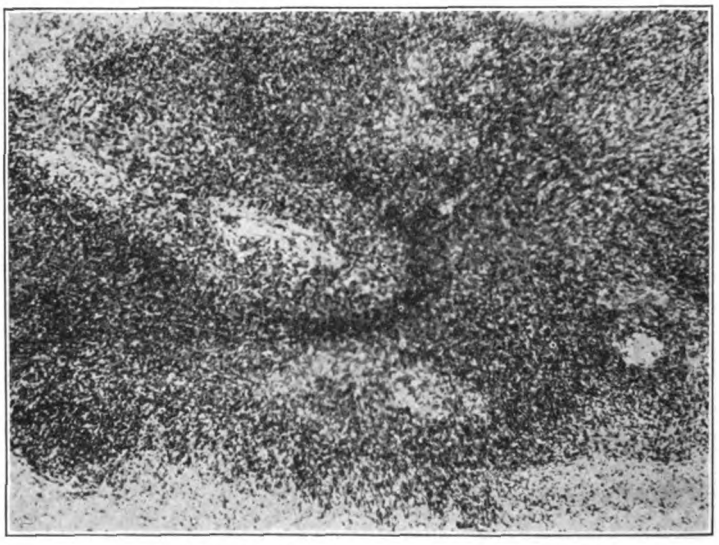


FIG. 129. TUBERCULOUS MENINGITIS

In child aged 15 months. Cresyl violet stain. Tubercle formation in walls of meningeal vessels

It seems that the more or less malignant character of a tuberculous meningitis is dependent upon the degree of immunization following preceding infections of other organs. In a young child who, in connection with a pulmonary tuberculosis, immediately develops a tuberculous meningitis, one may find a meningitis with diffuse, dense infiltration of the piarachnoid with lymphocytes, macrophages, and polymorphonuclear leukocytes. The rapid course of the disease, leading to early death, leaves no time for the formation of necrotic centers or tubercles. The demonstration of tubercle bacilli in stained sections is one help in differentiating this from other types of meningitis.

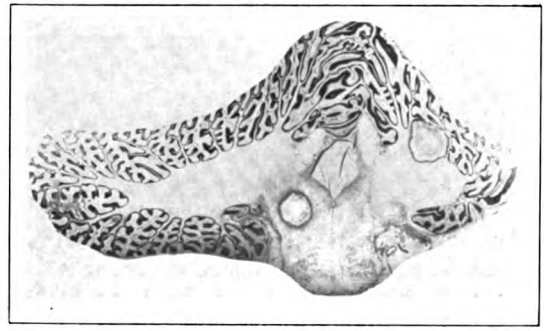


FIG. 130. CHRONIC TUBERCULOSIS OF CEREBELLUM AND MENINGES: TUBERCULOMAS IN CEREBELLUM

Necrotic center in both tuberculomas is surrounded by dark-staining zone of cellular infiltration, consisting of proliferated fibroblasts and fibrillary astrocytes, intermingled with lymphocytes and plasma cells. Cresyl violet stain

(Courtesy Dr. C. Davison)

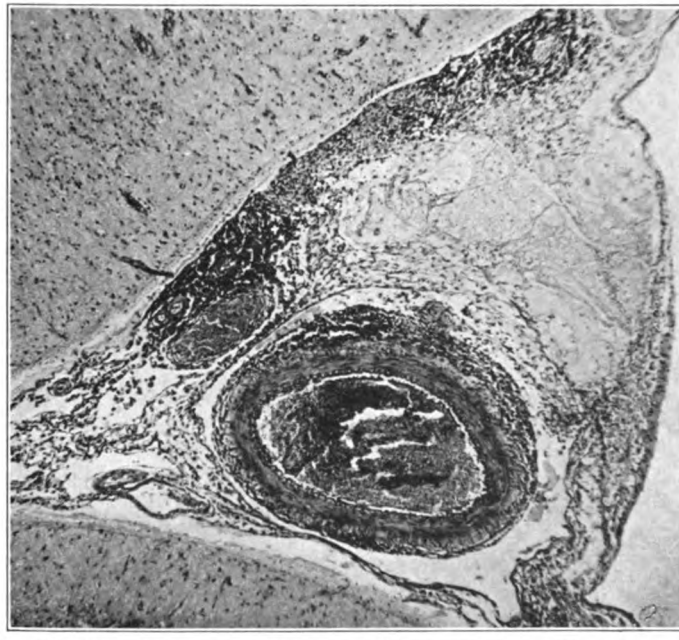


FIG. 131. CHRONIC TUBERCULOSIS OF CEREBELLUM AND MENINGES: MILIARY TUBERCLE IN PIARACHNOID OF SYLVIAN FISSURE

Same brain as in fig. 132. Grossly, tubercle appeared as small yellowish nodule, approximately 2 mm. in diameter. Histologic picture shows perivascular cellular infiltration around meningeal vessels, necrotic area filled with shadows of cells, and faded outlines of connective tissue fibers. Van Gieson stain

Rabbits vaccinated with living human tubercle bacilli did not develop meningitis following intrameningeal infection, while nonvaccinated controls were killed.

It is known from clinical evidence that a tuberculous meningitis may heal. It is an undecided question whether the fulminant type just described may be successfully overcome by the defense reaction of the meninges. In most old cases with histories of previous meningitis, one will find tubercle formation and a very marked thickening of the connective tissue. In addition, the chronic tuberculous encephalitis is included in the histologic picture.

In tuberculous leptomeningitis the inflammation may spread along the pial sheaths of the blood vessels into the brain and spinal cord, producing tuberculous meningo-encephalitis (myelitis). The necrosis may affect the outer layers of the cortex, which are densely infiltrated with fragmented nuclei. One may find a mild proliferation of the perivascular connective tissue, with an infiltration of a few lymphocytes, plasma cells, and polyblasts. The brain itself is markedly edematous; swelling and distortion of myelin sheaths and axis-cylinders are seen, together with widespread degenerative changes of the cortical neurons. In the outer zones severe neuronal disease may be found in cells with liquefied cytoplasm and pyknotic nuclei; in more distal zones we find swelling of the nerve cells, which show homogeneous pale-stained cytoplasm, large vesicular neucleus, and prominent nucleolus. In cresyl violet–stained sections the glia nuclei seem to be generally increased. In the outer layers many fragmented and granulated forms may be seen; in the lower layers there is an abundance of large, pale astrocyte nuclei intermingled with numerous microglial and increased oligodendroglial cells.

The histologic picture seems to indicate a diffusion of the toxins of the tubercle bacilli into the brain substance, producing severe necrosis of all the different elements in the neighborhood of the meningitis and, in the more distant regions of the cortex, edema of neurons, myelin sheaths, and axis-cylinders, together with an active proliferation of the different types of glia.

An isolated occurrence of miliary tubercles without leptomeningitis in the ependymal lining of the ventricles has been described. One may find in the walls of the lateral, third, and fourth ventricles small nodules of the size of a pinhead. On microscopic examination they appear like small abscess formations, composed of polymorphonuclear leukocytes or small lymphocytes. With specific stains numerous tubercle bacilli are found.

TUBERCULOMA

A frequent form of tuberculosis of the central nervous system is the tuberculoma, a conglomeration of small tubercles in which caseation and

frequently encapsulation occur, thus producing a tumor-like structure. It is more often found in the brains of children than in those of adults. It occurs most frequently in the cerebellum, with next greatest frequency in the cerebral hemispheres, and least often in the brain stem. Its occurrence in connection with tuberculosis of other organs of the body, of lymph nodes, of the middle ear, and of the petrous portion of the temporal bone, suggests a metastatic origin rather than primary infection. The size of the tuberculoma may vary from that of small nodules a few millimeters in diameter to large conglomerations of the size of a hen's egg. The larger tuberculomas may often be removed as a solid mass from the surrounding softened brain tissue; in other cases they are adherent to the overlying meninges. The inner part is caseous, sometimes softened, calcified, or, in rare cases, transformed into an abscess.

Microscopically, the granuloma in its early stages is formed by miliary tubercles arising in the outer sheaths of small cerebral vessels. Other nodules are added and the center of this conglomeration finally becomes caseous. The surrounding brain tissue reacts to the tuberculous toxins in a manner similar to that described above in relation to tuberculous meningitis. Softening occurs with an ensuing formation of gitter cells and a walling off of the tubercle. The attempt at repair, however, is soon interrupted by the formation of new tubercles that destroy the newly formed capillaries and connective tissue–glia scar. The process of softening and attempt at repair starts anew in the outer zones, until the nerve tissue finally succeeds in arresting further growth of the granuloma by formation of a connective tissue wall. If this is not achieved and the process breaks through into the meninges, a lethal tuberculous meningitis is produced. In the center of a large tuberculoma, multiple islands of necrotic debris, surrounded by circular collagenous connective tissue capsules, testify to these successive stages (fig. 130).

In most tuberculomas the periphery still presents a zone of growth. It is infiltrated with epithelioid and lymphocytic cells, and many large multinuclear giant cells of the Langhans type are seen. Fibroblasts, capillary sprouts, and collagenous fibers are intermingled with these cells—all forming together the tuberculous granuloma tissue (fig. 132).

Sometimes a tuberculoma may be differentiated only with difficulty from a gumma. Besides the fact that the latter has become exceedingly rare, the microscopic make-up of its center, in which argyrophile fibers are formed, helps to establish a differential diagnosis.

Calcified or softened tuberculomas with pus formation may be grossly mistaken for calcified or encapsulated abscesses. Under the microscope, however, the presence of the tuberculous granulations in the periphery and the demonstration of giant Langhans cells will correct any doubt that may

have arisen on gross inspection. The tubercle bacillus can be demonstrated only in the very beginning of the existence of the tuberculoma, within the centers of the small nodules.

In the spinal cord the tuberculoma is a rare finding. If it occurs, it is usually single, in contrast to the multiple tuberculomas of the brain. Grossly it appears as a round formation with a center that is formed by concentric layers or that may be softened and surrounded by edematous tissue.

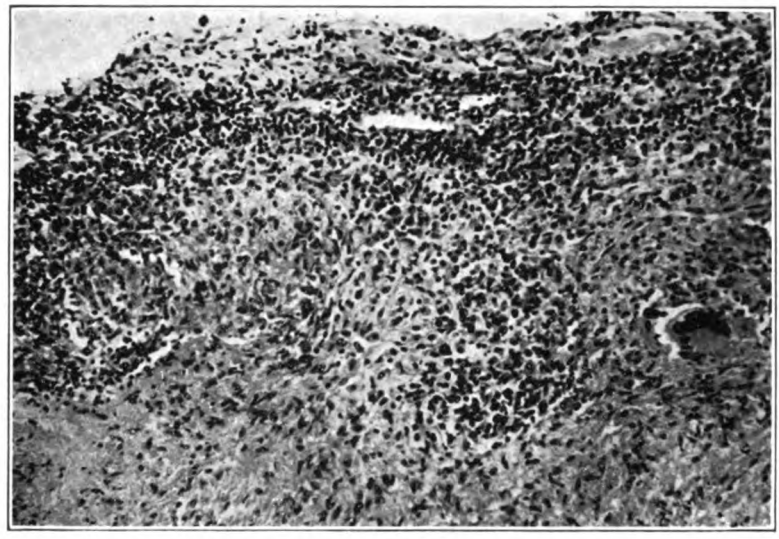


FIG. 132. TUBERCULOUS MENINGO-ENCEPHALITIS

Meningitis with tuberculous granulation tissue in cerebral cortex in case of abdominal tuberculosis. Van Gieson stain. Langhans giant cell at right

POTT'S DISEASE

From a practical standpoint, compression of the spinal cord following tuberculosis of the vertebrae, or Pott's disease, is more significant than tuberculosis of the spinal cord itself. The disease may begin as a caseous osteitis of the vertebral bodies that spreads through the intervertebral disks to other vertebrae and also involves the periosteum. The caseous granulation tissue of the periosteum advances upon the dura mater of the spinal cord after destruction of the posterior common ligament. It grows and fills out the epidural spaces, encircling and compressing the spinal cord. Compression of blood vessels may produce edema or even softening at the segments of the spinal cord that are involved. Usually the process does not invade the piarachnoid or the spinal cord itself.

This tuberculous spondylitis may lead to abscess formation, with infiltration of the epidural spaces with pus. The effect of the pressure upon the spinal cord is similar to that produced by tuberculous granuloma tissue. If the lumbar vertebrae are involved, the pus spreads also into the surrounding muscular tissues, frequently producing an abscess of the psoas muscle (fig. 133).

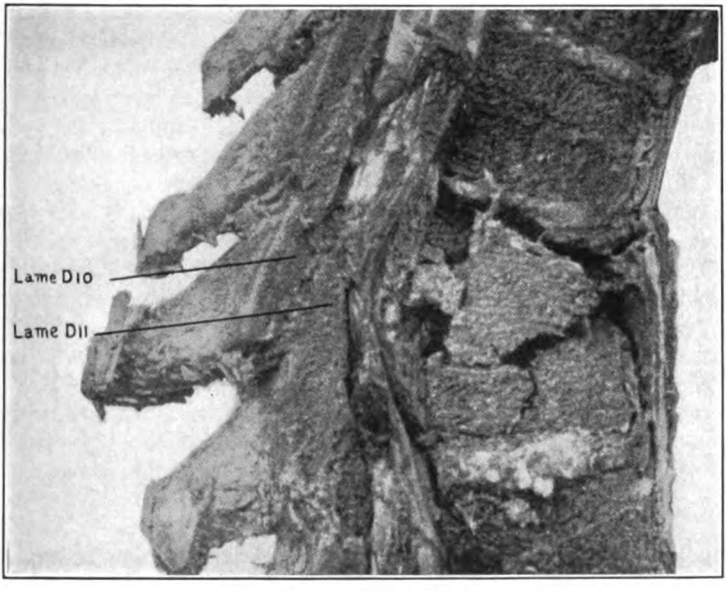


FIG. 133. POTT'S DISEASE

Sequestrum formation in tenth and eleventh dorsal vertebrae, with abscess compressing spinal cord

(Sorrel, E., and Sorrel-Déjérine [Mme E.]: Tuberculose osseuse et ostéo-articulaire, 1932. Courtesy Masson & Cie)

A third possibility of lesion of the spinal cord following tuberculous spondylitis is that of compression by a gibbus developing through displacement of the caseated and sequestered vertebrae. Such a compression may be followed by complete interruption of conduction of nervous impulses at this level. Even if the spinal cord itself is not directly compressed, the compression of blood vessels and nerves within the intervertebral foramina may produce softening or secondary ascending and descending degeneration within the spinal cord.

Syphilis of the Central Nervous System

SYPHILITIC MENINGITIS

The different changes described in relation to tuberculous meningitis may also be found in syphilitic infection, i.e., (1) formation of a specific granuloma, the gumma, and (2) diffuse syphilitic infection. Sometimes it is impossible to make a differential diagnosis from the histopathologic picture alone, especially if neither tubercle bacilli nor spirochetes can be demonstrated. It seems that granulomatous meningitis develops mostly in the late, tertiary stage of the disease and is more frequently found in adults. But even during the primary stage of the infection a very rapidly progressing diffuse leptomeningitis may develop. Among 12,162 cases of primary and secondary syphilis, acute meningitis was observed in 12.8 per cent (Frazier and Mu).

The condition is characterized by diffuse infiltration of the piarachnoid with numerous lymphocytes and only a few or no plasma cells. The site of predilection is again the base of the brain from the chiasm to the pons, with spreading into the cranial nerves, especially the eighth, seventh, second, fifth, and third, in this order of frequency. The spinal meninges too are frequently involved, the predilection being for the lower dorsal and lumbosacral segments. If this acute infection is overcome, an active proliferation of connective tissue fibers develops, which in the chronic stage transforms the piarachnoid into a thick rind that may be free of cellular infiltrations or may show only a thin line of lymphocytes at the borderline of the cortex.

GUMMA

The gumma is the analogue of the tubercle. It is a granulation tissue originating like the tubercle from the connective tissue of the vessel wall or from the leptomeninges. It consists of a dense accumulation of fibroblasts, lymphocytes, and plasma cells forming cuffs around the many newly formed vessels. The center of this granulation tissue becomes necrotic and is finally filled with a fibrous meshwork that does not stain with fuchsin (van Gieson method) but does stain under silver impregnation methods (Klarfeld-Achucárro). The formation of these connective tissue fibers and blood vessels differentiates the central necrosis of the gumma from the necrotic center of the tubercle. In the latter, caseation begins at a stage at which connective tissue proliferation has not yet begun. Therefore the centers of the tubercles do not show silver-stainable fibrils and newly formed blood vessels, but constitute a homogeneous, unstained area. Multinuclear cells may also be found in the luetic granulation tissue. They usually do not assume the appearance of the Langhans type with marginal position of the nuclei. The meningeal vessels show characteristic changes.

The adventitia and media are infiltrated with lymphocytes and plasma cells. The intima shows an intense proliferation of elongated, spindle-shaped cells, causing narrowing of the lumen. The elastica interna is split up into different layers of elastic fibers, while the endothelial cells may be normal.

Formation of the gummatous granulation may be localized or it may spread diffusely into the pia, invading the sulci and the peri- and endoneurium of the cranial nerves (meningitis gummosa). Under the influence of antisyphilitic treatment the granulation tissue may disappear and be replaced by a connective tissue scar, leading to a thickening of the piarachnoid with adhesions to the brain cortex. Gummas have become exceedingly rare, while at the beginning of the century they were still a frequent pathologic finding.

From the piarachnoid the syphilitic infection may spread either to the brain and spinal cord or to the dura mater. In the latter case the leptomeninges form a compact mass with the thickened dura mater, which shows an intense proliferation of connective tissue fibers, and sometimes calcification. The convexities of the brain are the site of predilection. Charcot taught that "pachymeningitis cervicalis hypertrophica" is predominantly of syphilitic origin. At present, however, trauma, alcoholism, and various infections are considered as other etiologic factors that may produce this rare localized pachymeningitis. Its effect upon the spinal cord will be discussed later.

The different histopathologic changes that may be produced by the toxins of Treponema pallidum within the brain and spinal cord may be classified into four groups: (1) meningo-encephalitis (meningomyelitis) syphilitica; (2) vascular syphilis; (3) general paresis; (4) tabes dorsalis.

Each of these four different types may occur isolated in its pure form; they may, however, occur also in different combinations. This has led many observers to the belief that there may be a direct relationship between the manifold manifestations of syphilis—an idea that is opposed by those who adhere to the theory of the specific character of each form. Such combinations are those of meningo-encephalitis syphilitica with vascular syphilis, of tabes dorsalis with general paresis, of general paresis with meningo-encephalitis syphilitica, and of tabes dorsalis with meningomyelitis syphilitica. These combinations have greatly influenced the theories concerning the etiology of the different forms. The influence that meningitis of the dorsal and lumbar spinal cord may have upon the production of tabetic changes in the posterior columns of the spinal cord, and the influence of cerebral syphilis upon the histopathologic picture of general paresis in the cortex, have been the subject of frequent and ardent discussions in the literature.

SYPHILITIC MENINGO-ENCEPHALITIS

The meningeal inflammatory process proceeds along the pial sheaths of the blood vessels into the brain and spinal cord substance. It produces either a diffuse perivascular cellular infiltration that cannot be differentiated from other forms of encephalitis, or the specific granulation tissue of encephalitis gummosa. Isolated or multiple gummas may be found in every

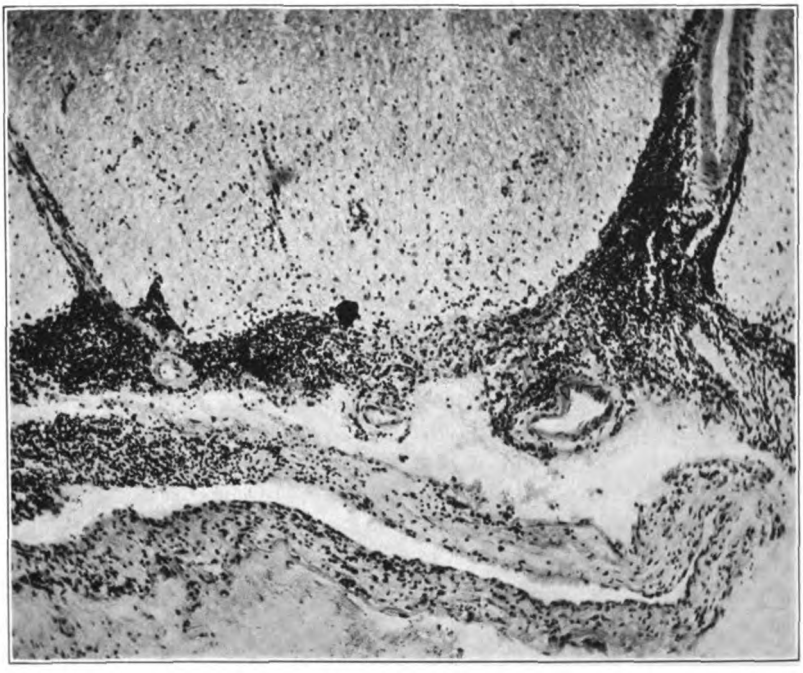


FIG. 134. SYPHILITIC MENINGITIS

Dense cellular infiltration of piarachnoid adjacent to brain stem and of wall of large vein. Infiltration continues along perivascular spaces into medulla oblongata. May-Gruenwald stain

part of the cortex and brain stem. It seems that larger nodules corresponding to the tuberculomas so frequently described by the older pathologists have disappeared. Jakob states that within the last ten years he has observed only five instances; similar statements are made by other neuropathologists in different parts of Europe and the United States. Cerebrospinal syphilis has always been considered a manifestation of the tertiary period of syphilis. But since gummatous changes have been found as early as six months after appearance of the primary lesion, and

diffuse meningo-encephalitis in the early part of the secondary period, this idea should be revised.

The changes of the nervous tissue in the region of the inflammatory foci or the gummas consist in edema, softening, degenerative changes of neurons, demyelinization of nerve fibers, and a mild proliferation of fibrous glia. They are similar to the changes described as seen in the tuberculoma. The degree of pathologic change depends upon the extent of the vascular changes and of the granulation tissue. The latter usually forms a wider

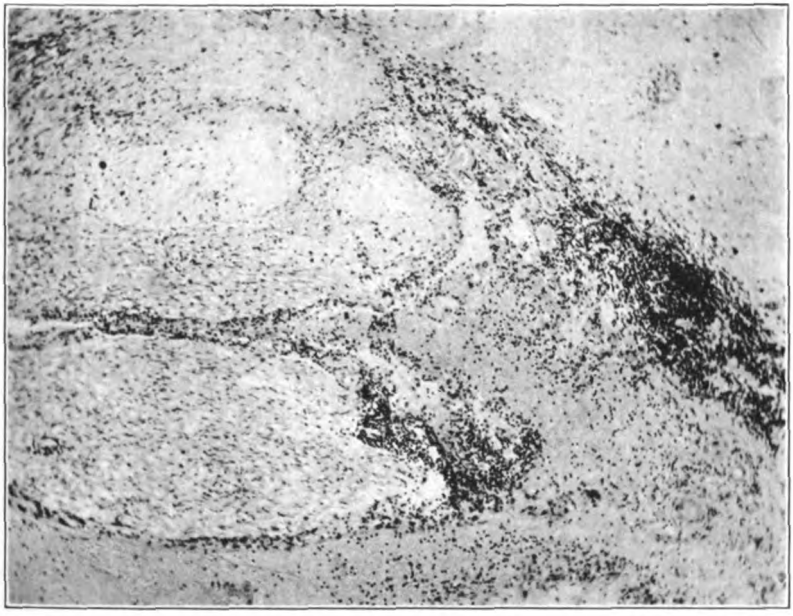


FIG. 135. SYPHILITIC NEURITIS
Cellular infiltration of perineurium of two cranial nerves close to their exit. May-Gruenwald stain

zone around the center than do the tuberculous granulomas. Diffuse histologic changes remote from the encephalitic foci or from isolated gummas have also been described. They consist of diffuse atrophy of cortical neurons and localized degeneration of certain nuclei (oculomotor, Edinger-Westphal, olivocerebellar), or of systemic degeneration in the form of amyotrophic lateral sclerosis (fig. 196) and the often disputed isolated pyramidal tract degeneration (Erb's spastic spinal paralysis). It is difficult to understand such nuclear or systemic degeneration without assuming the existence of an inherent factor that makes these structures

more vulnerable to the destructive action of the syphilitic toxins. The changes in the immediate environment of the inflammatory and gummatous foci may easily be understood as a direct action of the syphilitic toxins. The frequent demonstration of Treponema pallidum in these foci supports such an assumption.

The improvement in early diagnosis and treatment of syphilitic infections should have some bearing upon the character of the histologic picture. The diffuse meningitis, if healed, changes into a diffuse fibrous thickening of the piarachnoid, with disappearance of the cellular infiltrations. The gummatous granulations are also replaced by a connective tissue scar or they may disappear, leaving cysts behind. The scar tissue may be incrusted with calcium salts or may even undergo transformation into cartilaginous tissue. Such final stages, however, are not specific for syphilis. Only in connection with the clinical history and histologic changes found in other organs of the body is it possible to differentiate them from the changes in tuberculous infection or the sequelae of other inflammatory diseases.

The cranial nerves within the skull will naturally be affected by the various pathologic processes of the piarachnoid. Especially those at the base of the anterior fossa are most vulnerable. Early involvement of the optic nerve—a valuable aid in clinical diagnosis—may be in the form of a peri- and endoneuritis with cellular infiltration of the connective tissue septa spreading to the adventitia of the endoneural vessels; or degenerative changes of the nerve fibers, without marked inflammatory reactions, may dominate the histologic picture. In the first case the breaking down of myelin sheaths and axis-cylinders is secondary to the toxic and nutritive changes following the inflammation. After the removal of the debris the process may heal by formation of dense connective tissue proliferation, as in the diffuse meningitis. The changes in the olfactory and oculomotor nerves are similar, though not much attention has been paid to them in histologic study. The hypophysis does not escape the effects of the basal meningitis. Diffuse inflammatory reactions as well as gumma formation in this organ have been described. It is always difficult to correlate pituitary symptoms observed clinically with these histologic changes, because at the same time the infundibulum and tuber cinereum are also affected by the syphilitic infection (fig. 136).

SYPHILITIC MENINGOMYELITIS

Syphilis of the spinal cord may present itself in a "parenchymatous" (Winkelmann) or in an "interstitial" form. In the first case, we find atrophy of the anterior horn cells combined with perivascular round cell infiltration, gliosis, and mild meningitis (clinically manifested in spinal

muscular atrophy and amyotrophic lateral sclerosis). In the second form, myelomalacia on a vascular basis is added to the meningomyelitis. The infection may spread from the piarachnoid into the spinal cord in the same manner as it does in the brain. It seems that the middle and lower dorsal segments are the site of predilection in syphilitic myelitis. However, this fact is true not only for syphilis; in many other infections of the spinal cord the inflammatory reaction is most pronounced at this level. Many theories

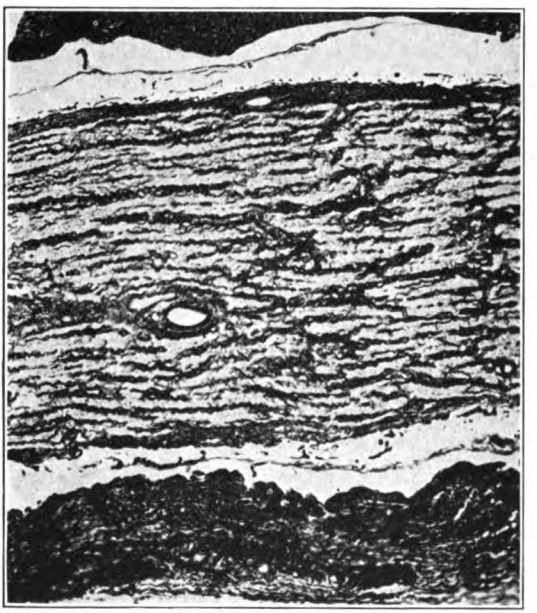


FIG. 136. OPTIC ATROPHY IN SYPHILITIC MENINGO-ENCEPHALITIS

Longitudinal section through optic nerve. Van Gieson stain. Thickening of piarachnoid. Increase of endoneurium, connective tissue, and glia. Degeneration of nerve fibers

have been advanced to explain the facts. The most plausible seem to be those based on anatomic considerations: The spinal canal is narrower in these segments than in the cervical and lumbar regions. The segments themselves are longer and therefore the distribution of blood supplied by the segmental spinal arteries is over a wider area, with resultant slowing up of circulation. The condensation of the fiber tracts into a narrow space reduces the amount of glia and mesenchymal tissue available for defense reactions. In addition, the connection of the lymphatics of the spinal

nerve roots at these levels with the lymphatics of the thorax may play a role in the transmission of infectious disease.

The myelitis is mostly restricted to a few segments. These appear grossly softened. The dura at this level is usually adherent to the piarachnoid and the spinal cord itself. Microscopically the granulomatous tissue may be seen extending along the anterior and posterior fissures and along the septa of the larger vessels. The perivascular inflammatory reaction within the spinal cord may vary from mild to excessive small round cell and plasma cell infiltration, with or without syphilitic arteritis. The occlusion of the vessels will lead to foci of softening with ensuing repair. The neurons show changes ranging from mild chromatolysis to complete destruction. There is also a breaking down of myelin sheaths and axis-cylinders. Only in the presence of gummatous granulation tissue or syphilitic arteritis can the diagnosis of a syphilitic myelitis be made. It should always be remembered that syphilis may be combined with other infections and that it favors the development of tuberculosis.

VASCULAR SYPHILIS

In the description of the inflammatory reaction of the piarachnoid in the different forms of syphilitic meningitis, it was mentioned that the process invades also the meningeal vessels, producing phlebitis and a periarteritis that later becomes a meso- and endarteritis. The syphilitic toxins may also affect the cerebral vessels predominantly without producing meningitis and encephalitis. It is to these types of primary meso- and endarteritis in their different manifestations that we give the name of vascular syphilis. Like the meningeal and cerebral inflammation they may occur in two forms, a diffuse infiltrative and a gummatous type. The vessels most involved are the basilar artery and the larger arteries of the brain. The adventitia of the vessel is densely infiltrated with lymphocytes intermingled with plasma cells. The media also shows such infiltrative foci and sclerosis of the muscular layers besides. The changes in the intima are characterized by a proliferation of the intima itself, with formation of many fibroblasts intermingled with small round cells. The endothelium remains intact in some cases; in others, there is a formation of different layers of endothelial cells; these are separated from the intima by a newly formed elastic membrane. Instead of diffuse lymphocytic infiltration of the adventitia, gumma formation may occur, and may also be seen in the proliferated intima.

The proliferation of the intima seems to continue after the inflammatory processes of the adventitia have given way. Such cases of chronic syphilitic vascular disease without cellular infiltration of the adventitia and with

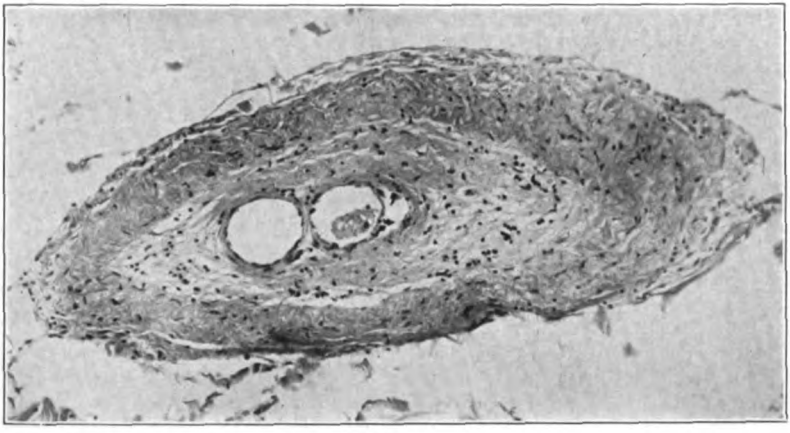


FIG. 137

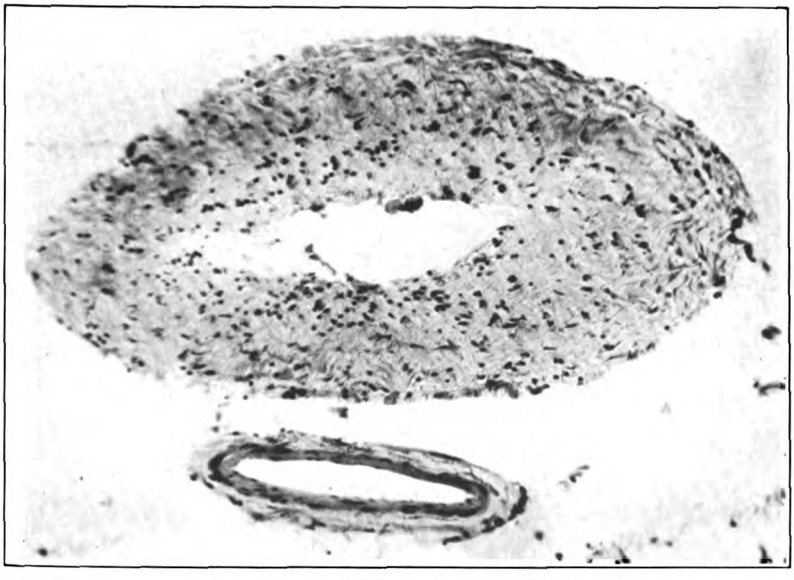


FIG. 138

FIGS. 137, 138. SYPHILIS OF BLOOD VESSELS

Artery and vein in posterior piarachnoid of dorsal spinal cord: cerebrospinal syphilis in man aged 28. Van Gieson stain

Fig. 137. Hyperplastic sclerosis in artery, with formation of two channels.

Fig. 138. Syphilitic panphlebitis

nerve roots at these levels with the lymphatics of the thorax may play a role in the transmission of infectious disease.

The myelitis is mostly restricted to a few segments. These appear grossly softened. The dura at this level is usually adherent to the piarachnoid and the spinal cord itself. Microscopically the granulomatous tissue may be seen extending along the anterior and posterior fissures and along the septa of the larger vessels. The perivascular inflammatory reaction within the spinal cord may vary from mild to excessive small round cell and plasma cell infiltration, with or without syphilitic arteritis. The occlusion of the vessels will lead to foci of softening with ensuing repair. The neurons show changes ranging from mild chromatolysis to complete destruction. There is also a breaking down of myelin sheaths and axis-cylinders. Only in the presence of gummatous granulation tissue or syphilitic arteritis can the diagnosis of a syphilitic myelitis be made. It should always be remembered that syphilis may be combined with other infections and that it favors the development of tuberculosis.

VASCULAR SYPHILIS

In the description of the inflammatory reaction of the piarachnoid in the different forms of syphilitic meningitis, it was mentioned that the process invades also the meningeal vessels, producing phlebitis and a periarteritis that later becomes a meso- and endarteritis. The syphilitic toxins may also affect the cerebral vessels predominantly without producing meningitis and encephalitis. It is to these types of primary meso- and endarteritis in their different manifestations that we give the name of vascular syphilis. Like the meningeal and cerebral inflammation they may occur in two forms, a diffuse infiltrative and a gummatous type. The vessels most involved are the basilar artery and the larger arteries of the brain. The adventitia of the vessel is densely infiltrated with lymphocytes intermingled with plasma cells. The media also shows such infiltrative foci and sclerosis of the muscular layers besides. The changes in the intima are characterized by a proliferation of the intima itself, with formation of many fibroblasts intermingled with small round cells. The endothelium remains intact in some cases; in others, there is a formation of different layers of endothelial cells; these are separated from the intima by a newly formed elastic membrane. Instead of diffuse lymphocytic infiltration of the adventitia, gumma formation may occur, and may also be seen in the proliferated intima.

The proliferation of the intima seems to continue after the inflammatory processes of the adventitia have given way. Such cases of chronic syphilitic vascular disease without cellular infiltration of the adventitia and with

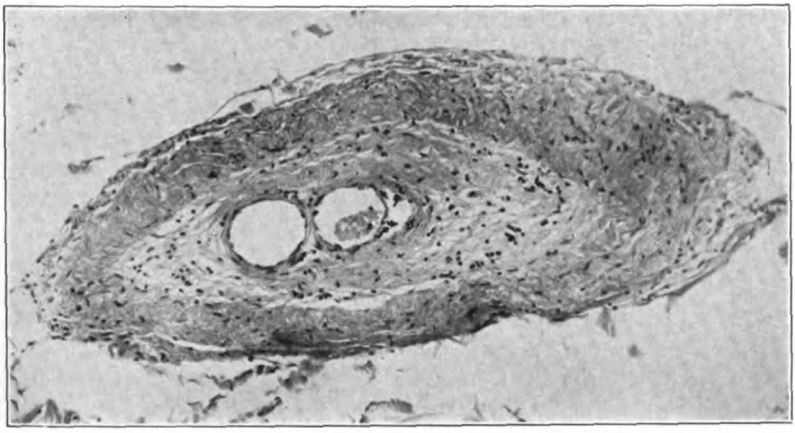


FIG. 137

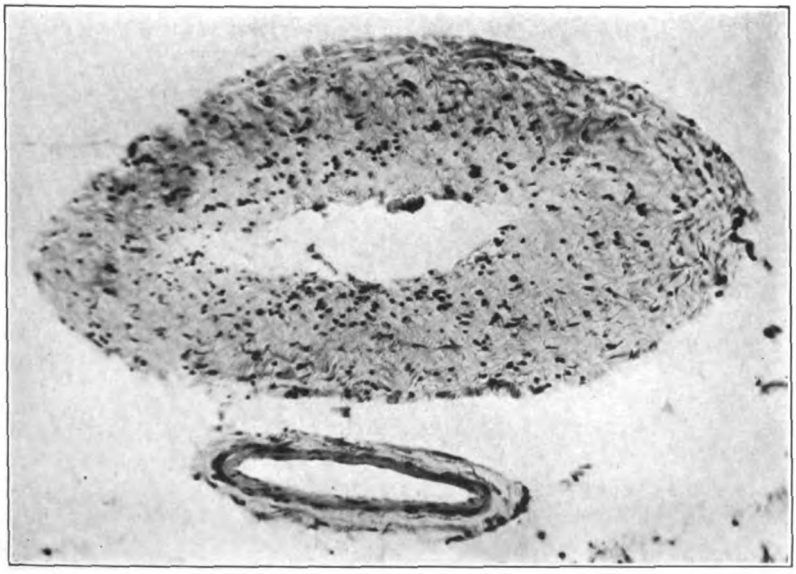


FIG. 138

FIGS. 137, 138. SYPHILIS OF BLOOD VESSELS

Artery and vein in posterior piarachnoid of dorsal spinal cord: cerebrospinal syphilis in man aged 28. Van Gieson stain

Fig. 137. Hyperplastic sclerosis in artery, with formation of two channels.

Fig. 138. Syphilitic panphlebitis

normal media have been described in cases of undoubted syphilitic etiology; but while their specific character is recognized by a number of pathologists, it is sometimes difficult to convince others of the syphilitic character of the endarteritis in the absence of a lymphocytic infiltration of the adventitia.

The intima proliferation in this isolated form of endarteritis and in the inflammatory forms very seldom shows degenerative changes. Cases have been described, however, in which a breaking down of the intima and media cells was accompained by fatty degeneration, i.e., atherosclerosis. If such changes are found in young persons in connection with other forms of syphiltic arteritis or even with a meningo-encephalitis of syphilitic origin,

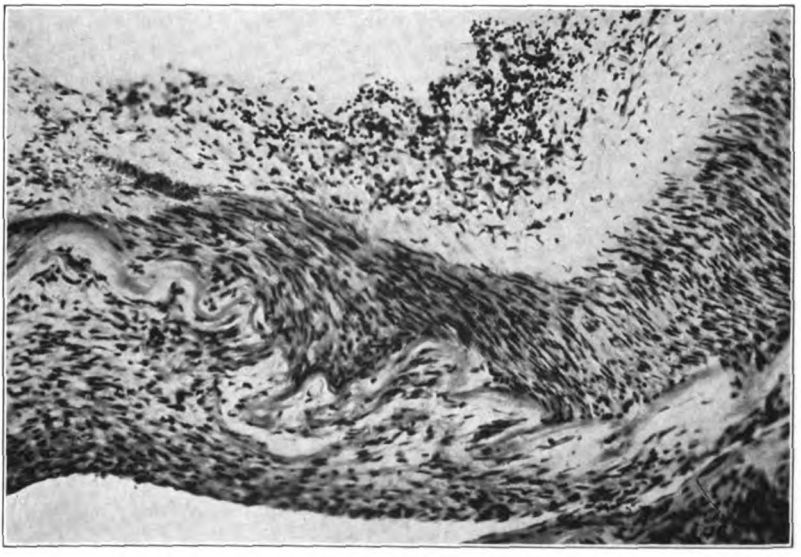


FIG. 139. SYPHILITIC ARTERITIS

Middle cerebral artery. Van Gieson stain. Proliferation of intima and infiltration of adventitia with lymphocytes and plasma cells

there is little doubt as to their etiology. If, however, they are found in the brains of individuals older than 50 years, together with syphilitic manifestations, they are very difficult to differentiate from the purely degenerative arteriosclerosis of old age (figs. 137–39).

In the brain substance itself, such vascular changes in the piarachnoid may be associated with hyaline degeneration of the walls of the smaller vessels. They stain deeply and diffusely red with van Gieson's method. Nissl and Alzheimer first described a disease process of the smaller cortical and pial vessels in syphilis that is characterized by a proliferation of the endothelial and adventitial cells. The capillaries of the cortex form new

sprouts and anastomoses but no infiltrative inflammatory reactions are noticed.

It is evident that all these different vascular changes must interfere with the blood supply of the nervous structures. The intima proliferation gradually narrows the lumens of the larger pial vessels. The proliferation of the endothelium aggravates this condition, which finally leads to thrombus formation and softening of the area of the brain that is supplied by these vessels. The changes in the smaller cortical vessels are followed by diffuse degenerative changes of the neurons in their neighborhood. These show swelling or dark-staining atrophic forms. Besides this, there are small areas in which the neurons have disappeared and a mild proliferation of protoplasmic glia may be seen. Foci of demyelinization may be added to this picture.

GENERAL PARALYSIS

Synonyms: German, *progressive Paralyse;* French, *paralysie générale.*

When Noguchi in 1913 discovered Treponema pallidum in the brains of general paresis patients, he contributed the final definite link in establishing the etiology of the disease. Before the work of Nissl and Alzheimer, the pathologist based his diagnosis mainly on the gross anatomic findings, i.e., thickening of the piarachnoid, with turbid appearance and adhesion to the brain surface, atrophy of the brain—chiefly of the frontal lobes—external and internal hydrocephalus, and, finally, the roughened surface of the ependymal lining of the ventricles. We know today that all these signs are not characteristics of general paresis alone, but in their combination they are still a valuable guide.

In comparing the weights of paretic brains with normal averages, Foertig found that about 32 per cent were normal, and 13 per cent above and 55 per cent below the average. Histologic examination of the dura mater may reveal a mild perivascular infiltration with plasma cells and lymphocytes and an increase in connective tissue. The changes in the piarachnoid are more marked, especially over the frontal poles. Plasma cells are found around the pial vessels or in the arachnoidal meshwork, together with lymphocytes, mast cells, and mulberry cells. The cellular infiltration, however, may be minimal, and a diffuse thickening of the connective tissue may dominate the picture (fig. 141). The outer layer of the cortex shows a dense meshwork of fibrous glia fibers that may be seen penetrating into the pia. A similar intensive glia reaction is seen along the infiltrated vessels. The perivascular spaces of the cortex in typical cases are densely infiltrated with plasma cells and lymphocytes, forming cuffs of sometimes five or more rows. In the adventitia, after staining by the Turnbull method, one finds iron within cells and free or accumulated in microglia cells, chiefly in the cortex or the striatum (fig. 142).

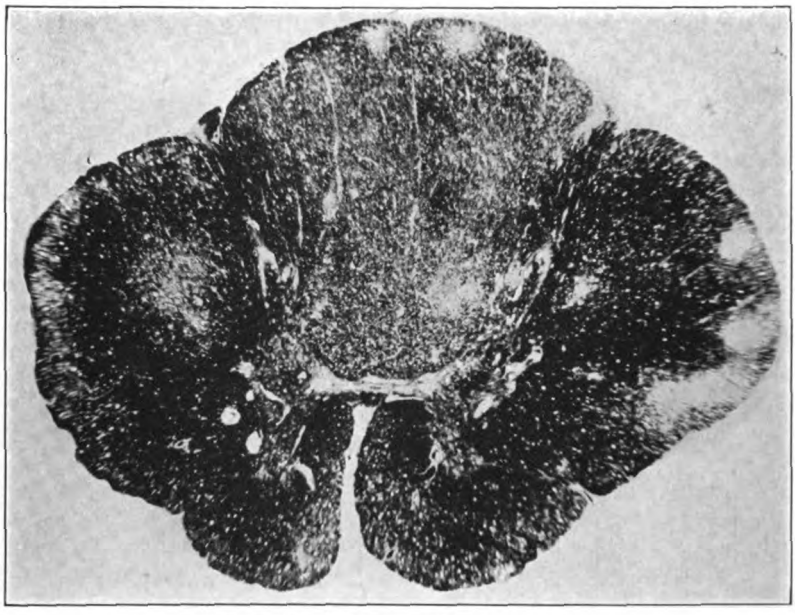


FIG. 140. SYPHILITIC MYELOPATHY
Syphilis of spinal cord with syphilitic arteritis and phlebitis. Weil stain. Disseminated areas of demyelinization, edema, and necrosis

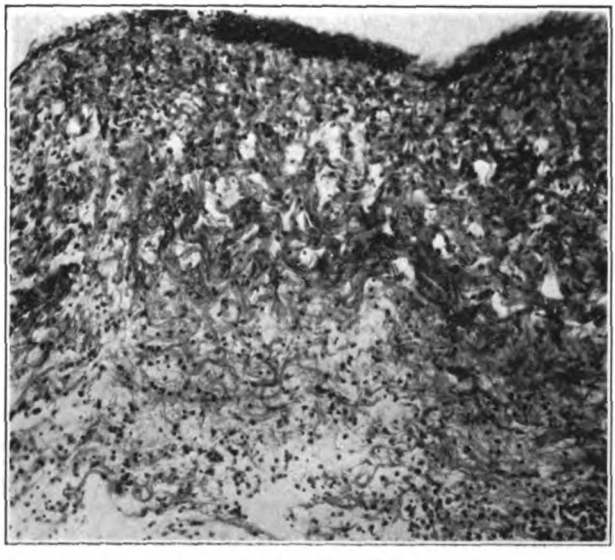


FIG. 141. GENERAL PARESIS
Chronic leptomeningitis. Increase in connective tissue fibers. Van Gieson stain

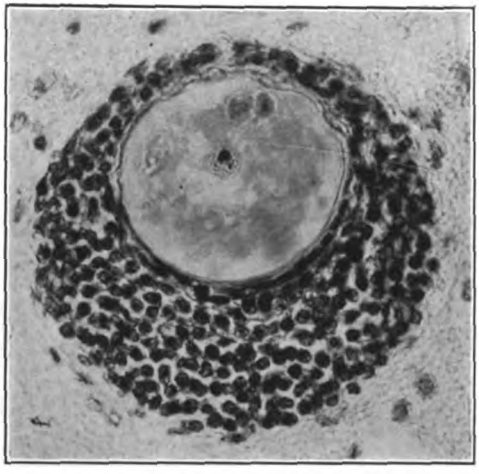


FIG. 142. GENERAL PARESIS

Perivascular infiltration of cortical vessel with plasma cells and small mononuclear cells. Hematoxylin-eosin stain

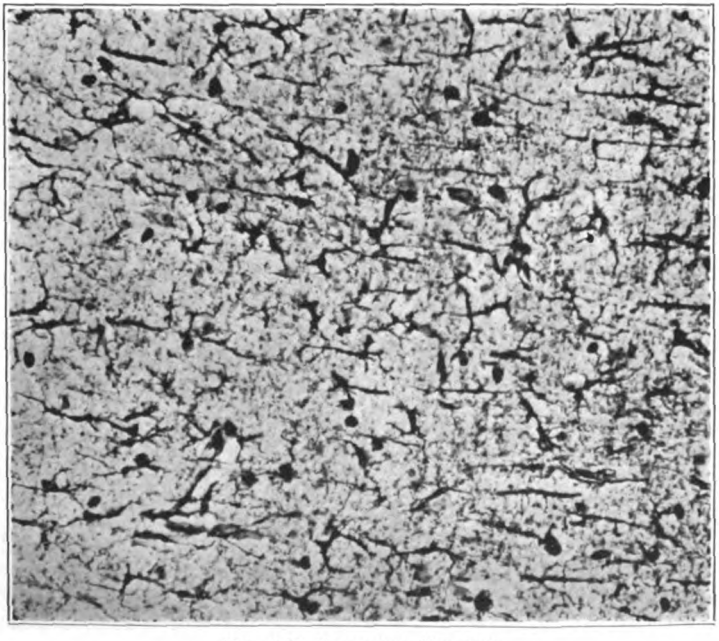


FIG. 143. GENERAL PARESIS

Hyperplasia and hypertrophy of microglia in cerebral cortex (rod cells). Stern method (Weil-Davenport modification)

The neurons are severely diseased. The attempt of earlier investigators to establish a definite histopathologic picture has been abandoned since we have learned how many varieties of neuronal degeneration may occur—shrunken forms, incrustation, swelling with disappearance or transformation of the Nissl structures into ringlike bodies. It has been emphasized

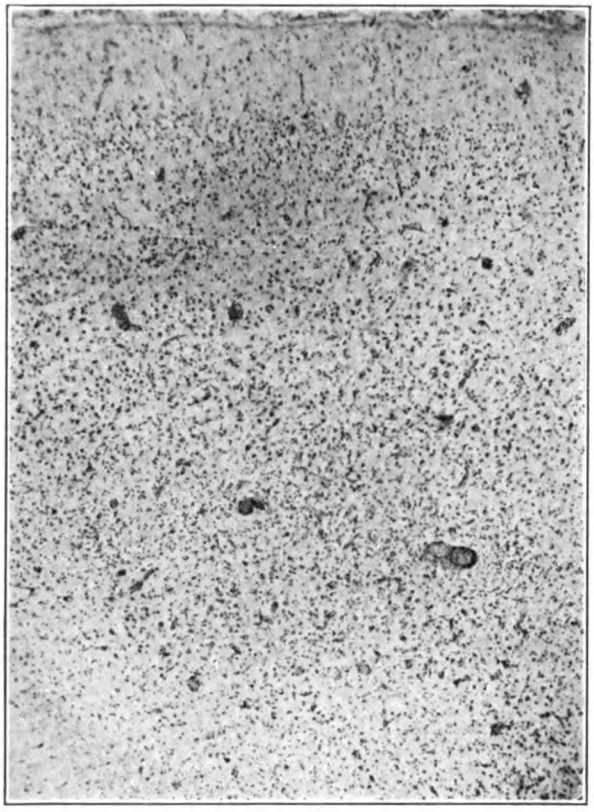


FIG. 144. CYTO-ARCHITECTURE OF CEREBRAL CORTEX

Area FC in case of general paresis. Diminution in number of neurons. Loss of definite cyto-architecture. Increase in glia nuclei. Perivascular cellular infiltration. Cresyl violet stain

that dark-staining, shrunken forms are frequently seen in the second and third layer and that they stain red with eosin and acid fuchsin. The same phenomenon, however, may be seen in intoxications of the brain, e.g., following liver disease.

The irregular disappearance of neurons destroys the cyto-architecture of the cortex. In some areas the gray appears extremely poor in cells; in

others, there seems to be an increase in nuclei under low magnification; this, however, under stronger lenses is explained by the finding of an increase in glia nuclei. The latter belong to astrocytes, which have increased in number and form a denser fiber meshwork, and to microglia, which, in

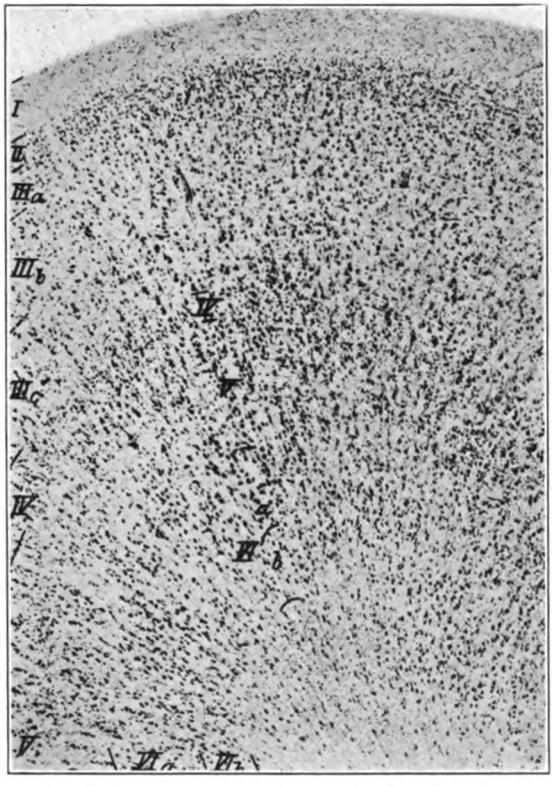


FIG. 145. CYTO-ARCHITECTURE OF CEREBRAL CORTEX
Normal area FC. Cresyl violet stain. (Cf. fig. 144)
(Economo, C. von: Zellaufbau der Grosshirnrinde des Menschen. Courtesy Julius Springer)

special stains, shows hypertrophic forms such as large rod cells (*Stäbchenzellen*), or groupings in rosettes and stars (figs. 143–45).

Disease of the nerve fibers may affect myelin sheaths and axis-cylinders alike. In sections stained for myelin sheaths, zones of demyelinization have frequently been described as observed in the hemispheres, cerebellum, basal

ganglia, and spinal cord; these are either diffuse or in the form of multiple plaques similar to those seen in disseminated sclerosis. The fibrous glia proliferation in these foci is not as pronounced as that seen in the latter disease. The number of axis-cylinders in the outer zones of the cortex seems to be reduced; they show serpentine forms, granulation, and swelling. Secondary degeneration does not seem to follow the destruction of the myelin sheaths.

The ependymal lining of the ventricles shows massive proliferation (ependymitis granulosa), producing the uneven surface that has been described by the earlier pathologists. The subependymal tissue adjacent to the papillae may show a mild increase in glia nuclei (fig. 146).

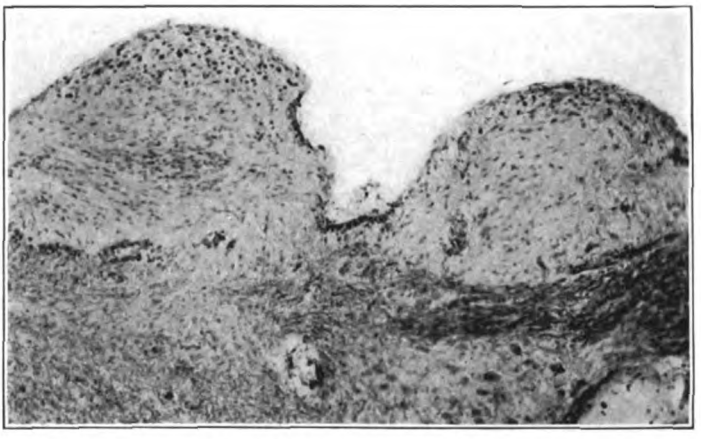


FIG. 146. GENERAL PARESIS
Papillomatous granulations of subependymal tissue of ventricular wall. Van Gieson stain

Colloidal Degeneration.—In rare cases, a peculiar change in the walls of the cortical vessels has been described. They appear markedly swollen and glassy, staining homogeneously dark red in van Gieson preparations or homogeneously dark purple with cresyl violet. In the environment of the vessels, various-sized masses of material having the same staining reactions may be found. This colloidal degeneration is considered a coagulation necrosis. It is not confined to the vessels of the cortex, but may also be seen in different parts of the brain and the pia.

Lissauer's Paralysis.—It has been mentioned that general paresis may be associated with other syphilitic manifestations. Simultaneous occurrence of gummas seems to be very rare. More frequently, a diffuse syphilitic meningitis or vascular syphilis has been described in such combination.

In Lissauer's paralysis the central and posterior regions of the brain are more severely affected than the frontal lobes. Besides the histologic changes of general paresis, severe parenchymatous destruction in the form of a status spongiosus is found; this may be confined to isolated gyri or to the third layer only.

In recent years the good results of the different forms of fever therapy on the course of general paresis have stimulated interest in investigation of the histologic changes that accompany the clinical improvement. Jahnel states that in patients who have had treatment with salvarsan or bismuth compounds, fewer spirochetes are found than in untreated controls. Spirochetes were found in 8 of 10 cases of general paralysis not treated with malaria, but only in 6 out of 39 treated cases (Kopeloff and Blackman). Jahnel demonstrated spirochetes in the brain in 50 per cent of untreated patients.

The changing character of general paresis under the influence of improved methods of treatment is best illustrated by the following tabulation of statistics based on 10,240 cases from fifteen New York State hospitals during two periods, from 1920 to 1925 and from 1926 to 1931 (Cheney).

Period	Percentage of Cases	
	Released or Improved	Dead within 4 Years
1920–25	9.9	82.1
1926–31	21.9	41.0

The interpretation of the histologic picture following fever therapy is extremely difficult because one does not know the condition of the brain before treatment. However, the fact seems to be established that the character of the perivascular infiltration changes. The cells are less numerous and the plasma cells are replaced by lymphocytes. It is known that malaria treatment produces an acute leptomeningitis, with infiltration of lymphocytes and macrophages. It seems further to be established that the degenerative process affecting the cortical neurons is arrested. Those observers who have described a restoration of the cyto-architecture to more normal conditions assume a regenerative ability in the neurons that has never been demonstrated under other conditions in the adult human brain.

TABES DORSALIS

Synonym: French, *ataxie locomotrice.*

The old textbook description of tabes dorsalis as representing essentially a degeneration of the nerve fibers of the posterior columns of the spinal cord must be completely revised in view of the progress of modern histopatho-

logic investigation of the disease. It is true that on gross anatomic examination the most pronounced changes are found in the spinal cord. The latter appears markedly atrophic and its posterior surface is flattened or even concave. The posterior roots appear thinner than normally, and their gray color is in marked contrast to that of the usually well preserved, white anterior roots. The piarachnoid is normal in some cases ("true," uncomplicated tabes dorsalis) or may show inflammatory changes and even marked thickening with adhesions. In transverse sections from different levels of the spinal cord one will find, in preparations stained for myelin sheaths, a symmetric bilateral degeneration of the long ascending fibers

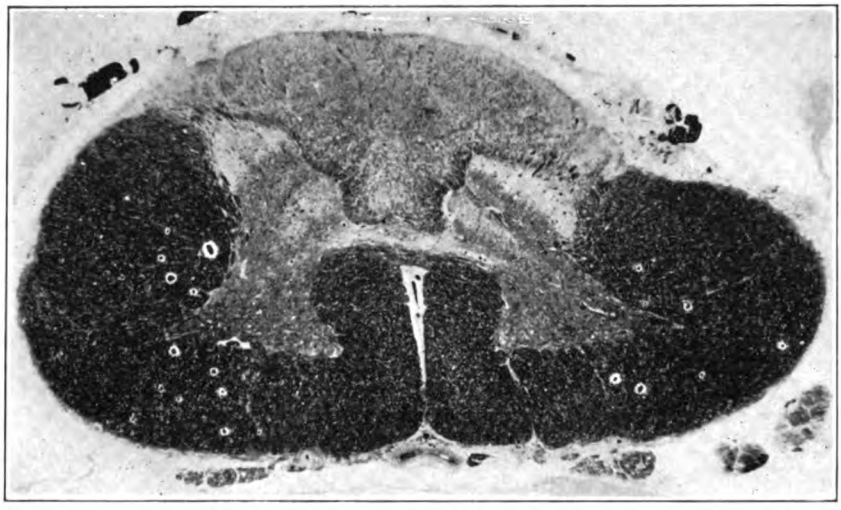


FIG. 147. TABES DORSALIS

Transverse section through cervical spinal cord. Complete demyelinization of posterior columns. Weil stain

of the posterior columns. The extent of the unstained area will vary according to the age of the disease process and the number of segments involved. As a rule, degeneration will be found in those fibers that arise from the lumbosacral and lower dorsal segments, i.e., the columns of Goll in cervical segments. In far advanced or typical cases, however, in which the cervical segments are also affected (tabes cervicalis), the whole field of exogenous fibers in sections through cervical segments is unstained by myelin sheath stains. The axis-cylinders in these regions have also disappeared. In longitudinal sections, the whole area of degenerated nerve fibers is seen to be filled with a dense mass of fine glia fibers that take the course of the original nerve fibers (isomorphous fibrous glia reaction). The

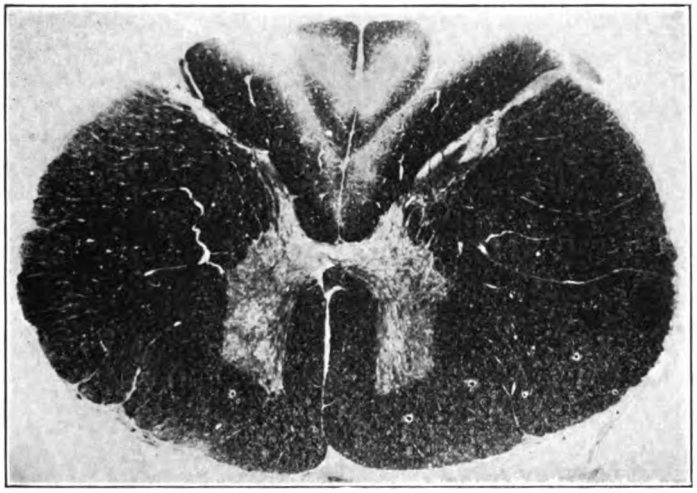


FIG. 148. TABES DORSALIS

Transverse section through dorsal spinal cord. Demyelinization in posterior columns resembling myelin formation in spinal cord of human embryo at approximately 7 months

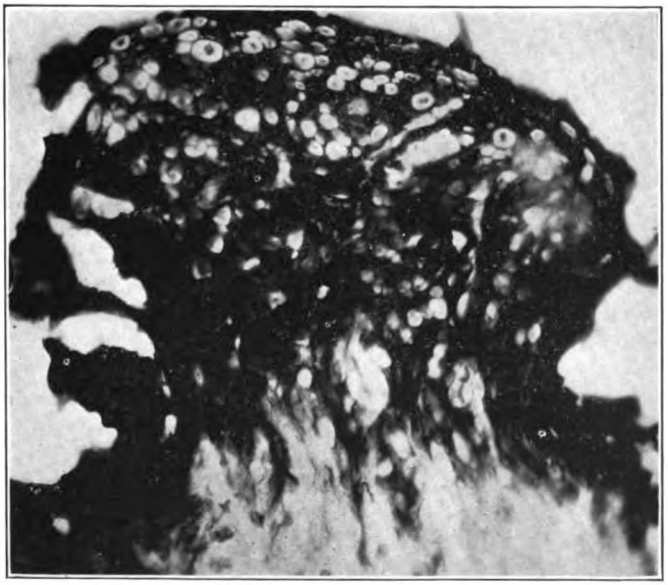


FIG. 149. TABES DORSALIS

Increase in fibrous glia at zone of entrance of posterior roots. Holzer stain

density of this glia scar is more pronounced and the fibers are more numerous than one is accustomed to find them in ascending secondary degeneration of the posterior columns following transverse lesion of the spinal cord or of posterior roots at lower segment levels (fig. 149).

The blood vessels within the demyelinated areas show hyaline degeneration of their walls, but there is no mesenchymal proliferation. The piarachnoid usually shows mild thickening, but syphilitic meningitis is not

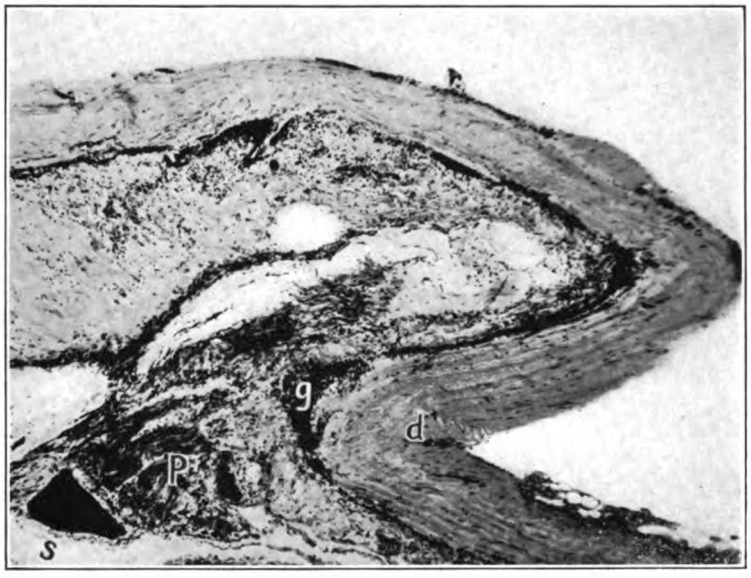


FIG. 150. TABES DORSALIS

Oblique section through dorsal segment of spinal cord. Van Gieson stain. Granulation tissue at inner surface of dura mater and accompanying posterior roots. d = dura mater. g = granulation tissue. p = posterior roots. s = subarachnoidal spaces

an essential feature of tabes dorsalis. It may be an addition to the picture, just as gummatous reaction, endarteritis, or general paresis may be. In advanced cases with degeneration of the anterior roots, retrograde degeneration of anterior horn cells is found. Richter described, as a constant occurrence in tabes dorsalis, presence of granulation tissue at the entrance of the posterior roots into the subarachnoidal space, and in some cases spirochetes have been demonstrated in the roots (fig. 150).

Degenerative changes are not confined to the afferent fibers of the spinal cord; they are seen also in the second, fifth, eighth, and ninth cranial nerves. Here one will find, in advanced cases, complete degeneration of the nerve

fibers, with marked proliferation of the peri- and endoneurial connective tissue. Degenerative changes in the afferent rami communicantes of the sympathetic nerves have also been described.

The different theories offered in attempts to explain this predilection of the degenerative process for the afferent fiber systems of the spinal cord and the brain stem may be divided into two groups. The first group seeks the lesion outside the spinal cord and explains the degeneration of the posterior columns as a secondary process. Mild histologic changes in the cells of the posterior root ganglia have been thought to represent the primary lesion. Inflammatory reactions at the point of penetration of the posterior root into the dura mater or leptomeninges have been accused of exerting a toxic effect or mechanical pressure upon the entering fibers. Finally, it has been thought that the syphilitic toxin circulating in the cerebrospinal fluid attacks the root fibers during their course through the subarachnoidal space. The second group of theories assumes either a toxic lesion at the point of entrance of the posterior roots into the spinal cord (Redlich-Obersteiner zone), where they lose their myelin sheaths for a short distance, or transfers the process into the spinal cord itself, either assuming a toxic agent acting upon the more sensitive long ascending fibers, or citing lymphatic circulatory disturbance in connection with meningitis as the cause of the degenerative process.

The last-named theories cannot explain the selective involvement of fibers of lumbosacral and lower thoracic origin in cases without or with only mild meningitis. The theories that assume inflammatory lesions around the posterior root at the site of perforation of the dura mater or in the subarachnoidal space have to take refuge in more or less vague hypotheses to explain why the anterior roots are spared. The idea that the point of attack is at the zone of entrance of the posterior root into the spinal cord is a more simple explanation of the histologic picture. In this connection, it should be pointed out that in cases of recent origin *Abbau* products may be found within the entrance zone, while they are absent in the root itself. Furthermore, in sections stained by Anderson's victoria blue method, a dense proliferation of glia fibers is seen at the Redlich-Obersteiner zone, a fact that has not been emphasized before. In view of all these conflicting theories one may well, however, agree with Spielmeyer's statement that at the present stage of knowledge it is difficult to explain the essential tabetic degeneration on the basis of histologic interpretation.

Blastomyces Infections

The different forms of Blastomyces that have been found to invade the meninges of the brain are: (1) Coccidioides immitis, an ascomycete with endospore formation, which grows mycelium and aerial hyphae in cultures;

(2) Cryptococcus meningitidis (Torula histolytica or Cryptococcus hominis), a yeast different from the forms that are used for commercial alcoholic fermentation; it never forms endospores, reproduces by budding, and forms a mycelium in cultures; (3) Monilia albicans (Oidium albicans), which produces a purulent meningitis; in cultures it ferments sugar and forms a mycelium.

Usually the invasion of these yeasts follows lesions elsewhere in the body, preferably in the skin or, in the case of Torula, in the lungs, liver, spleen,

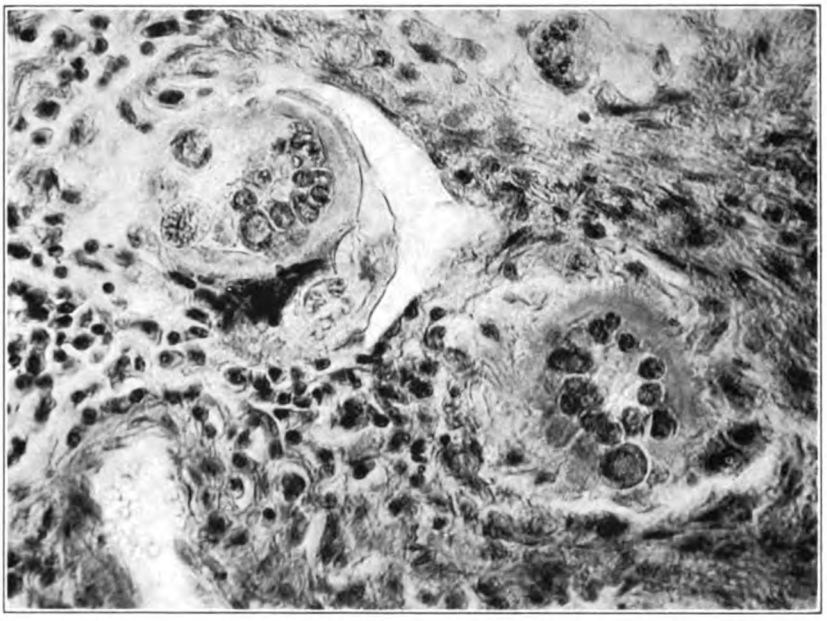


FIG. 151. COCCIDIOIDES IMMITIS MENINGITIS

In man, following infection of lung. Van Gieson stain. Round endospores are seen within capsules, surrounded by cellular infiltration

and kidneys. The lesions produced by Coccidioides are granuloma formations that may closely resemble tuberculous infection. The granuloma consists of epithelioid cells that undergo caseous necrosis in the periphery and that may be mixed with giant cells. The meningitis produced is characterized by massive cellular infiltration consisting of polymorphonuclear leukocytes mixed with small round cells. The presence of capsules containing the round endospores facilitates the diagnosis (fig. 151).

In Cryptococcus infection the reaction of the brain and meninges is much milder than in the first-mentioned disease. In cases of recent origin the Torula cells may be seen free or inclosed in large giant cells in the arach-

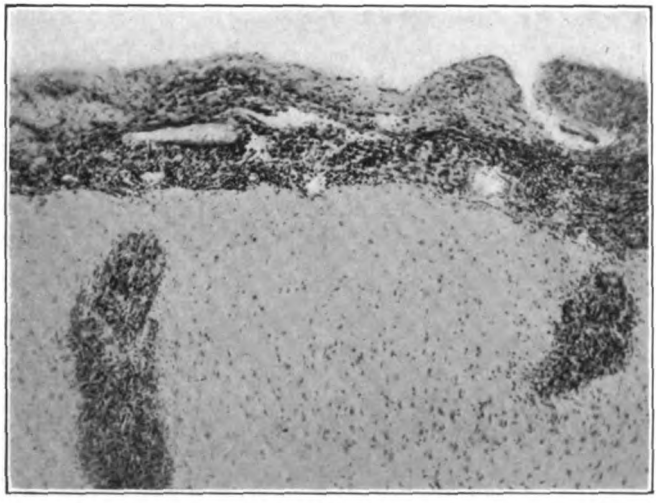


FIG. 152

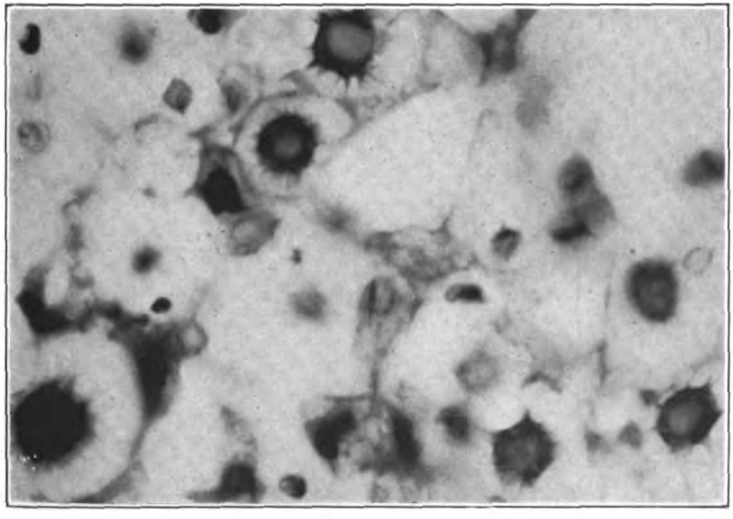


FIG. 153

FIGS. 152, 153. CRYPTOCOCCUS (TORULA) MENINGO-ENCEPHALITIS

Fig. 152. Meningitis and encephalitis. Cresyl violet-eosin stain.

Fig. 153. Cryptococcus cells from cortical focus, after formalin fixation, showing starlike appearance and shrinkage of mucous capsule. Cresyl violet-eosin stain

(2) Cryptococcus meningitidis (Torula histolytica or Cryptococcus hominis), a yeast different from the forms that are used for commercial alcoholic fermentation; it never forms endospores, reproduces by budding, and forms a mycelium in cultures; (3) Monilia albicans (Oidium albicans), which produces a purulent meningitis; in cultures it ferments sugar and forms a mycelium.

Usually the invasion of these yeasts follows lesions elsewhere in the body, preferably in the skin or, in the case of Torula, in the lungs, liver, spleen,

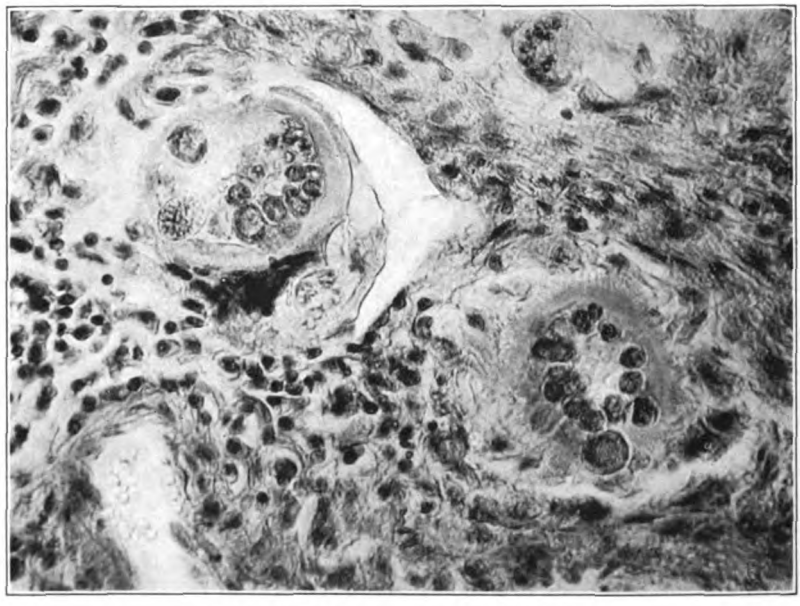


FIG. 151. COCCIDIOIDES IMMITIS MENINGITIS

In man, following infection of lung. Van Gieson stain. Round endospores are seen within capsules, surrounded by cellular infiltration

and kidneys. The lesions produced by Coccidioides are granuloma formations that may closely resemble tuberculous infection. The granuloma consists of epithelioid cells that undergo caseous necrosis in the periphery and that may be mixed with giant cells. The meningitis produced is characterized by massive cellular infiltration consisting of polymorphonuclear leukocytes mixed with small round cells. The presence of capsules containing the round endospores facilitates the diagnosis (fig. 151).

In Cryptococcus infection the reaction of the brain and meninges is much milder than in the first-mentioned disease. In cases of recent origin the Torula cells may be seen free or inclosed in large giant cells in the arach-

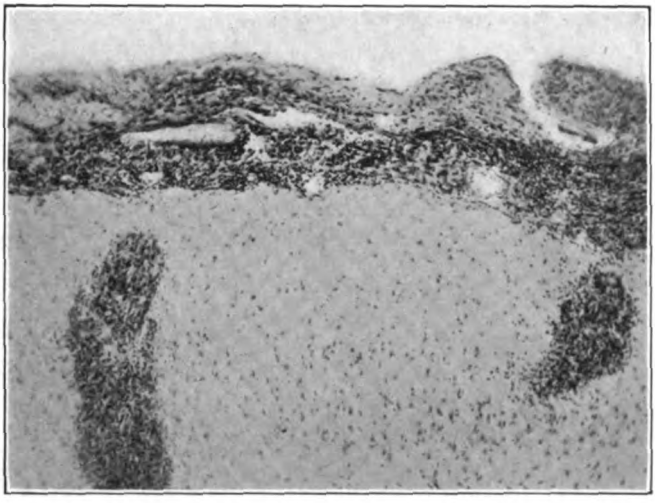


FIG. 152

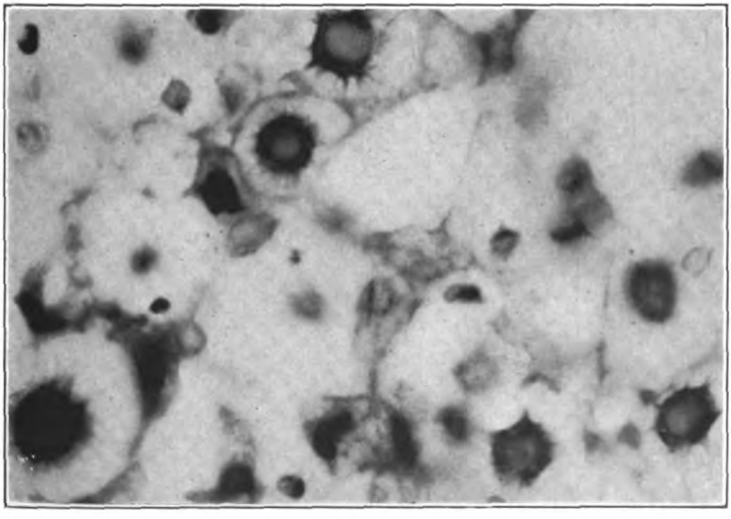


FIG. 153

FIGS. 152, 153. CRYPTOCOCCUS (TORULA) MENINGO-ENCEPHALITIS

Fig. 152. Meningitis and encephalitis. Cresyl violet-eosin stain.

Fig. 153. Cryptococcus cells from cortical focus, after formalin fixation, showing starlike appearance and shrinkage of mucous capsule. Cresyl violet-eosin stain

noidal meshes, with a mild, small cellular reaction. Their invasion of the brain follows the pia septa and the larger vessels. In fresh brains the lesions cannot be detected with the naked eye, but after formalin fixation one sees numerous small cysts resembling soap bubbles. Under miscroscopic examination such foci are seen to be filled with numerous yeast cells surrounded by a gelatinous mass, the coagulation of which by the formaldehyde may be responsible for the foamy appearance. Many yeast cells show budding; their size is variable, from 1 to 13 microns; with cresyl violet they stain purple, and with Gram's stain dark blue. The disease may become chronic, with increase of connective tissue in the meninges, intense gliosis of the outer layer of the cortex, and formation of centers of caseous necrosis

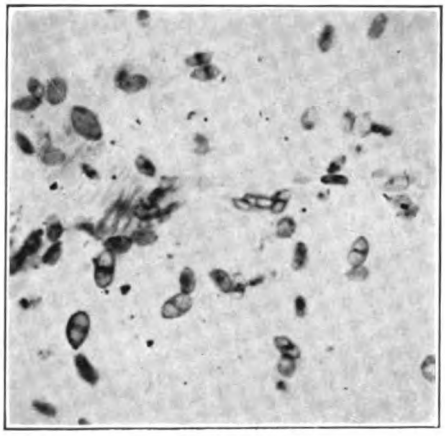


FIG. 154. SPOROTRICHUM MENINGITIS
Spores in spinal fluid. Methylene blue stain

surrounded by fibrous glia, large phagocytic endothelial-like cells, and lymphocytes. Foci of anemic softening around vessels thrombosed by the yeast cells are seen, together with the same cyst formation that has been described in the acute cases (figs. 152, 153).

Monilia albicans (Oidium albicans) infection of the meninges produces a purulent meningitis with intense polymorphonuclear and lymphocytic cellular reaction. In the brain lesions the gelatinous matrix that surrounds the Torula cells is absent. Granulations with central necrosis, similar to those described in connection with chronic Torula infection, are found. In many cases it is difficult to make the differential diagnosis from histologic study alone, and culture of the yeast cells must decide the question.

In addition to the Blastomyces infection, Trichomycetes and Hyphomycetes infections have been described as occurring in the central nervous

system. In Trichomycetes infections, Actinomyces (Streptothrix) is occasionally found. It forms brain abscesses that are filled with a thick oily or mucoid mass and that do not show a definite capsule formation histologically. The diagnosis is secured by demonstration of the dense mass of mycelium with its radiations and clublike forms in the periphery. The dark blue staining with Gram's method is characteristic.

Sporotrichum is the representative of the Hyphomycetes that occasionally produces a meningitis of malignant type. It is characterized by an intense cellular infiltration of the piarachnoid with lymphocytic cells intermingled with polymorphonuclear leuckocytes. The diagnosis can be established only by demonstration of the hyphae with their attached oval spores in smears or cultures of the spinal fluids (fig. 154).

With attention focused on the possibility of an infection of the central nervous system by yeast cells in cases of primary lesions of the skin, bones, or inner organs, it should be possible to demonstrate other kinds of Blastomyces infections in addition to those that have been cited above.

Protozoal Infections

The most important infection produced by a protozoon—syphilis, caused by Treponema pallidum—has been discussed above. Trypanosoma cruzi (Schizotrypanum cruzi) is the etiologic factor in Chaga's disease, an encephalitis with mild meningitis and nonspecific perivascular infiltration that occurs in South America. Trypanosoma gambiense is confined to tropical climates and produces sleeping sickness.

Plasmodium, the malaria parasite, does not seem to invade the brain directly. However, it can be demonstrated to be present in the blood vessels of the brain, within red blood corpuscles, without inducing an inflammatory reaction. Brain purpura following occlusion of capillaries by the parasite-infected red blood cells seems to be more frequent.

Recently two protozoa that are usually found producing a chronic endemic form of encephalitis in laboratory animals have also been found in man (Wolf and co-workers). They are Toxoplasma and Encephalitozoon. The first is a protozoon harbored in capsules that break at maturity and set free the parasites. Its invasion of the brain brings about a mild granulomatous reaction in the form of accumulation of small round cells, fibroblasts, and glia cells without any specific arrangement. Such an encephalitis has been described in wild and laboratory rats. In man it is transmitted directly from mother to fetus and detected in the newborn in the form of retinal and brain invasion.

Encephalitozoon is mostly endemic in rabbits (cuniculi); sometimes as many as two-thirds of a colony may be infected without manifesting acute lethal disease. Ignorance of this fact has caused many disappointments

noidal meshes, with a mild, small cellular reaction. Their invasion of the brain follows the pia septa and the larger vessels. In fresh brains the lesions cannot be detected with the naked eye, but after formalin fixation one sees numerous small cysts resembling soap bubbles. Under miscroscopic examination such foci are seen to be filled with numerous yeast cells surrounded by a gelatinous mass, the coagulation of which by the formaldehyde may be responsible for the foamy appearance. Many yeast cells show budding; their size is variable, from 1 to 13 microns; with cresyl violet they stain purple, and with Gram's stain dark blue. The disease may become chronic, with increase of connective tissue in the meninges, intense gliosis of the outer layer of the cortex, and formation of centers of caseous necrosis

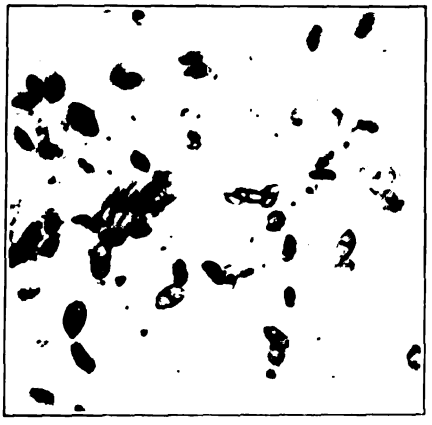


FIG. 154. SPOROTRICHUM MENINGITIS
Spores in spinal fluid. Methylene blue stain

surrounded by fibrous glia, large phagocytic endothelial-like cells, and lymphocytes. Foci of anemic softening around vessels thrombosed by the yeast cells are seen, together with the same cyst formation that has been described in the acute cases (figs. 152, 153).

Monilia albicans (Oidium albicans) infection of the meninges produces a purulent meningitis with intense polymorphonuclear and lymphocytic cellular reaction. In the brain lesions the gelatinous matrix that surrounds the Torula cells is absent. Granulations with central necrosis, similar to those described in connection with chronic Torula infection, are found. In many cases it is difficult to make the differential diagnosis from histologic study alone, and culture of the yeast cells must decide the question.

In addition to the Blastomyces infection, Trichomycetes and Hyphomycetes infections have been described as occurring in the central nervous

system. In Trichomycetes infections, Actinomyces (Streptothrix) is occasionally found. It forms brain abscesses that are filled with a thick oily or mucoid mass and that do not show a definite capsule formation histologically. The diagnosis is secured by demonstration of the dense mass of mycelium with its radiations and clublike forms in the periphery. The dark blue staining with Gram's method is characteristic.

Sporotrichum is the representative of the Hyphomycetes that occasionally produces a meningitis of malignant type. It is characterized by an intense cellular infiltration of the piarachnoid with lymphocytic cells intermingled with polymorphonuclear leuckocytes. The diagnosis can be established only by demonstration of the hyphae with their attached oval spores in smears or cultures of the spinal fluids (fig. 154).

With attention focused on the possibility of an infection of the central nervous system by yeast cells in cases of primary lesions of the skin, bones, or inner organs, it should be possible to demonstrate other kinds of Blastomyces infections in addition to those that have been cited above.

Protozoal Infections

The most important infection produced by a protozoon—syphilis, caused by Treponema pallidum—has been discussed above. Trypanosoma cruzi (Schizotrypanum cruzi) is the etiologic factor in Chaga's disease, an encephalitis with mild meningitis and nonspecific perivascular infiltration that occurs in South America. Trypanosoma gambiense is confined to tropical climates and produces sleeping sickness.

Plasmodium, the malaria parasite, does not seem to invade the brain directly. However, it can be demonstrated to be present in the blood vessels of the brain, within red blood corpuscles, without inducing an inflammatory reaction. Brain purpura following occlusion of capillaries by the parasite-infected red blood cells seems to be more frequent.

Recently two protozoa that are usually found producing a chronic endemic form of encephalitis in laboratory animals have also been found in man (Wolf and co-workers). They are Toxoplasma and Encephalitozoon. The first is a protozoon harbored in capsules that break at maturity and set free the parasites. Its invasion of the brain brings about a mild granulomatous reaction in the form of accumulation of small round cells, fibroblasts, and glia cells without any specific arrangement. Such an encephalitis has been described in wild and laboratory rats. In man it is transmitted directly from mother to fetus and detected in the newborn in the form of retinal and brain invasion.

Encephalitozoon is mostly endemic in rabbits (cuniculi); sometimes as many as two-thirds of a colony may be infected without manifesting acute lethal disease. Ignorance of this fact has caused many disappointments

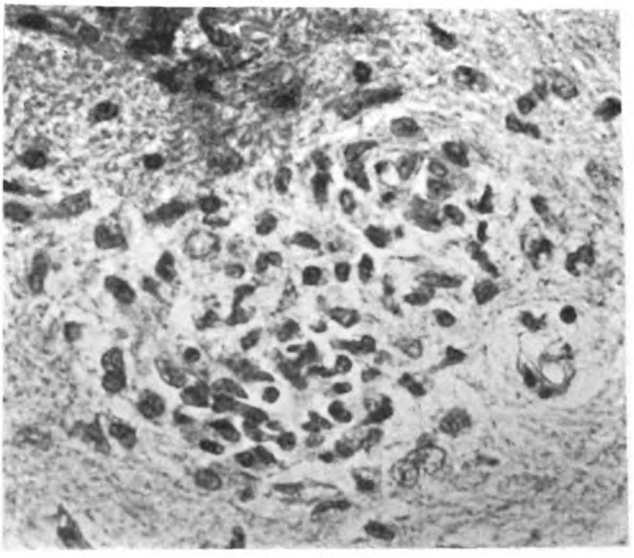


FIG. 154 A

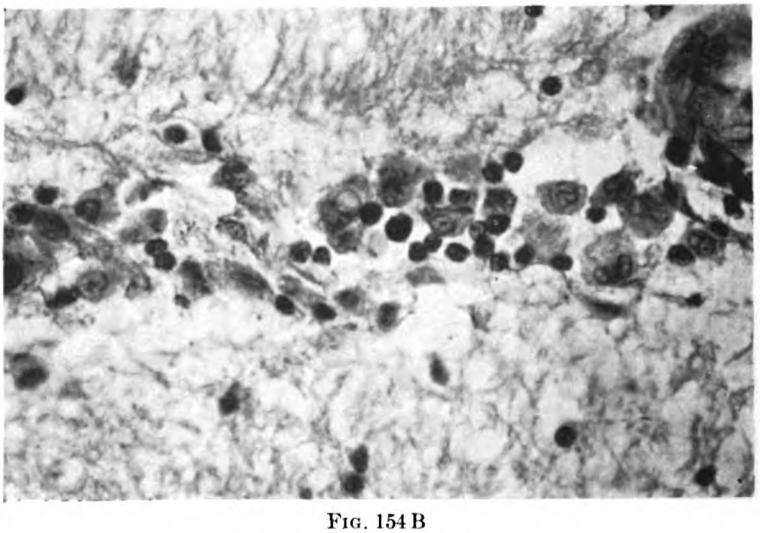


FIG. 154 B

FIGS. 154 A, 154 B. ROCKY MOUNTAIN SPOTTED FEVER

Fig. 154 A. Focus of proliferated glia cells in neighborhood of small blood vessel ("paravascular" focus). Hematoxylin-eosin stain.

Fig. 154 B. Perivascular cellular infiltration with lymphocytes, histiocytes, and some plasma cells. Hematoxylin-eosin stain

(Courtesy U. S. Army Medical Museum. Negatives 84768, 84755)

and led to many publications that had to be corrected later, because the encephalitis found in the rabbit brain was erroneously ascribed to a given experiment. Guinea pigs and other laboratory animals may be infected with this protozoon if kept with already infected ones. Encephalitozoon is a small rodlike parasite that may be seen in the necrotic center of the granuloma. In man it seems to be transmitted in the same way as Toxoplasma.

Rickettsia encephalitis has played only a minor role in the United States. Rocky Mountain spotted fever, caused by Dermacentroxenus rickettsii and transmitted by ticks, has occurred sporadically both in the Rocky Mountain region and in the eastern United States. The histopathology of the encephalitis is the same as that of the epidemic typhus of world war fame on the European continent. The latter is transmitted by lice. The histologic picture somewhat resembles that of epidemic encephalitis of virus origin. There is a mild perivascular round cell infiltration around the blood vessels of both the gray and the white matter. In the neighborhood of these there develop small glia foci, consisting of micro- and oligodengroglia. The mild histologic reaction is in sharp contrast to the rapidly developing and lethal clinical picture (figs. 154A, 154B).

Acute Disseminated Encephalomyelitis

In 1872 Westphal described in 3 cases of smallpox and in 1 case of typhoid fever an acute syndrome consisting of disturbance of speech, difficulty in swallowing, ataxia, tremor of the head and extremities, and paraplegia. He was impressed by the similarity of the clinical picture to the description that Charcot and Vulpius had given of the recently discovered disseminated sclerosis. He stated, however: "This disease [disseminated sclerosis] runs such a typical chronic course that nobody will be inclined to think that I could expect disseminated gray plaques to be seen in the central nervous system, if one of these accutely diseased patients accidentally came to autopsy."

In 1874 Westphal published the autopsy reports of 2 cases of smallpox (varioloid) that he described as "disseminated myelitis." The first was complicated by a severe decubitus, the second by perityphlitis, pelvic abscess, and peritonitis. The brain in both cases showed no gross abnormalities, no petechial hemorrhages. In both, the author described multiple foci of softening in the spinal cord with a "tremendous" accumulation of compound granular corpuscles, indicating, when judged by our present knowledge, softening consequent on interruption of blood supply (thrombosis). Similar histologic pictures have been described under the terms "chronic necrotizing encephalomyelitis" (Riser) or "multiple degenerative softening" (Hassin).

These two publications are cited in detail because of a prevailing tendency to group together, under the designation "acute disseminated encephalomyelitis," neurologic symptoms similar to those described by Westphal as following numerous infections like smallpox, vaccination, measles, antirabic treatment, typhoid fever, influenza, scarlatina, varicella, and mumps. Furthermore, an attempt has been made to deduce a common etiology (virus and allergy) and pathology for this group and to include in it other diseases with suggestive similar pathology but different clinical course (disseminated sclerosis).

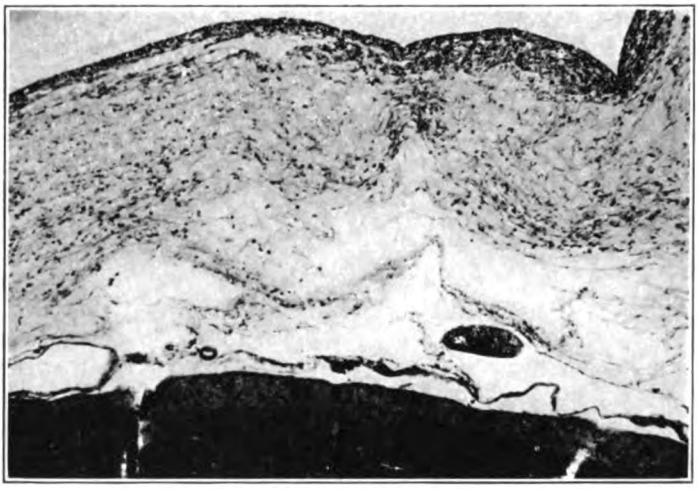


FIG. 155. ENCEPHALITIS FOLLOWING MEASLES
Piarachnoid covering cerebral cortex. Van Gieson stain. Edema and mild increase in collagenous fibers

From the pathologic point of view one may differentiate a group of cases in which, after measles (following termination of the rash), vaccination (in from ten to fourteen days), smallpox, and antirabic treatment, the clinical syndrome of acute disseminated encephalomyelitis develops. This group of conditions is characterized by the following histologic features: around blood vessels of the subcortical white matter, of the brain stem, and of the subependymal tissue, around the periphery of the spinal cord, or around its blood vessels, are found zones of demyelinization with simultaneous destruction of axis-cylinders and a perivascular gliosis, consisting mostly of microglia. Lymphocytic infiltration of the perivascular lymphatics may vary in intensity, may be combined with plasma cell formation, and may be found in areas where demyelinization is absent (fig. 159).

Encephalitis Following Measles.—As an example of this type of histopathologic reaction, a more detailed description of encephalitis following measles will be given. At autopsy, marked congestion of the meningeal vessels has been reported, together with numerous pin point rings of pink color in the white matter of the brain and spinal cord. Grossly these may be mistaken for small petechial hemorrhages, but on microscopic examination they appear as demyelinated areas around blood vessels. In sections stained for myelin sheaths, the white matter has a moth-eaten appearance.

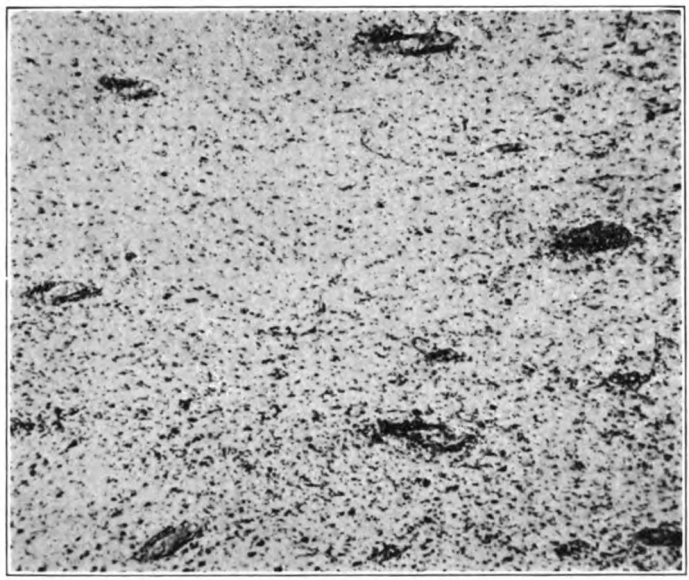


FIG. 156. ENCEPHALITIS FOLLOWING MEASLES

White matter of cerebral cortex. Cresyl violet stain. Increase of glia nuclei with cuffing around blood vessels

Chiefly around thin-walled veins the myelin sheaths and axis-cylinders have disappeared, and in the surrounding regions both show swelling and fragmentation. In sections stained with cresyl violet, there is in these areas a marked increase of glia nuclei, which extend into the neighboring region and belong mostly to proliferated microglia and astrocytes. Only a few lymphocytes and plasma cells may be encountered perivascularly. The mesenchymatous tissue does not participate in the disease process. The endothelium of the vessels may be swollen but there is no increase in connective tissue fibers. The process is most pronounced in the white

matter of the brain, the subependymal zones, and the marginal zones of the spinal cord. But the gray matter is not spared. Pictures of degenerated cortical neurons throughout, and of foci of glia proliferation in the basal ganglia, the nuclei of the pons, and the cerebellum have been reported. It seems that in early cases the demyelinization is not very pronounced (figs. 155–58).

Attempts have been made to group together epidemic encephalitis, acute disseminated sclerosis, and acute disseminated encephalomyelitis

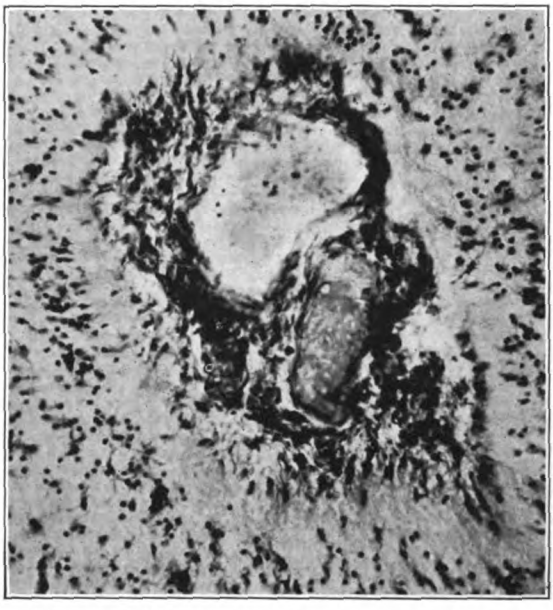


FIG. 157. ENCEPHALITIS FOLLOWING MEASLES
Proliferation of microglia around blood vessels

as observed following vaccination, and to deduce from certain common histologic findings a common etiology, i.e., the action of a filtrable virus. If the essential histopathologic characteristics of the three diseases are compared, one will object immediately to the inclusion of epidemic encephalitis. Its pronounced inflammatory exudation, the severe neuronal disease with neuronophagia, with predilection for the midbrain, is in marked contrast to the mildness or absence of perivascular lymphocytic infiltration in the postvaccinal encephalitis and that following measles, in which perivenous glia cell proliferation dominates. The similarity in the zones of demyelinization in the two latter diseases and disseminated sclerosis is

FIG. 158. ENCEPHALITIS FOLLOWING MEASLES
White matter of cerebral cortex. Weil stain. Multiple areas of demyelinization

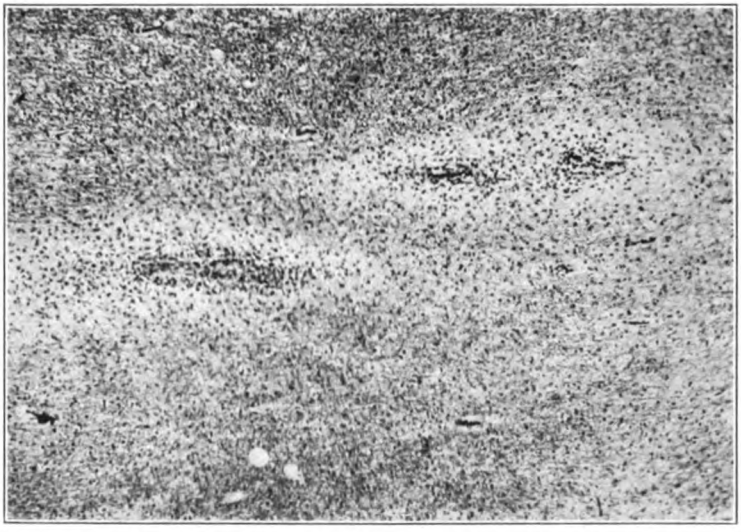


FIG. 159. ENCEPHALITIS FOLLOWING CHICKENPOX
White matter of cerebral cortex of child. Van Gieson stain. Perivascular areas of necrosis with mild glia proliferation and perivascular round cell infiltration

matter of the brain, the subependymal zones, and the marginal zones of the spinal cord. But the gray matter is not spared. Pictures of degenerated cortical neurons throughout, and of foci of glia proliferation in the basal ganglia, the nuclei of the pons, and the cerebellum have been reported. It seems that in early cases the demyelinization is not very pronounced (figs. 155–58).

Attempts have been made to group together epidemic encephalitis, acute disseminated sclerosis, and acute disseminated encephalomyelitis

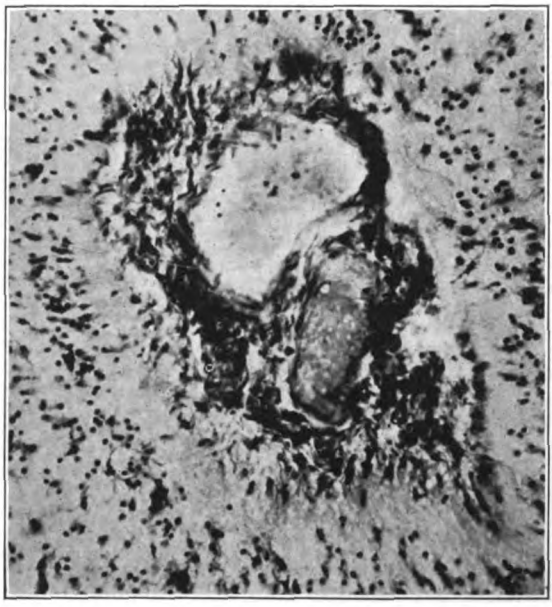


FIG. 157. ENCEPHALITIS FOLLOWING MEASLES
Proliferation of microglia around blood vessels

as observed following vaccination, and to deduce from certain common histologic findings a common etiology, i.e., the action of a filtrable virus. If the essential histopathologic characteristics of the three diseases are compared, one will object immediately to the inclusion of epidemic encephalitis. Its pronounced inflammatory exudation, the severe neuronal disease with neuronophagia, with predilection for the midbrain, is in marked contrast to the mildness or absence of perivascular lymphocytic infiltration in the postvaccinal encephalitis and that following measles, in which perivenous glia cell proliferation dominates. The similarity in the zones of demyelinization in the two latter diseases and disseminated sclerosis is

FIG. 158. ENCEPHALITIS FOLLOWING MEASLES
White matter of cerebral cortex. Weil stain. Multiple areas of demyelinization

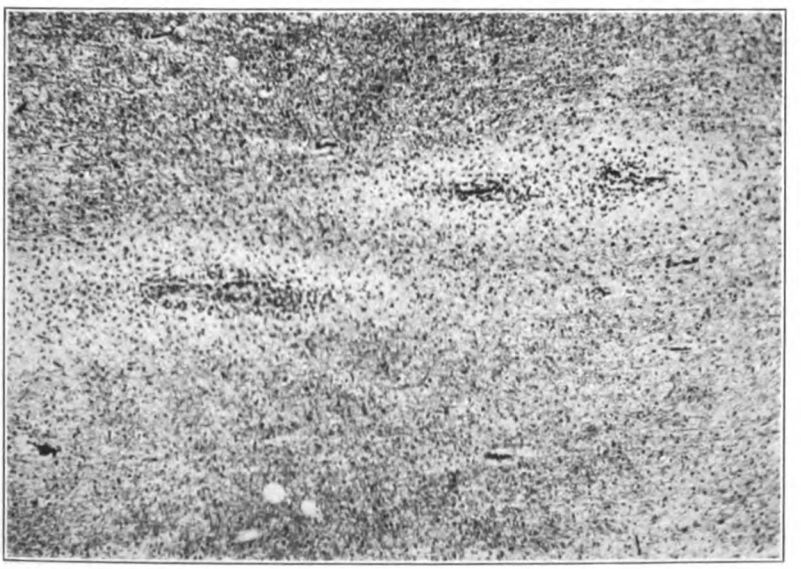


FIG. 159. ENCEPHALITIS FOLLOWING CHICKENPOX
White matter of cerebral cortex of child. Van Gieson stain. Perivascular areas of necrosis with mild glia proliferation and perivascular round cell infiltration

only apparent. In the exanthem they are smaller and bound to the blood vessels, while in disseminated sclerosis such dependence cannot always be demonstrated. Furthermore, severe destruction of axis-cylinders is the rule in the foci of demyelinization in measles encephalitis, while it is the exception in disseminated sclerosis. It has not been proved that encephalitis following antirabic treatment is produced by the same virus that is responsible for rabies. The working hypothesis has been advanced that another unknown virus, already present as a saprophyte in the nervous tissue, is activated by the smallpox and measles virus and produces disease of the central nervous system. It appears premature at the present stage of our knowledge to build such a hypothesis on histopathologic evidence.

In studying brain lesions in the exanthems, it is important to know that they may be produced as secondary to disease of other organs. In encephalitis following measles, brain purpura has been described in connection with a pneumonia or abscess formation, and purulent meningitis in connection with an otitis media.

Disseminated Sclerosis

Synonyms: German, *multiple Sklerose;* French, *sclérose en plaques.*

The inclusion of this disease in a discussion of infectious diseases does not mean that its infectious etiology is definitely established. It has been added here in order to point out, on the one hand, certain conformities with the group of encephalitides following the acute infectious exanthems, and in order to discuss, on the other hand, the histopathologic features that have led many observers to assume an infectious origin.

The more important theories as to the etiology of the disease may be divided into two groups, those assuming an exogenous cause and those ascribing to it an endogenous origin. The first group assumes the agency of either a specific filtrable virus (Bullock) or a spirochete (Kuhn-Steiner). The second group cites metabolic disturbances (lipolytic ferments, Marburg, Brickner; endotoxins, Dawson, Hassin, Weil), a primary disease of the glia (Müller-Strümpell), venous thrombosis (Putnam), or anaphylactic reactions (Ferraro) as being responsible for the destruction of the myelin sheaths. The diagnosis of the disease may sometimes be established only at the autopsy table. In the white matter of brain and spinal cord there may be detected disseminated grayish or reddish foci that on exposure to air stain more intensively. Older foci offer resistance to the cutting knife, while more acute foci are softer. In sections stained for myelin sheaths, multiple unstained areas are seen in the white matter; these may extend into the gray matter and are sharply limited (figs. 160, 161). In sections stained with cresyl violet, these foci are filled with numerous glia nuclei

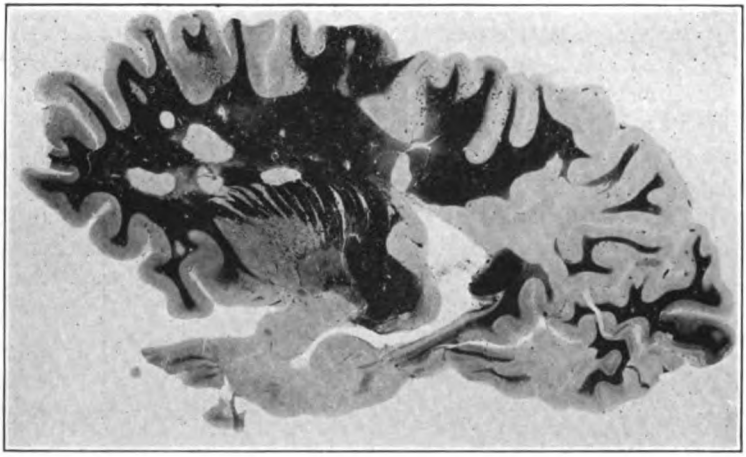


FIG. 160. DISSEMINATED SCLEROSIS

Sagittal section through brain. Loyez stain. Multiple demyelinated plaques in white matter of frontal and central regions. Nearly complete demyelinization of white matter in parts of parietal, occipital, and temporal lobes

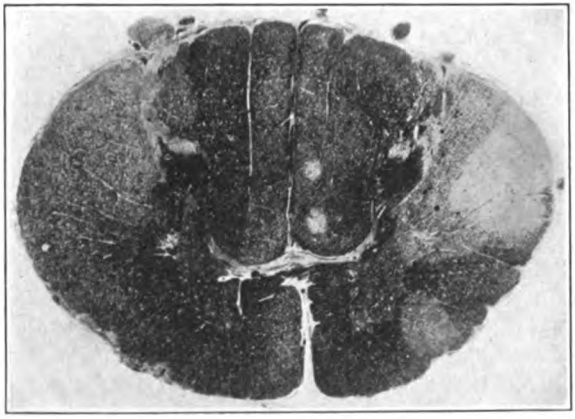


FIG. 161. DISSEMINATED SCLEROSIS

Transverse section through dorsal spinal cord. Weil stain. Multiple plaques in posterior and lateral columns

that, in more acute plaques, form a dense wall at the outer periphery. Around the blood vessels within the foci and in neighboring regions, lymphocytes and plasma cells intermingle with compound granular corpuscles.

This perivascular infiltration may vary considerably and may even be totally absent in certain cases. In others, marked perivascular edema has been reported, with production of a wide fluid-filled area in the extended Virchow-Robin spaces (fig. 162). In sections stained by Holzer's or Anderson's method, older plaques stain intensely blue and contain a dense meshwork of glia fibers (fig. 30). In more acute foci, the glia fiber formation is less pronounced, and glia cells with abundant cytoplasm and fat-laden gitter cells predominate. Cajal and Hortega stains reveal an abundance of microglia and astrocytes, the latter showing an increase in number outside the demyelinated foci also. The axis-cylinders are better pre-

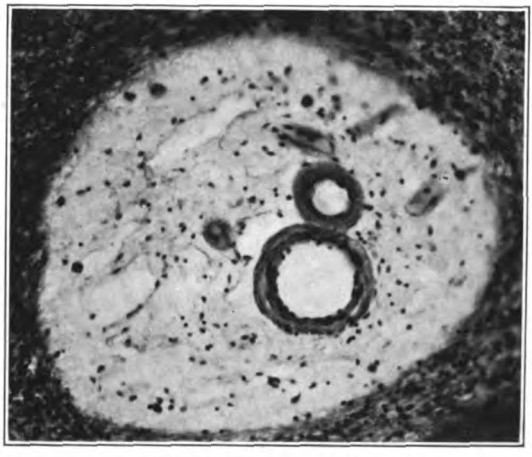


FIG. 162. DISSEMINATED SCLEROSIS
Parietal cortex. Perivascular edema. Van Gieson stain

served than the myelin sheaths. In longitudinal sections through plaques of the spinal cord, many well preserved axons may be seen. This explains the relatively rare occurrence of secondary degeneration of fiber tracts of the spinal cord. The walls of the smaller vessels within and outside of the foci show hyalinization, staining intensely blue in Mallory preparations. The piarachnoid is frequently edematous, with a mild infiltration of lymphocytes and plasma cells and some increase in connective tissue fibers.

It has been emphasized that the demyelinated foci are most frequently found in the neighborhood of the ventricles and the central canal, suggesting a spread of the hypothetic toxic agent by way of the cerebrospinal fluid. Wohlwill, in criticizing Putnam's idea that postinfectious encephalitis and disseminated sclerosis are identical, states: "The matter in which a pathological process spreads is much more important for its specificity than its

histological composition. It is not true that in postinfectious encephalitis venous thrombi are pathogenetic."

The perivascular infiltration with lymphocytes and plasma cells has been cited in favor of the theory of an infectious etiology in disseminated sclerosis. It should be emphasized here again that such mesenchymal reaction may occur in noninfectious toxic processes (plasma cells in alcoholic degeneration) and that it is not the rule in all cases. The intense proliferation of fibrous glia has been explained as merely a reparative phenom-

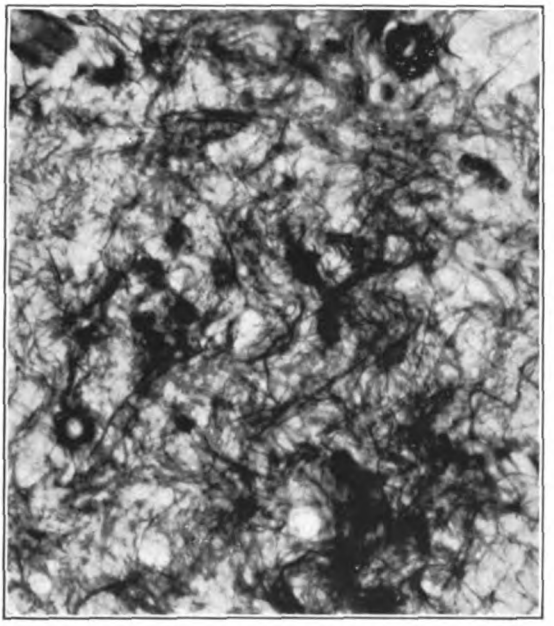


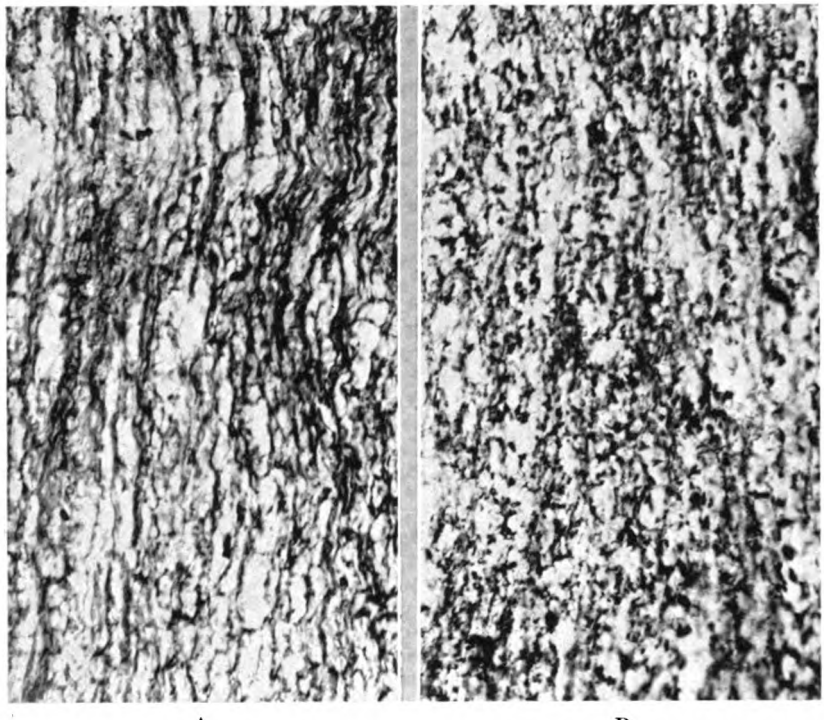
FIG. 163. DISSEMINATED SCLEROSIS

Proliferation of neuroglia. Plaque in subthalamic region. Anderson's victoria blue stain. Formation of dense meshwork of glia fibers

enon. However, the fact that astrocyte proliferation and increase in interfascicular glia are also seen, in early stages, outside of the demyelinated foci, does not favor such an assumption. Besides, the intensity of the glia sclerosis surpasses by far any reparative process that we are accustomed to find in the central nervous system. On the other hand, intense glia proliferation cannot be held liable as the primary factor leading to destruction of myelin sheaths, because the two processes occur simultaneously and the fibrous sclerosis follows later.

In this connection, it may be of interest to cite the histologic picture of an

experimental endogenous intoxication following severe liver damage. After ligation of the common bile duct in dogs, a pronounced glia proliferation, accompanied by extensive destruction of myelin sheaths, is found around the lateral ventricles or, in some cases, in the white matter of the hemi-



A B

FIG. 164. EFFECT OF URINE FROM CASE OF DISSEMINATED SCLEROSIS UPON RAT SPINAL CORD

Longitudinal sections. Weil stain

A. Effect of concentrated normal urine after 16 hours of incubation at 37 C.

B. Effect of disseminated sclerosis urine after precipitation of myelolytic substances with acetone from their alcoholic solution. In contrast to result in A, myelin sheaths in B are broken up into numerous black-staining globules, an effect similar to that of sodium taurocholate (cf. fig. 46)

spheres. The absence of perivascular cellular infiltration and the presence of generalized severe disease of neurons with neuronophagia, however, are important differential points (Weil and Crandall). It can be demonstrated that after incubation with rat spinal cords, the serum of such dogs contains substances that act destructively upon nervous tissue. In the urine and spinal fluid of patients suffering from disseminated sclerosis, in more than

two-thirds of all cases, test tube experiments will demonstrate substances that break up myelin into fine globules in the same way as may be seen after incubation of spinal cords in bile salt solutions (Weil) (figs. 46, 164).

In disseminated sclerosis, the neurons are usually spared. Even in spinal cords with plaques covering more than one-half of the white matter, the anterior horn cells appear normal or show only mild changes; but never has as severe a disease of the gray matter been found as that occurring in the encephalitis following measles. In the lower cortical zones bordering sclerotic plaques, neuronophagia of degenerated neurons occurs.

Attempt has been made to deny the status of a clinical and pathologic entity to disseminated sclerosis. The theories of Marie and Oppenheim, that many infectious diseases may be responsible for the pathologic changes, are still supported by their clinical authority. It has been pointed out that arteriosclerosis, carbon monoxide poisoning, and certain exogenous toxins (Aspergillus) may produce disseminated demyelinization, though the intense fibrous glia reaction could not be demonstrated. In short, any experiment producing demyelinization has been cited in favor of the author's pet theory concerning the origin of disseminated sclerosis. Frequently not enough attention was paid to the fact that besides demyelinization there is also severe necrosis of axis-cylinders and of glia in these foci. Such changes result from injection of potassium cyanide (Ferraro), production of multiple venous thrombi (Putnam, Hurst), and intramuscular injection of extracts of suspension of human brain (Ferraro and Jervis). Besides acute disseminated encephalomyelitis, neuromyelitis optica has been claimed to be identical with acute disseminated sclerosis.

Considering the clinical picture of the chronic disease, with its remissions and acute exacerbations, and the uniformity of the histopathologic reaction, with its primary demyelinization and glia proliferation independent of vascular channels, one is still justified in assuming a specific character for the disease, though the etiologic factor is as yet unknown.

Diffuse Sclerosis

The study of another group of diseases characterized by primary demyelinization of the white matter, i.e., those comprised in the category of diffuse sclerosis, has added to this uncertainty. It seems that a number of disease processes have been identified with this diagnosis, and the unsettled status of the problem is attested by the different names that have been applied—"encephalitis scleroticans periaxialis diffusa" (Schilder), *sclérose intracérébrale centrolobaire et symétrique* (Marie and Foix), *leucoencéphalite subaiguë* (Claude and Lhermitte), "progressive degenerative subcortical encephalopathy" (Globus and Strauss), *sklerosierende Entzündung des Hemisphärenmarks* (Spielmeyer). At present the term

"Schilder's disease" or "diffuse sclerosis" is best suited to cover our ignorance as to the etiology of the different forms. Pelizaeus-Merzbacher disease (chronic familial diffuse sclerosis), with its patchy demyelinization of the white matter, may be added to this group. In sheep there occurs a congenital demyelinization disease—sway-back—that seems to be of a

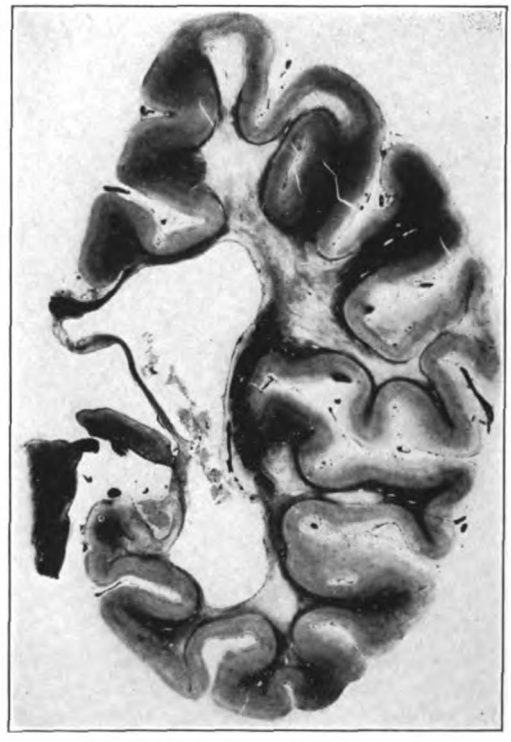


FIG. 165. SCHILDER'S DISEASE

Case of 14 years' duration. Vertical section of brain through parietal and temporal lobes. Demyelinization of subcortical region, with preservation of Meynert U fibers. Dilatation of both lateral ventricle and inferior horn. Weil stain

pathology similar to that of diffuse sclerosis (Innes). The classification of Spatz and Hallervorden's cases of concentric demyelinization of the white matter of the cerebral hemispheres is not yet clear. Jervis and Kyndwall described Schilder's disease as occurring in ergotamine intoxication.

The common characteristic of all these different forms is a complete demyelinization of the white matter of the hemispheres that, however, spares the arcuate fibers (U fibers) and only seldom invades the gray matter.

The gross appearance of the brain may sometimes allow of some conclusion as to the age of the condition. In acute cases, the consistency is soft, that of the white matter mushy. In older cases with extensive glia sclerosis, considerable resistance to the cutting knife and a hard consistency are found. It has been stated that histologically the acute cases present a predominance of compound granular corpuscles, large giant astrocytes, and perivascular infiltration of lymphocytes and plasma cells, as contrasted with the chronic cases, which present a minimum of cellular glia proliferation and predominance of a dense meshwork of glial fibers.

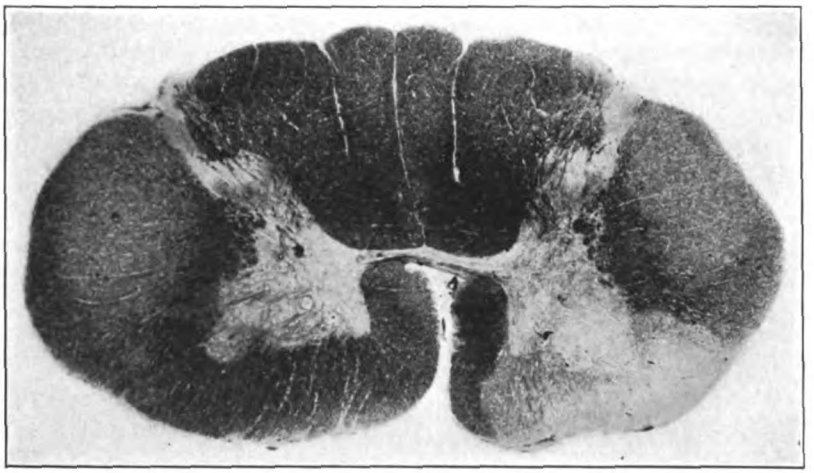


FIG. 166. SCHILDER'S DISEASE

Same case as in fig. 165. Transverse section through fifth cervical spinal cord segment. Paling in area of both crossed pyramidal tracts; descending secondary degeneration. Demyelinated sclerotic plaques in anterior column. Weil stain

As in disseminated sclerosis, the process of demyelinization affects the white matter of both brain and spinal cord. Sometimes it appears impossible to differentiate a case of diffuse sclerosis from an advanced case of disseminated sclerosis (figs. 165, 166).

An attempt has been made to separate cases occurring in children from adult cases, as a distinct disease entity, by pointing out the fulminant clinical course and the corresponding intense degenerative changes in the first group. Another attempt has been that of subdividing the cases reported in the literature into an inflammatory, a degenerative, a neoplastic, and a sclerotic group. The difficulty of carrying out such a classification will be impressed upon the pathologist if he knows of the variation of the histologic picture within a single case from the acute to the chronic stage. The pres-

ence or absence of perivascular lymphocytic infiltration is not a criterion of inflammation in an advanced chronic case, and it seems impossible to state from the histologic picture of glia proliferation, with its manifold bizarre forms, whether one is dealing with a stimulation of glial growth by some unknown noxious toxin or with a neoplastic process. The idea that metabolic disturbances either of the myelin sheaths themselves or of the surrounding glia may be responsible for the breaking down of myelin has more recently been added to the older, classic idea.

The whole problem becomes still more complicated by the addition of a familial type of diffuse sclerosis occurring in early childhood. In isolated instances such familial occurrence has also been reported in relation to disseminated sclerosis. At the present stage of our knowledge it is impossible to state the differences in etiology of all these different groups of primary demyelinization with simultaneous glia proliferation and sclerosis.

IX

INTOXICATIONS

To be exact, infections of the nervous system are only a special type of intoxication produced by the toxic metabolic products of micro-organisms. The micro-organisms themselves may produce mechanical damage by thrombus formation or other interference with blood supply (blastomycosis). In the same way in which bacterial toxins may produce different forms of tissue reaction according to their concentration and specific nature, other toxins of known or unknown chemical constitution produce manifold histopathologic pictures in the nervous system. Bacterial toxins do not always produce inflammation. The reaction may vary from a mild edema of the meninges or perivascular sheaths through mesenchymatous cellular proliferation and glia proliferation to severe necrosis of the nervous parenchyma. In the same way, various other toxins may produce tissue changes of a purely degenerative character, a "-pathy" without progressive cellular changes, or an inflammatory reaction. What has been said about the dissemination of bacterial toxins applies of course to other intoxications. Age, constitutional disposition, preceding disease, and other factors that influence the permeability of the blood vessels will also determine the intensity and distribution of the different exogenous and endogenous toxins.

Traditionally the toxins that may affect the nervous system are subdivided into an exogenous and an endogenous group. Such a classification is not altogether satisfactory, because it is based neither on chemical constitution nor biologic effect. We know only very little about the nature of most of the endogenous toxins, as deriving either from the products absorbed from the gastro-intestinal tract or from intermediary products of metabolism. As for the exogenous toxins, one might suggest subdividing these, according to their possible effect on the cytoplasm, into lipolytic (alcohol, ether, snake toxins), and protein-precipitating (lead, mercury, arsenic). It seems that most of the exogenous toxins do not attack the central nervous system tissues directly, but act indirectly either through damage to the liver (phosphorus, alcohol), with subsequent endo-intoxication, or through damage to the endothelium and the walls of the blood vessels, followed by perivascular hemorrhages and softening (arsenic, carbon monoxide).

The peripheral nervous system is exposed to the direct effects of these toxins circulating in the blood and the lymphatic fluids. The tissue rac-

tion may be either a simple degeneration of myelin sheaths and axis-cylinders, without any inflammatory phenomena (neuropathy), or a proliferative change in the peri- and endoneurium (interstitial neuritis). Two infectious diseases are known to produce intoxication of the nervous system *par distance*—diphtheria and tetanus. In both of these the micro-organisms do not always invade the central nervous system, but their toxins may be secreted into the circulation from a localized focus. The neuritis in diphtheria is an inflammatory reaction, an interstitial neuritis. Besides inflammatory meningitis and encephalitis, severe degenerative changes of nuclei in the central nervous system, frequently in the medulla oblongata, have been reported. In tetanus intoxication the histologic changes described as occurring in anterior horn cells were very mild; they appeared in the form of central chromatolysis or were of such a nonspecific nature that it was doubtful whether they could have been produced by simultaneous fever or hemorrhage.

Most of the acute intoxications that produce death immediately do not present any histologic changes of nervous tissue that can be seen under the microscope. Only in the chronic cases with repeated damage can degenerative and reactive phenomena be observed. This applies in the case of dementia praecox treatment with metrazol, in which the intensity of the brain pathology corresponds to the dose injected and to the duration of treatment. An exception in this are some experimental conditions, such as death by ether anesthesia as described above (figs. 10, 167). In the following section a few examples of the pathology in the more frequent intoxications are given.

Alcohol

Ethyl alcohol may produce either a neuropathy in the peripheral nerves (with predilection for the nervus peroneus) and the spinal cord roots, or less frequently an interstitial neuritis of the hemorrhagic type. The changes that have been reported as occurring in the neurons of the brain and spinal cord following experimental intoxication (chromatolysis, swelling, nuclear degeneration) are very indefinite. In chronic alcoholism in man, the brain is frequently markedly swollen and presents an acute internal hydrocephalus. Most of the changes in the central nervous system seem to be produced by lesions and proliferation of the endothelium of the blood vessels, leading to multiple hemorrhages and reparative phenomena. The dura mater may therefore present the picture of pachymeningitis haemorrhagica and subdural hemorrhages. In the piarachnoid of the convexities there may be found the remains of old hemorrhages and a fibrous thickening without marked cellular infiltration.

The brain is atrophic, and the histologic picture presents multiple small

hemorrhages, hyalinization of the vessel walls, and proliferation or degeneration of the endothelium. In addition, there is, according to some observers, a generalized severe degeneration of the cortical neurons, with predilection for the third layer of the frontal and central convolutions. The myelin sheaths of the finer fibers of the cortex are destroyed, and foci of demyelinization are seen in the white matter, with predilection for the genu of the corpus callosum. Proliferation of fibrous glia accompanies these degenerative processes.

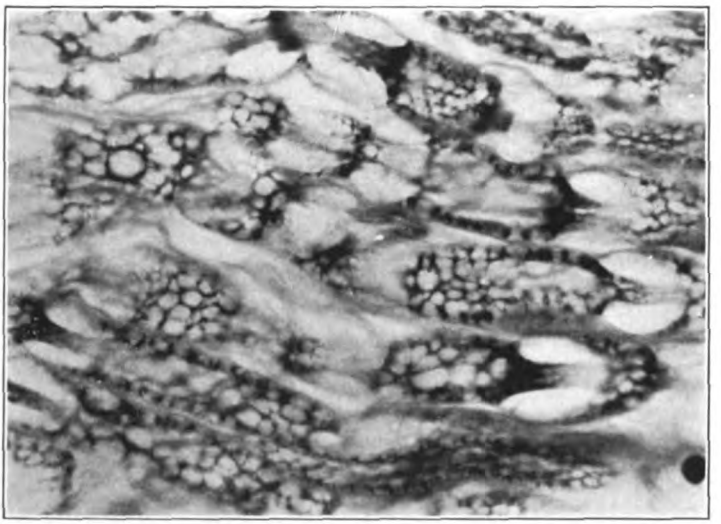


FIG. 167. EXPERIMENTAL ETHER NARCOSIS
Duration, 3 hours. Swelling of myelin sheaths in posterior root of spinal cord of cat. Light green-fuchsin stain

Since Wernicke's investigations, attention has been drawn to the proliferation of capillary sprouts and fibroblasts as an expression of a selective stimulation of the mesodermal derivatives. It may lead to multiple small hemorrhages. This process, which is found most frequently in the region of the aqueduct of Sylvius and the corpora quadrigemina, has been described as "polio-encephalitis haemorrhagica superior" (fig. 168).

The designation of these pathologic changes as an inflammatory process is not quite correct. In acute, lethal cases no perivascular cellular infiltration is found; the new formation of capillaries and hemorrhages dominates the picture. Intense perivascular lymphocytic infiltration may indicate metastasis of an infection elsewhere in the body (Luethy and Walthard). There has been frequent discussion of the question as to whether this pathol-

ogy of the brain is a direct effect of the alcohol on nervous tissue or whether it is secondary to an endogenous intoxication following disease of other organs (liver, kidney). It has been pointed out that hypothetic endotoxins may invade the central nervous system by way of the liquor. The frequency with which the region around the aqueduct is affected, the fibrous glia proliferation in the subependymal tissue and the outer layers of the cerebral cortex, speak in favor of such an assumption. However, more recently the idea has prevailed that a disturbance of the vitamin metabolism, following disease of the gastric mucous membrane and the liver, is the primary factor

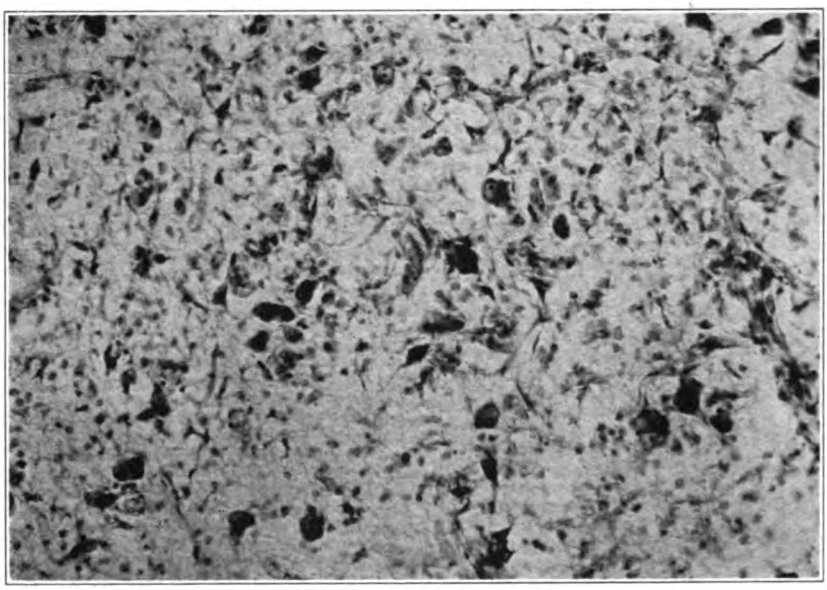


FIG. 168. WERNICKE'S DISEASE ("POLIO-ENCEPHALITIS HAEMORRHAGICA SUPERIOR")
Midbrain, gray matter around aqueduct of Sylvius. Cresyl violet stain. Proliferation of glia and sprouting of capillary endothelium

in production of the brain pathology described above. Since it has been demonstrated clinically that alcoholic neuropathies are cured rapidly following intake of vitamin B_1 (thiamine), a solid basis has been provided for such a theory. Alexander produced in pigeons, kept on a diet deficient in vitamin B_1, lesions similar to those described above in relation to Wernicke's disease.

Methyl alcohol produces changes similar to those caused by ethyl alcohol—extensive degeneration of neurons and of vascular endothelium, with subsequent hemorrhages in the midbrain, pons, and medulla oblongata. In addition, there seems to be a selective affinity for the neurons of the retina, the destruction of which is responsible for the blindness in this intoxication. To this classification should be added also many commercial solvents,

inhalation of which produces neuropathies with the histopathologic picture of demyelinization of the peripheral nerve fibers. Examples are benzene, carbon tetrachloride, dinitrophenol, tetrachlorethane, thiophene (selective degeneration of the cerebellum). Certain other volatile solvents used in industry may have a similar effect—e.g., mixtures of isopropylic alcohol with the mono-ethyl ester of ethylene glycol.

Alkaloids and Narcotics

The histologic findings reported in intoxications following abuse of morphine and its derivatives comprise diffuse degeneration of neurons, fatty degeneration of the endothelium and the walls of the blood vessels, with increase of connective tissue fibers, and regressive changes of the glia. In some acute cases, brain purpura has been found. These vascular disturbances are followed by softening and disappearance of neurons in more or less extended areas of the cortex.

Cocaine, novocain, stovaine, and related substances used in local anesthesia produce changes similar to those induced by the morphine group if they are taken in large, toxic doses. Injected into the subarachnoidal space, they seem to produce mild degeneration of the spinal root fibers, with demyelinization and destruction of the axis-cylinders, which is responsible for the retrograde degeneration of anterior horn cells. Upon experimental injection of these substances into the subarachnoidal space in dogs, a peripheral zone of demyelinization of the spinal cord, with intense staining of the myelin sheath debris in sudan III preparations, has been reported.

The distribution of different drugs within the central nervous system has been studied experimentally. There are different theories concerning the fundamental facts governing such differential distribution. While O. and C. Vogt assume a chemical affinity of varying degree for the different anatomic areas of the brain (pathoclisis), Spielmeyer and his co-workers try to explain such differences on the basis of vascular supply.

The figures of table 14 will give an idea of such a relative distribution as regards atropine and quinine (Veit and Vogt).

We must assume that mild pathologic changes of the neurons following clinical application of these different drugs can be repaired. Experimental proof has been presented after prolonged ether and chloroform narcosis. When the animals were killed after a narcosis of several hours' duration, swelling and chromatolysis of anterior horns and cortical neurons were found, together with edema of nerve fibers. After complete recovery from the effect of the narcosis, these structures were found to be in normal condition (figs. 9, 10, 167).

The effect of narcotics upon the nervous tissues is not confined to the duration of the narcosis, but a prolonged after-effect takes place. Experi-

mental evidence is given by the demonstration of alcohol and chloroform in brains many hours after death, and by the binding power of brain tissue for bromal hydrate, which is greater than that of muscles. The latter have a tendency to shrink in bromal hydrate solutions, while brain tissue shows marked swelling, an effect that is produced also in ether and chloroform narcosis (cf. chap. IV).

The destructive effect of the narcotics upon nervous tissue is evidenced by the increase of cholesterol and phospholipids in the blood following ether and chloroform narcosis. This increase is still present after twenty-four hours.

TABLE 14.—*Relative Distribution of Atropine and Quinine in Animal Brains*

Concentration in spinal cord = 1

	Cerebral Cortex	White Matter	Caudate Nucleus	Midbrain	Cerebellum	Pons	Medulla Oblongata	Liquor	Liver
Atropine	3.3		2.2	1.2	2.5	1.3	1.3	1.4	
Quinine	3.1	1.0	2.3	1.4	2.1		1.7	0.1	14.0

LEAD AND ARSENIC

It is difficult to decide whether the histopathologic changes following intoxications with these inorganic substances are produced by direct action upon the nervous parenchyma or are secondary to severe damage of other organs of the body, as the kidneys and liver. In normal tissue the presence of lead can be demonstrated, increasing with age. There is a possibility that the extensive use of tetra-ethyl lead in gasoline mixtures, and inhalation of it with automobile exhaust gas, may have some connection with such an increase. Lead itself has been demonstrated in small amounts in the brain following chronic intoxication. The organic arsenic compounds that are used pharmaceutically, such as salvarsan, tryparsamide, neoarsphenamine, etc., pass only in minimal amounts through the hematoencephalic barrier.

In encephalopathia saturnina in young children, typical myelin sheath degeneration has been described as affecting both cerebrum and cerebellum. The histologic changes reported as found in the brains of painters or lead workers comprised cortical atrophy with chronic leptomeningitis, diffuse degenerative disease of the neurons, diffuse demyelinization, glia proliferation, and perivascular edema. In some cases, proliferation of mesenchymal and glia cells around blood vessels, with formation of granuloma-like structures, has been described.

The changes in the peripheral nerves consist in globulation of myelin

sheaths with the ensuing processes of repair, proliferation of Schwann's sheath cells, and finally a breaking down of the axis-cylinders.

The effect of arsenic preparations upon the central nervous system seems to be secondary to disease of the blood vessels. Two kinds of foci of degeneration in the white matter following arsphenamine medication have been described: (1) hemmorhagic foci following degenerative lesions of the blood vessel walls, and (2) nonhemmorhagic foci in the form of perivascular necrotic areas, with demyelinization, compound granular corpuscles, and microphages. Fatty degeneration of the vascular endothelium is present in most cases (Russell).

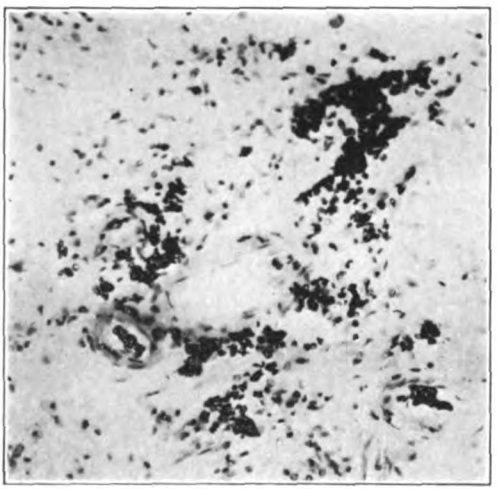


FIG. 169. EXPERIMENTAL ARSENIC INTOXICATION

Injection of 1.5 Gm. of tryparsamide into rabbit, with death after 10 days. Perivascular cerebral hemorrhage

(*Courtesy Dr. N. K. Lazar*)

Occurrence of brain purpura, together with diffuse hemorrhage into the plexus chorioideus and the piarachnoid, or of edema of the leptomeninges, has been described in instances of death following treatment with salvarsan, and after experimental injection of large doses of tryparsamide in rabbits. Occasionally larger foci of hemorrhagic softening seem to occur. The vascular endothelium in such cases is diffusely swollen and shows fatty degeneration together with hyalinization or necrosis of the blood vessel walls. The ensuing disturbance of blood supply may be responsible for the nonspecific, severe degenerative neuronal changes that have been reported following intoxication from large doses of arsenic. The basal ganglia and the pons seem to be mostly involved; the cerebellum and the cerebral cortex usually seem to escape the morbid process (figs. 169–71).

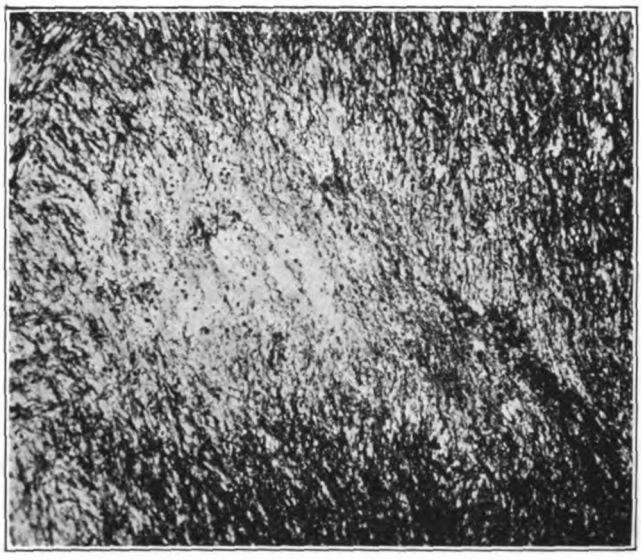


FIG. 170. EXPERIMENTAL ARSENIC INTOXICATION

Same experiment as in fig. 169. Focus of demyelinization in optic chiasm in neighborhood of hemorrhage. Weil stain

(Courtesy Dr. N. K. Lazar)

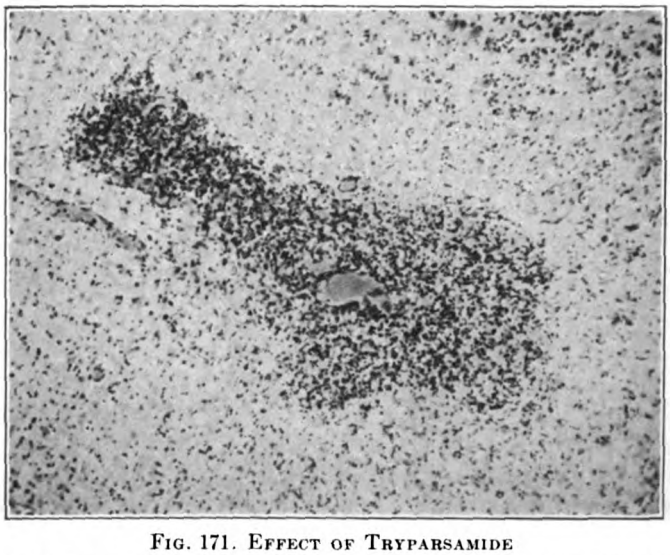


FIG. 171. EFFECT OF TRYPARSAMIDE

In case of cerebrospinal syphilis in which treatment was followed by sudden blindness. Organized perivascular hemorrhages in occipital lobe. Van Gieson stain

It seems that preparations containing pentavalent arsenic (atoxyl, tryparsamide, stovarsol) are more toxic than those containing trivalent arsenic. In a study of a large series of syphilitic patients treated with arsphenamines, it was found that among 1,212 cases, 19 per cent in the latest stages and 14.3 per cent in the early stages showed complications produced by the treatment with arsenic. Among 252 such cases with complications, 6 died of "hemorrhagic encephalitis." Table 15 illustrates the incidence of various complications encountered following treatment with various preparations (Cole).

Thallium may be added to this group. It has been used as a hair remover, but polyneuropathies, loss of sleep, and other nervous symptoms have been undesired side effects.

TABLE 15.—*Clinical Complications Following Application of Arsenical Preparations in Syphilis*

Type of Arsenical	No. Cases				
	Hemorrhagic Encephalitis	Dermatitis	Icterus	Gastro-intestinal Disorder	Nitritoid Crisis
Arsphenamine	1	46	7	32	15
Neoarsphenamine	1	21	8	12	4
Sulfarsphenamine	4	1		8	
Tryparsamide	1	1		1	

INSULIN AND METRAZOL

The widespread use of these two drugs in shock therapy of dementia praecox justifies a more detailed description of their toxic effect upon the central nervous system when used repeatedly in relatively large doses. Both in autopsy reports on patients who died of hyperinsulinism (adenoma of the pancreas) and in experiments with animals, the outstanding pathologic features were severe disease of the neurons in the form of liquefactions, vacuolation, and homogenization (De Morsier and Mozer; Teerbruegge; Weil, Liebert, and Heilbrunn) (fig. 172). There was only a mild gliosis, or none, quite in contrast to the effect of metrazol upon both the human and the animal brain. Following from three to six weeks of treatment, generalized hypertrophy and hyperplasia of astrocytes, oligodendroglia, and microglia were found. Disease of the neurons, however, was negligible (Weil and Liebert) (fig. 173).

CARBON MONOXIDE

The effect of this poisonous gas is twofold. On the one hand, it deprives the central nervous system of the much needed supply of oxygen by its

combination with hemoglobin to form methemoglobin; on the other, it paralyzes the vasomotor nerves of the blood vessels, and the ensuing circulatory disturbances, stasis and thrombus formation, are mainly responsible for the histopathologic changes. In acute cases of gas poisoning (illuminating gas, gasoline fumes in closed garages) the brain is markedly hyperemic, with intense injection of the vessels of the piarachnoid and the white matter. Minute perivascular hemorrhages are seen, chiefly in the internal capsule and the globus pallidus. If death occurs only after several days, severe neuronal disease and softening in its different gradations

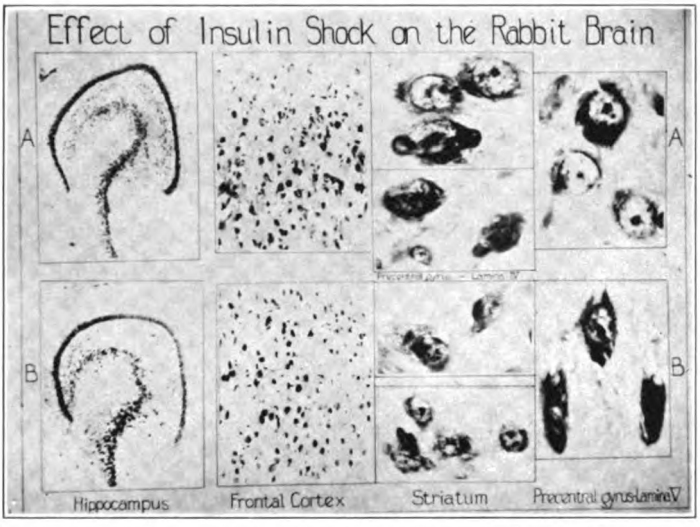


FIG. 172. EFFECT OF INSULIN INJECTIONS ON RABBIT BRAIN

A, control. B, rabbit brain after injection of 402 units of insulin in 46 injections. Diminution in number of neurons in different parts of brain and severe disease of remaining neurons. Cresyl violet stain

develop. The occurrence of foci of softening in the globus pallidus, with extension into the neostriatum or the midbrain nuclei, has been emphasized by most observers. The sensitiveness of this area to vascular disturbances has been explained on the basis of the relatively underdeveloped capillary network. Other foci of softening are found in the cerebral cortex, in the cornu Ammonis, and in the cerebellum (fig. 174).

If the attack of poisoning is survived, complete recovery, with scar formation in the necrotic areas, may take place. The damage of the vasomotor nervous regulation, however, cannot be repaired and is responsible for a slowly progressive disseminated softening that may be the cause of sudden death following cerebral hemorrhage (fig. 175).

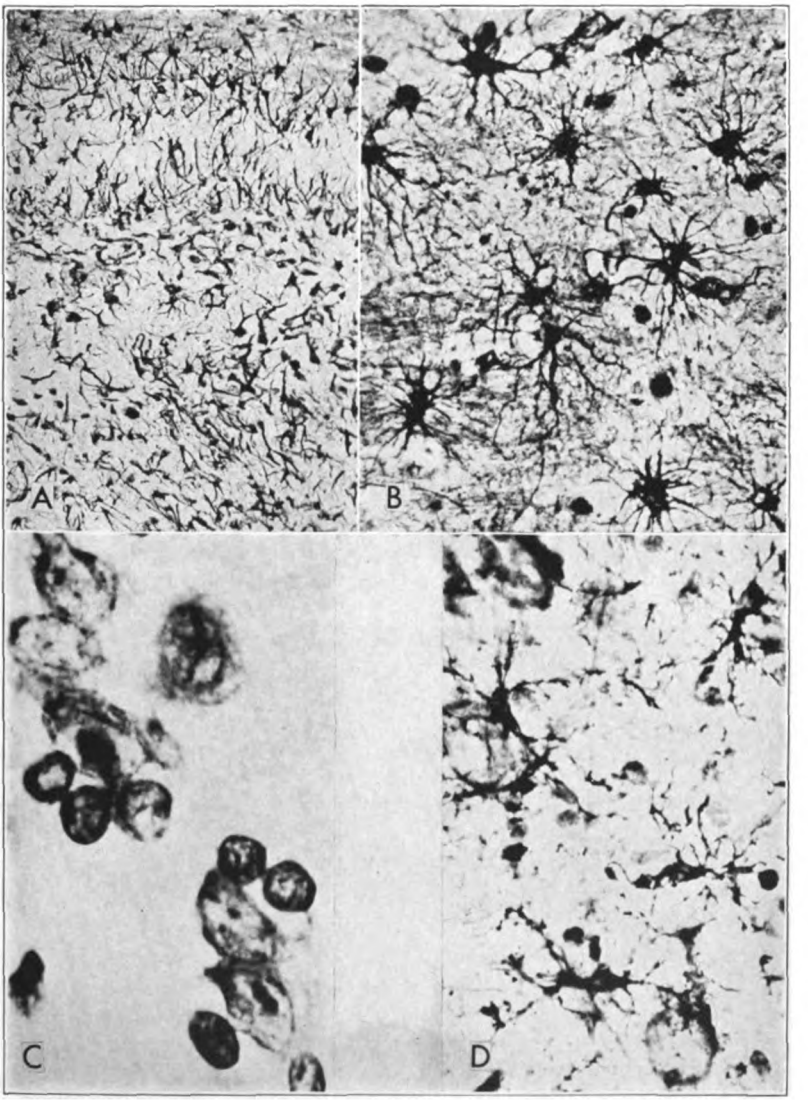


FIG. 173. EFFECT OF METRAZOL INJECTIONS UPON GLIA

A, C, D, from rabbit injected for 41 days with total of 870 mg. of metrazol. B, 19-year-old male, 3 year dementia praecox case, injected with total of 477 cc. of metrazol solution in 53 treatments. A, B, hyperplasia and hypertrophy of astrocytes. Cajal method. C, hyperplasia and hypertrophy of oligodendroglia in caudate nucleus with beginning degeneration of neurons. D, hypertrophic microglia in cerebral cortex

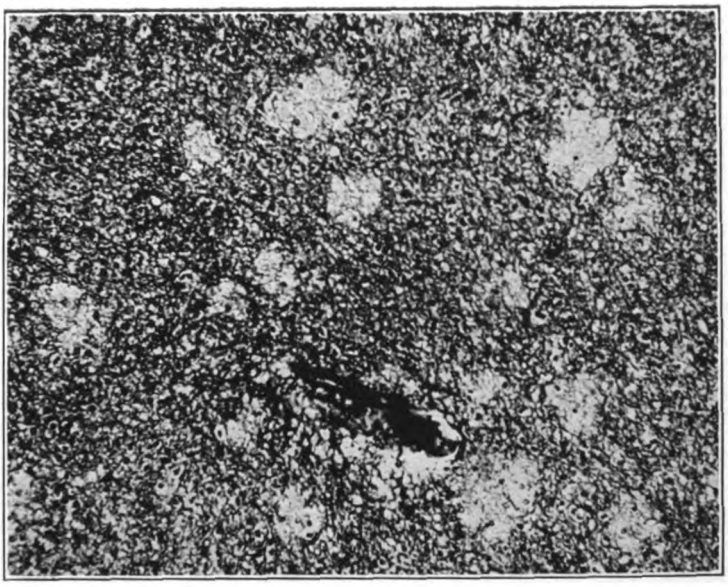


FIG. 174. CARBON MONOXIDE POISONING

Medulla oblongata. Van Gieson stain. Stasis in blood vessel, with perivascular edema. Multiple foci of edema in environment, with demyelinization

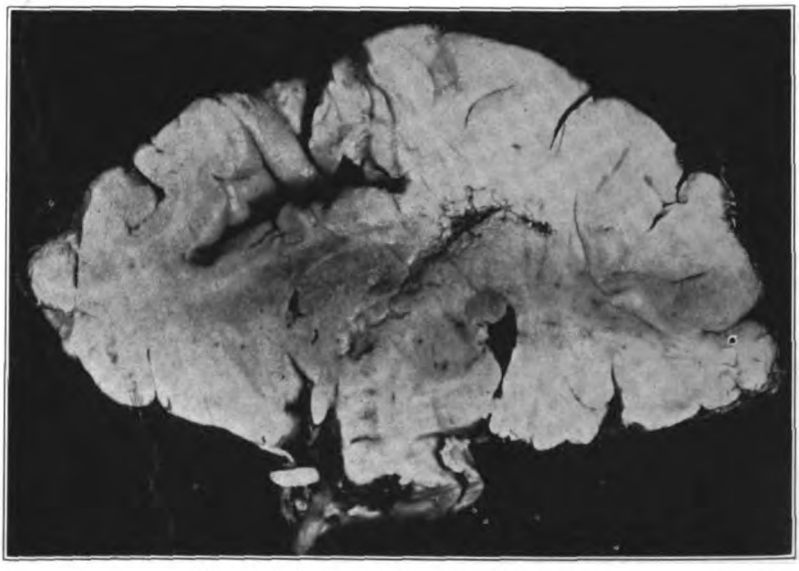


FIG. 175. CARBON MONOXIDE POISONING

After survival of several weeks following inhalation of automobile exhaust gas. Sagittal section through brain. Necrosis of internal capsule, extending into corona radiata of parietal region and into globus pallidus

Endogenous Intoxication

As in the preceding group, it is difficult to decide in endogenous intoxication whether the histopathologic changes observed in the central and peripheral nervous system are due to a direct toxic effect on the nervous structures or indirectly follow damage of the blood vessels.

MEAT POISONING

In meat poisoning (absorption of ptomaines from the gastro-intestinal tract) or in botulism, widespread swelling of the capillary endothelium of the brain, with ensuing disturbances of circulation, has been described. Experiments with Clostridium botulinum produced a marked degeneration of the cortical neurons, which reacted with swelling and chromatolysis (Schübel).

LIVER DISEASE

It is now generally conceded that following severe disease of the liver, with impairment of its physiologic function, brain disease develops. This may represent a direct toxic action of intermediary products of metabolism that escape detoxication in the liver, or lack of certain metabolic substances. Recent experiments in dogs (Weil and Crandall) have demonstrated that following ligation of the common bile duct the serum of these animals has a destructive effect upon rat spinal cord in test tube experiments, beginning approximately on the fourth day following the operation. The brains of such dogs, removed after two or three weeks, show generalized severe degeneration of the neurons, with simultaneous proliferation of the different types of glia and neuronophagia. There is also a hyaline degeneration of the vessel walls, and in some cases near the lateral ventricles, in others in the white matter of the cortex or in the striatum, a diffuse edema with formation of dense fibrous glia scars in some places. In human cases, following cirrhosis or yellow atrophy of the liver, or primary tumor or vascular obstruction of this organ, necrotic foci have been described in the striatum—a status spongiosus—with intense glia proliferation and hyalinization of the vessel walls and perivascular edema in the surrounding region. There is also widespread neuronal degeneration with neuronophagia. Active mesenchymal proliferation and perivascular cellular infiltration seem to be absent. Sometimes emphasis has been laid upon the occurrence of large pale oval or folded glia nuclei (Alzeheimer's glia cells), which also have been seen in the experiments in dogs. These cells have been demonstrated in about two-thirds of all cases of chronic liver disease in man (Stadler) (figs. 176, 177).

Wilson's Disease.—In this connection mention may be made of Wilson's disease and Strümpell's pseudosclerosis, which are considered identical diseases by most investigators. With few exceptions, marked cirrhosis of

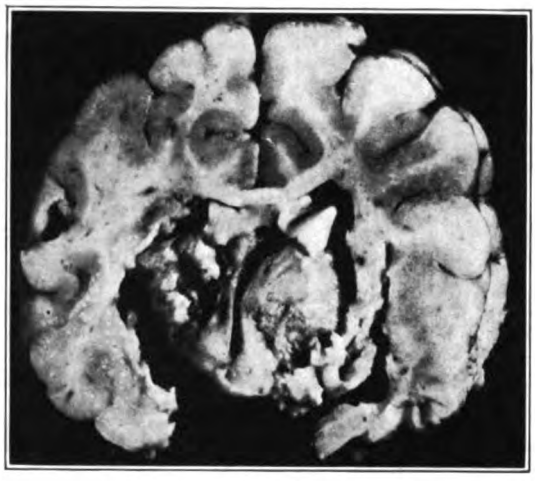


FIG. 176

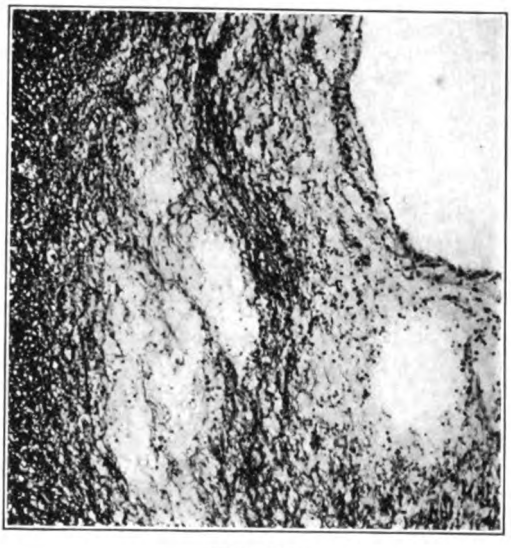


FIG. 177

FIGS. 176, 177. EXPERIMENTAL LIVER DISEASE

Ligation of common bile duct in dog. Brain removed after 21 days.

FIG. 176. Bilateral destruction of striate bodies.

Fig. 177. Another case. Spongy destruction with surrounding glia proliferation in wall of lateral ventricle. Weil stain

the liver has been found in such cases. The organ is small, with a granular surface. Microscopically a marked increase in connective tissue is seen, surrounding the atrophic and fatty-degenerated liver cells. In the brain a bilateral destruction of the striatum, with predilection for the putamen, is found. The latter structure may show only edema or a more severe cavity formation, with transition to complete breakdown. Wide empty spaces are found around the vessels, which may show hyaline thickening of their walls. In the surrounding areas, marked glia proliferation is seen, with

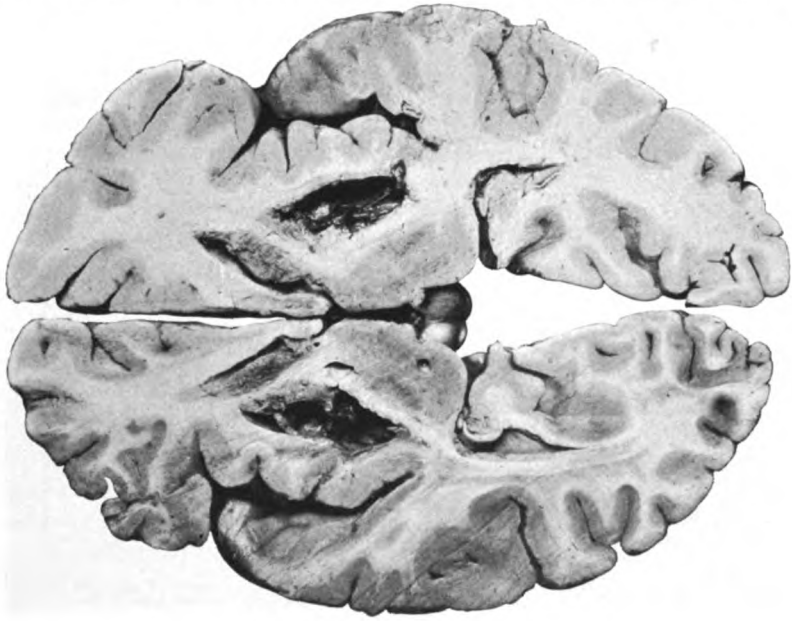


FIG. 178. WILSON'S DISEASE
Bilateral degeneration of putamen and globus pallidus
(*Goldstein, K.: in Handb. d. inn. Med., vol. 5, 1925. Courtesy Julius Springer*)

enlargement of the glia nuclei and formation of giant glia cells and gliophages. Compound granular corpuscles occur, but fibrous gliosis is mostly absent. The original conception of Wilson that these changes represent a localized disease of the putamen had to be corrected after similar degenerative changes were described in the nucleus caudatus and the cortex. Familial occurrence of these two diseases differentiates them from sporadic, isolated similar histopathologic changes in the brain in combination with severe liver disease. At present there is a division of opinion as to the relationship of the two organic diseases. One group assumes a toxic degenerative process of the brain following metabolic disturbances in con-

nection with disease of the liver. The other group sees in the appearance of brain and liver disease at the same time only a simultaneous expression of an inherited deficiency without any direct relationship between the two (fig. 178).

UREMIA

In uremia many histopathologic changes of the brain have been described; sometimes these may have been produced by an existing arteriosclerosis. That the toxic effect naturally is not produced by the accumulation of urea

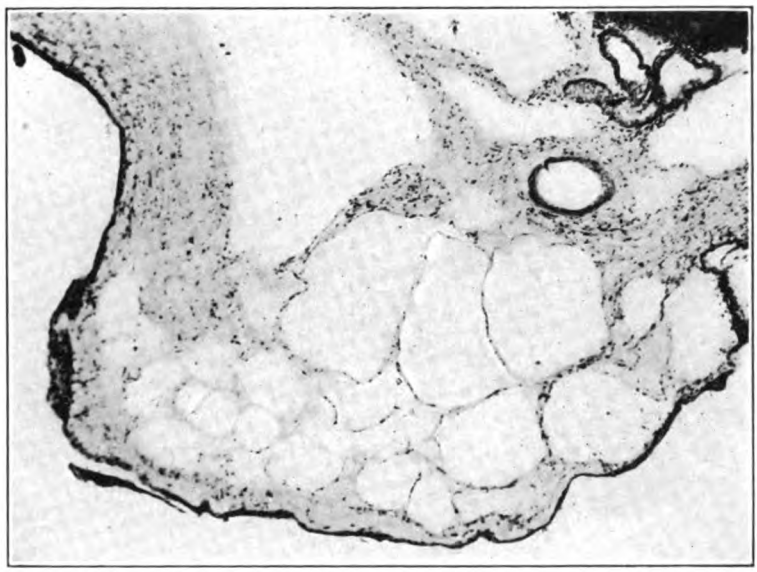


FIG. 179. UREMIA: EDEMA OF PIARACHNOID ("SEROUS MENINGITIS")
Van Gieson stain

alone, as was suggested, has been demonstrated in animal experimentation. The dysfunction of the kidneys, like that of the liver, leads to an accumulation in the circulation of numerous toxic products of metabolism that may act directly upon the nervous tissue or indirectly through the toxic effect upon the walls of the blood vessels, with ensuing nutritive disturbances. The diffusion of such toxic substances into the cerebrospinal fluid in uremia is demonstrated by its high creatine and uric acid concentration, which equals that of the blood. The toxic effect upon the vessel walls is revealed by fatty degeneration of the intima cells or hyaline degeneration of the media. Perivascular edema—accumulation of serous fluid with fibrin—

with and without generalized macroscopic edema of the brain, has been described in a large number of cases. In addition, the perivascular glia shows severe disease in the form of clasmatodendrosis followed by destruction of the astrocytes themselves. In sections stained by Cajal's gold sublimate method, such an area is characterized by its pale staining and spotted appearance (fig. 179).

The myelin sheaths may lose their staining qualities and scattered foci of demyelinization appear, along with only a mild glia proliferation. The neurons are diseased throughout. Pictures of ischemic disease, atrophy, and fatty degeneration predominate, leading finally to the disappearance of neurons in irregularly distributed foci. Organization of these foci (softening) is rarely seen—indicating either an insufficiency of the diseased glia or a very recent, perhaps agonal process. The cerebral cortex, striatum, and pons seem to be most severely though not exclusively involved. Atrophy of the choroid plexus, which was thought to indicate the place of elimination of the toxic substances (von Monakow), does not seem to be present in all cases. Further, the fibrous thickening of the piarachnoid covering the cortex is not as general as has been claimed.

AVITAMINOSIS

Inclusion here of a section on histologic changes in the nervous system following vitamin deficiency is only partly justified. We do not yet know whether the changes that have been described are due to a lack of vital substances, to a toxic effect of metabolic products, or to disease of other organs. Most of the material has been obtained from animal experimentation.

Recently it was reported that deficiency of vitamin A in the diet of laboratory animals led to retardation in growth of the skeleton—the skull and vertebral column included—while growth of the brain and spinal cord was not affected (Wolbach). This discrepancy led to herniation of the brain and distortion of the spinal nerve roots, with corresponding disturbances of nervous function. In man, deficiency of vitamin A seems to be a factor in night blindness.

More important for proper functioning of the nervous system is the vitamin B complex, especially B_1 (thiamine). The role of B_2 (riboflavin) and that of nicotinic acid are not yet entirely clear, though curative effects have been claimed for the latter in the treatment of pellagra and disseminated sclerosis. Vitamin B_6 (pyridoxine) also has been used with doubtful success in the latter disease, in parkinsonism, and in muscular disease. The therapeutic value of B_1 in the treatment of certain neuropathies has been established. Laboratory animals reared on a diet deficient in this vitamin develop paralysis of the extremities, and histopathologically a breaking down of myelin sheaths of peripheral nerves and the spinal cord is noticed.

Thiamine is essential in keeping up the glucose metabolism, e.g., in the myelin sheaths that of the galactolipids, which constitute about one-third of the lipids of the white matter. Thiamine acts as a coferment to the carboxylase that is necessary for the proper oxidation of glucose. Disturbance of this mechanism leads to accumulation of pyruvic acid and breaking down of the myelin complex (fig. 180).

Vitamin C (cevitamic acid) is more abundant in the brain of the fetus than in that of the adult: the fetal brain contains 73 mg. per 1000 Gm. of brain, the adult brain from 12 to 15 mg., the senile brain 7 mg. (Plaut and Buelow). Deficiency of this vitamin leads to scurvy, the hemorrhages of which may be responsible for the nervous and mental phenomena observed in this disease. Deficiency of vitamin D probably affects the central ner-

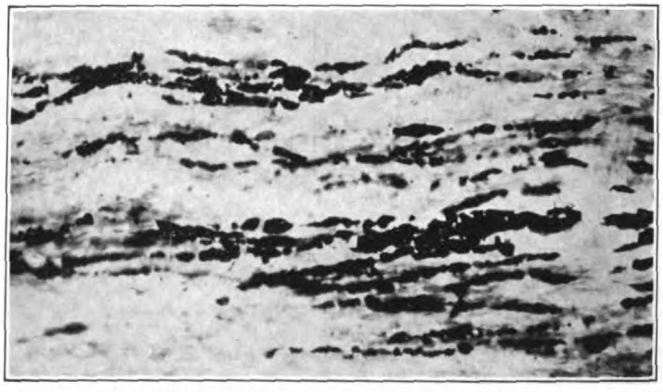


FIG. 180. DEGENERATION OF MYELIN SHEATHS IN AVITAMINOSIS
In rat fed for 45 days with diet deficient in vitamin B. Longitudinal section of spinal cord. Marchi method

vous system secondarily through the effects mainly of rickets in disturbing the growth of the vertebral column. Furthermore, the disturbed calcium metabolism probably is responsible for the convulsive seizures and the tetany.

Vitamin E (alpha tocopherol) was used in the treatment of amyotrophic lateral sclerosis (Wechsler), though there is still diversity of opinion as to the curative value of its effects, and nothing is known as to its influence upon the physiologic function of the nervous system.

SUBACUTE COMBINED DEGENERATION

Synonym: German, *funikuläre Myelose.*

This pathologic picture of the central nervous system is combined in approximately 90 per cent of all cases with pernicious (Addison-Biermer)

anemia and in nearly 100 per cent with achlorhydria. Pathologically, one finds an atrophy of the fundus glands of the stomach, which produce hydrochloric acid; at the same time, however, they also secrete another substance (X factor) that is essential in hemopoiesis. Absence of this factor leads to pernicious anemia and disturbance of the metabolism of myelin sheaths. Feeding of liver extract substitutes for this factor and leads to restoration of the normal blood picture and arrest of myelin sheath destruction. We must therefore assume that this essential "internal" vitamin is synthesized in the liver with the help of the X factor; it is not identical with thiamine.

The occurrence of subacute combined degeneration in connection with cancer of the stomach is explained by reason of the destruction of the fundus glands. Anemia in itself, i.e., lack of hemoglobin and oxygen, does not produce the disease. Similar histopathologic changes have been reported in ergotism and lathyrism; however, the etiologic factor in these cases is different.

The essential histopathologic feature of this disease is a severe destruction of the white matter of the spinal cord and, less frequently, of the brain. The bilateral symmetric distribution of the lesions in the spinal cord led earlier investigators to diagnose the condition as a systemic disease, a "funicular" myelitis. The disease process, however, begins with small foci of necrosis scattered throughout the posterior and lateral columns of the thoracic portion of the spinal cord and gradually spreads upward and downward. In the early stages, secondary degeneration of the ascending fibers in the cervical region and of the descending fibers in the lumbar region appears, following destruction of the corresponding axis-cylinders in the dorsal segments. In later stages the anterior columns and cervical and lumbar segments are likewise affected (figs. 181, 182).

The fatty degeneration of the vessel walls in these regions and the occurrence of petechial hemorrhages led earlier investigators to think that the disease of the nerve fibers was secondary to the vascular damage. But today the prevalent opinion seems to be that the degeneration of the vessel walls, of the nerve fibers, and of the glia is due to one and the same metabolic disturbance.

In early foci one may see in the white matter scattered areas with a sieve-like appearance (in German, *Lückenfelder*, "fields of holes"). The meshwork of these foci is formed by thin glia fibers. They surround large round scavenger cells that in sudan III sections are densely filled with fat globules. In these fields and their outer zones, intensely swollen and fragmented myelin sheaths are seen. Some of these stain diffusely, giving the appearance of becoming liquefied. The corresponding axis-cylinders show the same marked swelling and distortion in older lesions, but apparently not in

recent foci. The astrocyte nuclei within the foci are shrunken and hyperchromatic; their cytoplasm shows ameboid forms. Surrounding the foci there is a mild increase in glia nuclei and fine glia fibers in sections stained with victoria blue. However, this gliosis does not surpass in intensity the repair process in a secondary degeneration, and it does not invade the necrotic foci themselves. For this reason the older term—subacute combined "sclerosis"—is not justified (figs. 183–85).

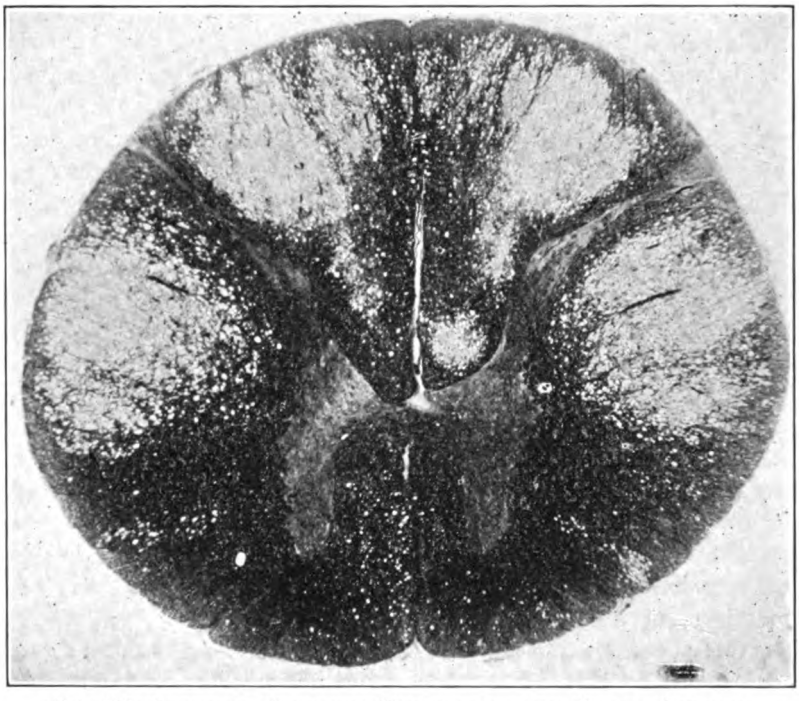


FIG. 181. SUBACUTE COMBINED DEGENERATION OF SPINAL CORD IN PERNICIOUS ANEMIA

Case of 8 months' duration. Transverse section through eighth dorsal spinal cord segment. Mallory stain. Areas of holes (*Lückenfelder*) in posterior and lateral columns

The blood vessels surrounded by the foci or in the immediate neighborhood may show hyaline changes of their walls. In the more remote zones there is a mild increase of the adventitial fibroblasts and infiltration with scattered small round cells. The piarachnoid shows a mild thickening without cellular exudates.

The areas of ascending degeneration in the posterior columns of the cervical segments or of descending pyramidal tract degeneration in the lumbar

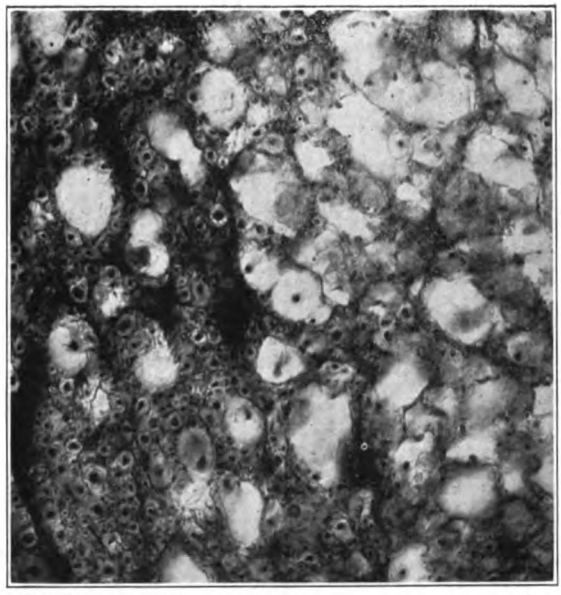


FIG. 182. SUBACUTE COMBINED DEGENERATION OF SPINAL CORD IN PERNICIOUS ANEMIA

Transverse section through anterior columns of dorsal spinal cord. Mallory stain. Intense swelling of myelin sheaths at right, in comparison with normal fibers at left

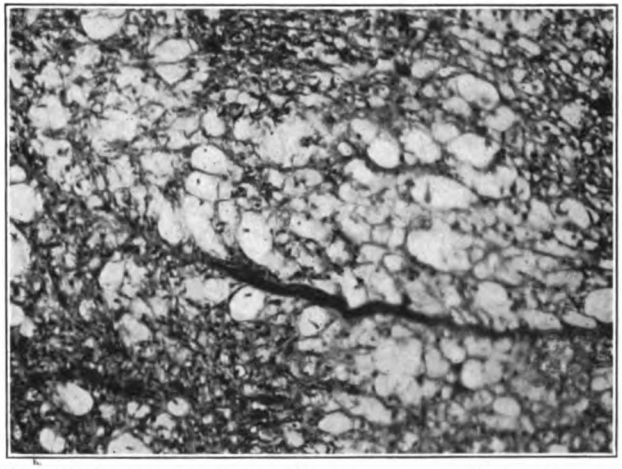


FIG. 183. SUBACUTE COMBINED DEGENERATION OF SPINAL CORD IN PERNICIOUS ANEMIA

Spongy appearance of spinal cord (*Lückenfelder*). Van Gieson stain

(Courtesy Archives of Neurology and Psychiatry)

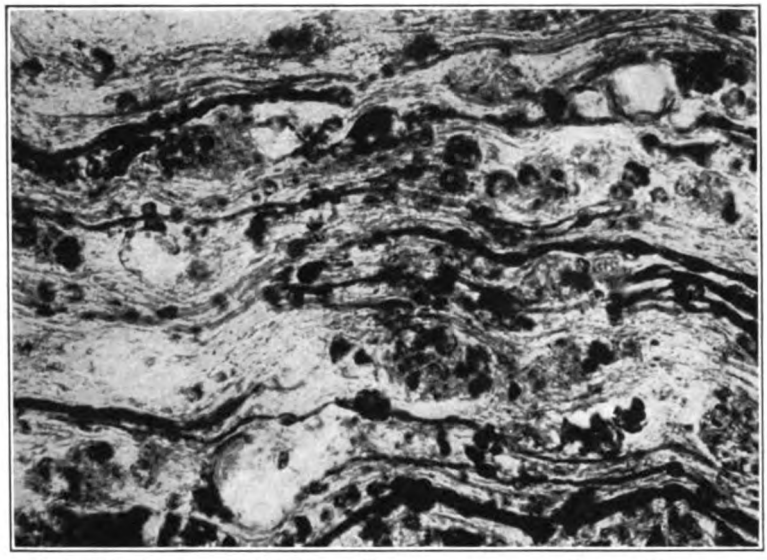


FIG. 184. SUBACUTE COMBINED DEGENERATION OF SPINAL CORD IN PERNICIOUS ANEMIA

Case of 8 months' duration. Longitudinal section through lateral column of dorsal spinal cord. Weil stain. Destruction of myelin sheaths: globular swelling and fragmentation

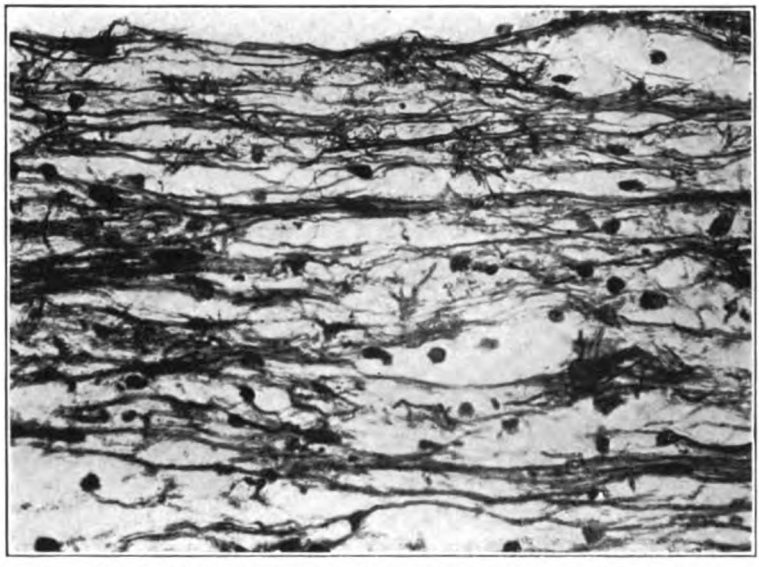


FIG. 185. SUBACUTE COMBINED DEGENERATION OF SPINAL CORD IN PERNICIOUS ANEMIA

Same case as in fig. 184, same segment. Anderson victoria blue stain. Spongy appearance without marked proliferation of fibrous glia

segments have a more homogeneous appearance and are easily differentiated from the sievelike foci. It seems that in older foci, in disease of long standing, a mild glia fibrosis may invade the necrotic areas from the periphery. It is claimed that under the influence of liver therapy such proliferation of fibrous glia is stimulated (Davison).

For the most part, the anterior horn cells are spared by the disease process. They may show retrograde degeneration following destruction of the anterior roots. In some cases of pernicious anemia, degeneration of peripheral nerves, with the picture of swelling and distortion of myelin sheaths and axis-cylinders, precedes the spinal cord disease, and the clinical picture changes accordingly.

The brain shows a different type of reaction. The large, empty foci of *Lückenfelder* are seen only occasionally in the white matter of the hemispheres. More frequent are foci of demyelinization around blood vessels, brain purpura, and perivascular glia proliferation. In cases that clinically presented severe psychosis, extensive neuronal degeneration has been described, combined with neuronophagia and intense glia proliferation.

It may be added that in tropical sprue, which shows clinically a blood picture of the pernicious anemia type, subacute combined degeneration of the spinal cord does not occur.

It has been claimed that leukemia may produce subacute combined degeneration of the spinal cord of the same type as that observed in Addison-Biermer (pernicious) anemia. But the older cases cited (Minnich, 1892; Müller, 1894; Nonne, 1897) did not show the typical *Lückenfelder* in the posterior and lateral columns. Only isolated foci in the posterior columns or very small multiple patches in the anterior and posterior columns, with swollen axis-cylinders and proliferated fibrous glia, were reported. Critchley and Greenfield (1930) described, as did Nonne, small areas of softening and fenestration, most pronounced in the dorsal segments. In longitudinal sections, however, these areas were round and did not show the long oval extension of the *Lückenfelder*. The axis-cylinders in the area and in the neighborhood were swollen, and it seemed therefore that they presented areas of myelomalacia that could not be compared with the typical areas of pernicious anemia. Myelomalacia—softening of the spinal cord—is frequently found in leukemia in combination with infiltration of lymphocytic masses (as in lymphosarcoma and lymphogranuloma) into the spinal cord, following the connective tissue septa into the spinal meninges and nerve roots. The pressure of the rapidly growing masses interferes with vascular and lymphatic circulation, and the ensuing anemia—or hemmorhage—results in edema and softening.

X

INJURIES

The Brain

The pathologic changes of the brain following injury will depend upon whether the skull is intact or fractured. In the latter case, infection may be added as a complicating factor.

CONCUSSION

The clinical symptoms following concussion do not always have their equivalent in histopathologic changes. Injury may occur directly through a fall on the head, a blow, a collision, or an explosion, or indirectly as a consequence of a punch on the chin or a fall from a height. In many cases the microscopic findings have been negative despite commotio cerebri with unconsciousness of several days' duration. The slight widening of the perivascular spaces of the cortical vessels, or of pericellular spaces around neurons, as described by some observers, are not specific and must be evaluated with great care in paraffin-embedded material. On the other hand, there have been reported, in carefully conducted experiments, definite histopathologic changes of neurons, the intensity of which was in proportion to the severity of the lesion and the time elapsed (Windle). It seems that the brain stem, especially the medulla oblongata, is always more affected in concussion than the cerebral cortex (Bernes).

In other cases, diffuse hemorrhages into the subarachnoidal spaces have been seen; these may be isolated or combined with hemorrhages along the cortical vessels. In the case of a localized blow, the tissue directly underlying the lesion may be more severely involved. Epidural hemorrhages combined with subarachnoidal and multiple petechial hemorrhages in the adjacent cortex have been described, together with similar cortical lesions at the pole of the brain opposite to the local injury (contrecoup) (figs. 186, 187). Sometimes the tissues in the immediate neighborhood of a localized concussion may be relatively intact, while extensive hemorrhage may be found in the basal ganglia, midbrain, or pons. If the patient survives the accident, softening and repair will follow in the areas affected by the vascular lesion, with histopathologic pictures that will be similar to those described above in relation to other hemorrhagic lesions. They may present themselves in the form of multiple foci of softening in the cerebral

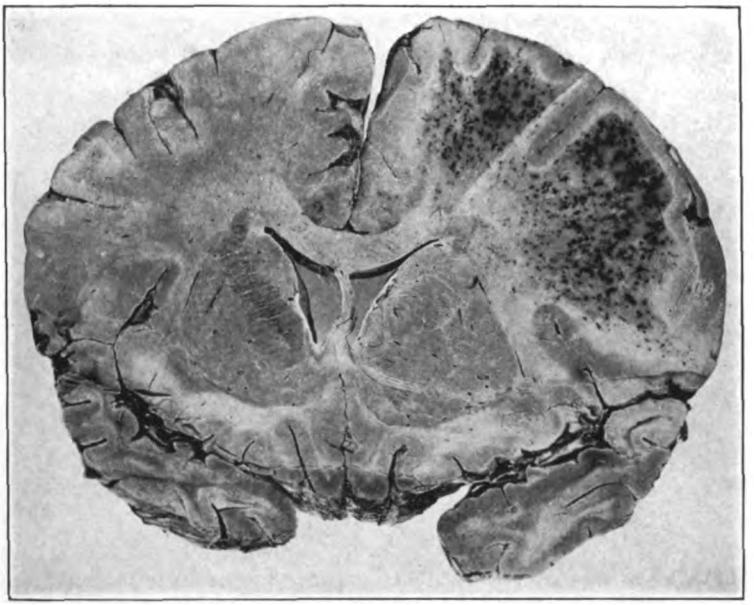


FIG. 186. BRAIN CONCUSSION

Result of airplane accident. Petechial hemorrhages confined to white matter of one cerebral hemisphere

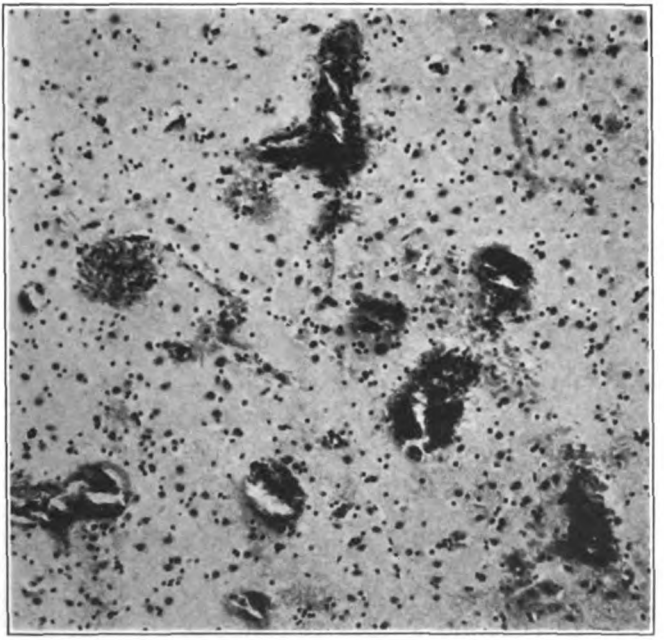


FIG. 187. BRAIN CONCUSSION

Result of automobile accident. Multiple perivascular hemorrhages in cerebral cortex. Van Gieson stain

and cerebellar cortex, or of simple disappearance of neurons in larger foci, with or without ensuing glia changes. Destruction of cortex without scar formation may produce the picture of état vermoulu ("worm-eaten state"), with formation of numerous small cavities surrounded by a thin fibrous glia wall. This process has also been described in arteriosclerotic brains. According to Spatz, in the latter case the destructive process affects a whole gyrus, while a traumatic lesion is localized on the crest of a gyrus only, with predilection for the lower surface of the frontal and temporal lobes. Extensive subdural hemorrhages are gradually encapsulated and absorbed. Subdural hemorrhages may lead to adhesions to the underlying cortex and localized scar formations. In some cases, where hemorrhage was absent, an accumulation of cerebral fluid was found underlying the focus of injury, at the site of the contrecoup, or more generalized serous meningitis was present.

In the brains of boxers who had been active over five years and who had frequently been "punch-drunk," traumatic encephalopathy was found in 60 per cent of cases, in the form of small cerebral and meningeal hemorrhages, parenchymatous scars, secondary degeneration, and glia foci.

SKULL FRACTURES AND BRAIN WOUNDS

In cases of fractured skull with direct lesion of the brain substance by bullets, knives, metal fragments, or other bodies, the pathologic picture is more complicated. Experimentally it has been demonstrated that lesions of the brain substance produced by sharp, cutting instruments heal under formation of a minute glia scar, while lesions caused by blunt instruments produce softening and intense mesenchymal proliferation. In the case of bullet wounds, however, the effect of the concussion produced by the impact of the rapidly moving bullet is added to the localized trauma. Therefore we must differentiate between the destruction of tissue in the immediate neighborhood of the wound and that in parts of the brain more removed from the lesion. In fresh lesions directly around the tube produced by the entering bullet, the brain tissue is edematous and loses its staining qualities. In the next zone, numerous hemorrhages around blood vessels intermingle with the necrotic brain tissue. In areas more remote from the lesion, there are found multiple small hemorrhages around capillaries and smaller arteries, with ischemic changes in the surrounding neurons, or one may see different stages of softening, varying with the length of time of survival. The further fate of such bullet wounds depends upon whether or not infection supervenes (fig. 188).

Healing of brain wounds under aseptic conditions can be studied relatively much better under experimental conditions or following operations.

A few days after the wound has been closed, intense proliferation of fibroblasts develops at the points where the skin is in direct contact with the underlying dura after the bone flap or the traumatic bone fragments have been removed. Numerous capillary sprouts develop at the same time, and a dense fibrous scar is formed, in which the piarachnoid is included and from which strands of fibrous tissue penetrate into the underlying cortex. From the latter a very intense proliferation of fibrous astrocytes advances into the connective tissue scar, forming with the mesenchymal fibers a densely entangled network. In the fresh scar, the mesenchymal fibers cannot be stained by van Gieson's method, but only by silver impregnation (Klarfeld-Achucárro); later, however, collagenous fibers are formed, the red staining of which by acid fuchsin indicates a more mature condition. This process

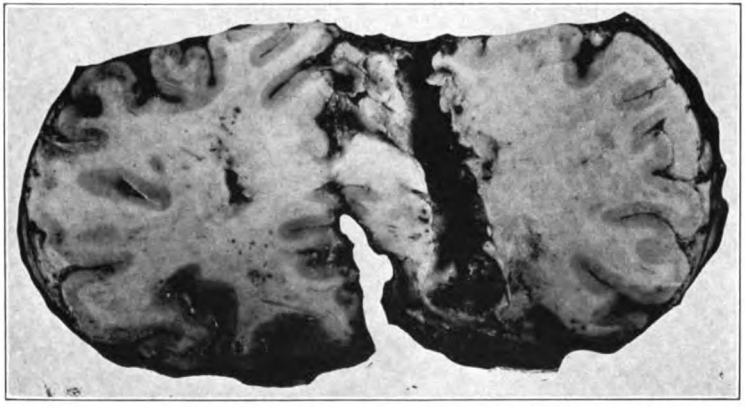


FIG. 188. BULLET WOUND THROUGH FRONTAL LOBE
After 1 month's survival

of repair may extend over many years. The connective tissue finally may become incrusted with calcium salts, offering considerable resistance to the cutting knife. Even metaplastic transformation into cartilaginous and bony structures has been described.

Like an organized focus of softening, these scars may frequently become infected, acting seemingly as bacterial traps. Such an infection may be localized for a long time, with liquefaction of part of the tissue and encapsulation of the abscess, or it may spread diffusely, producing a lethal meningo-encephalitis.

Small bone fragments, bullets, or operative sutures, if they are not infected, act as foreign bodies stimulating formation of an encapsulating wall

consisting of mesenchymal and glia fibers. Around fragments of silk sutures there may frequently be seen a formation of giant cells that have erroneously been described as tumor cells or Langhans cells of infectious granulomas (figs. 189, 214).

The Spinal Cord

Everything that has been said about injury to the brain applies also to the spinal cord. The functional disturbances following spinal cord lesion are

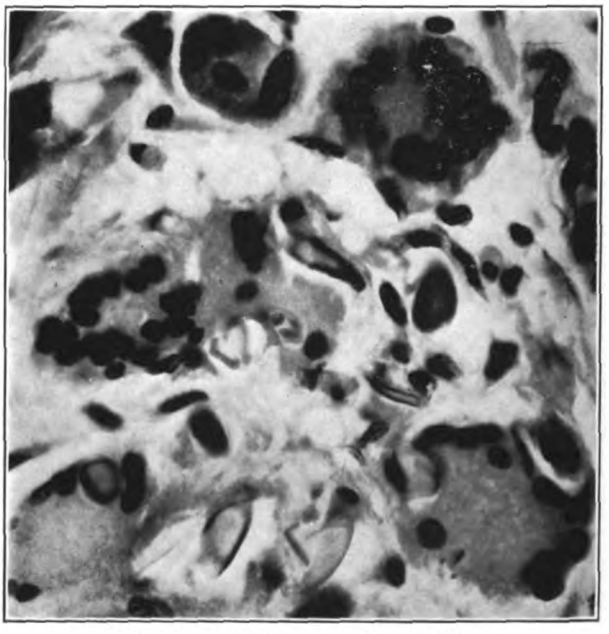


Fig. 189. Foreign Body Giant Cells
Formed around silk suture of peripheral nerve. Hematoxylin-eosin stain

usually severe and in the form of transverse segmental interruption of its fiber tracts.

CONCUSSION

Concussion of the spinal cord without fracture of the vertebral bodies may be produced by violence applied directly to the spine in the form of blows, a fall, a collision, or a bullet wound, or indirectly through a fall on the head or landing on the feet in a fall from a great height. Examination of the spinal cord usually reveals a diffuse swelling at the level of the direct lesion. The piarachnoid may be edematous or infiltrated with blood. In transverse

sections the spinal cord may present its normal configuration; in more severe cases of concussion the outlines of the gray matter may disappear and the cut surface may present a pulplike, softened appearance. A variation of this picture may be produced by the intermingling of small or large hemorrhages (hematomyelia) (fig. 190). As in concussion of the brain, these changes are not confined to the level of the direct lesion. In segments above and below scattered foci of softened tissue, petechial hemorrhages and

FIG. 190. HEMATOMYELIA

Destruction of posterior part of upper dorsal vertebrae by bullet; no direct lesion of spinal cord. Transverse section through dorsal spinal cord, segment below lesion. Hemorrhage into gray and white matter. Weil stain

cavity formation are found. These are accompanied by thrombus formation and stasis in the blood vessels.

Sudden fractures or dislocations of vertebrae may produce the histologic picture of concussion in addition to the severe damage at the site of the lesion. If the dura and piarachnoid are punctured in such cases, or as a result of bullet wounds, knife stabs, or surgical procedures, a condition similar to that following brain wounds is established. The process of healing is similar to that described in the case of operations, with formation of a dense connective tissue scar originating from the dura, and with the periostealand muscular tissue penetrating into the opened spinal canal.

consisting of mesenchymal and glia fibers. Around fragments of silk sutures there may frequently be seen a formation of giant cells that have erroneously been described as tumor cells or Langhans cells of infectious granulomas (figs. 189, 214).

The Spinal Cord

Everything that has been said about injury to the brain applies also to the spinal cord. The functional disturbances following spinal cord lesion are

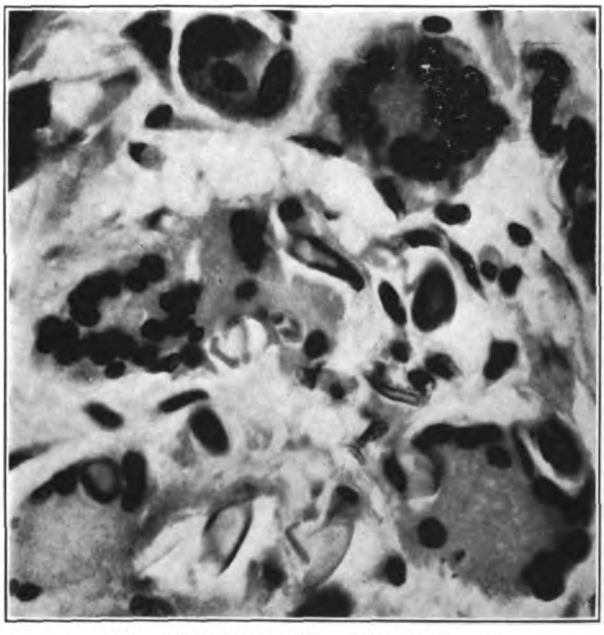


Fig. 189. Foreign Body Giant Cells
Formed around silk suture of peripheral nerve. Hematoxylin-eosin stain

usually severe and in the form of transverse segmental interruption of its fiber tracts.

CONCUSSION

Concussion of the spinal cord without fracture of the vertebral bodies may be produced by violence applied directly to the spine in the form of blows, a fall, a collision, or a bullet wound, or indirectly through a fall on the head or landing on the feet in a fall from a great height. Examination of the spinal cord usually reveals a diffuse swelling at the level of the direct lesion. The piarachnoid may be edematous or infiltrated with blood. In transverse

sections the spinal cord may present its normal configuration; in more severe cases of concussion the outlines of the gray matter may disappear and the cut surface may present a pulplike, softened appearance. A variation of this picture may be produced by the intermingling of small or large hemorrhages (hematomyelia) (fig. 190). As in concussion of the brain, these changes are not confined to the level of the direct lesion. In segments above and below scattered foci of softened tissue, petechial hemorrhages and

FIG. 190. HEMATOMYELIA

Destruction of posterior part of upper dorsal vertebrae by bullet; no direct lesion of spinal cord. Transverse section through dorsal spinal cord, segment below lesion. Hemorrhage into gray and white matter. Weil stain

cavity formation are found. These are accompanied by thrombus formation and stasis in the blood vessels.

Sudden fractures or dislocations of vertebrae may produce the histologic picture of concussion in addition to the severe damage at the site of the lesion. If the dura and piarachnoid are punctured in such cases, or as a result of bullet wounds, knife stabs, or surgical procedures, a condition similar to that following brain wounds is established. The process of healing is similar to that described in the case of operations, with formation of a dense connective tissue scar originating from the dura, and with the periostealand muscular tissue penetrating into the opened spinal canal.

There has been considerable discussion in the literature on the subject of brain and spinal cord lesions remote from the focus of trauma and on the absence of histologic changes in cases that clinically showed functional disturbances. On the one side, mechanical theories were advanced. It was suggested that the severe, sudden concussion might have produced a change of the colloidal make-up of the nervous elements, a "shaking up" of the colloidal particles, that resulted in a disturbance of function without necessarily producing microscopic changes. Others assumed changes of the membrane equilibrium of the neuron resulting from such colloidal changes or from changes of the electrical charge of the cellular membrane. The scattered foci of softening and hemorrhage were explained as due to laceration of nervous tissue following the sudden, earthquake-like motion. The histologic findings, however, did not always support such theories. The petechial hemorrhages were produced by diapedesis, not by rupture; and stasis in widened vessels was indicated microscopically by a homogeneous appearance of the blood cells, with disappearance of the outlines of the single cell and a reddish yellow staining of the mass of red blood cells in van Gieson preparations. The walls of such vessels may present a beginning necrosis, with disappearance of the nuclei of the muscular layers and finally hyalinization. Such findings have been cited in support of another theory, attempting to explain the histopathologic changes in concussion on the basis of circulatory disturbances. It is assumed that the sudden extension of vasomotor nerves, especially at the point of entrance of the cerebral and spinal vessels into the skull or the vertebral canal, or in their course through the subarachnoidal spaces, results in irreparable damage. The ensuing vasodilatation with stasis (spasm with ischemia, in the opinion of others) produces focal anemias with resulting softening. These last-named theories of a disturbance in vasomotor regulation would also explain the fact that sudden hemorrhages into the brain may occur many weeks after the concussion, during which time no functional disturbances have been noticed.

COMPRESSION

Compression of the spinal cord may be produced by dislocated or fractured vertebrae or intervertebral disks, by osteomas or chondromas of the vertebrae, by tumors or granulomatous masses invading the spinal canal, and finally by localized inflammatory processes of the meninges, by abscesses, cyst formation, or inflammatory reactions of the vertebral periosteum. In the case of a very slowly growing tumor, the spinal cord tissue may adapt itself to the gradually increased pressure, histologic damage may be very mild, and complete re-establishment of function may follow removal of the cause of compression. In rapidly growing infectious granulomas, a

localized toxic effect may be added to the mechanical compression owing to invasion of the spinal roots.

Macroscopically the spinal cord at the level of the compression may appear swollen, soft, mushy, and of a grayish red color. Microscopically the white matter appears sievelike and contains many empty spaces or meshes filled with compound granular corpuscles and fragments of myelin sheaths and axis-cylinders or cellular debris. In the regions around these foci the myelin sheaths and axons are swollen and partly disintegrated. There is only a mild fibrous gliosis around these foci. The blood vessels may be normal or show a mild hyalinization of their walls. In rare instances, severe hemorrhages or softening is found affecting the gray matter also. The alveolar zones may sometimes assume symmetric form and simulate at first sight a subacute combined degeneration of the pernicious anemia type. The segmental localization, however, and the absence of the typical extensive *Lückenfelder* help to establish the differential diagnosis. In some cases the myelopathy is not confined to the level of the compression. Distributed throughout the spinal cord there may be found isolated meshes filled with compound granular corpuscles, thickened vessel walls, and perivascular glia proliferation. Added to this picture is a secondary ascending and descending degeneration of posterior columns and pyramidal tract fibers, which, however, may be absent in a large number of cases. The neurons may show degenerative changes very early. Different stages of fatty degeneration may be found, without marked progressive glial reaction (figs. 191–93).

In the explanation of compression myelopathy, most authors agree that circulatory disturbances are responsible for the breaking down of the white matter. In the case of an extradural tumor or granuloma, the blood vessels supplying the spinal cord at the level of the invasion, and also the lymphatics of the spinal nerve roots, are compressed. Local anemia and stasis of blood and lymphatic fluid result, producing the edema and the damage of the sensitive myelin sheaths that have been described. This focal process in itself leads to the production of tissue debris, which may irritate the nervous tissue of the adjacent segment and thus be responsible for the microscopic changes reported as being found remote from the level of compression. This process may be compared to the inflammatory reaction in the region of a focus of anemic softening in the brain.

It is a disputed question whether some malignant neoplasms or granulomas (e.g., lymphogranuloma) act destructively upon the spinal cord *par distance* without invading the spinal canal, by producing toxins that invade the spinal cord by way of the lymphatics of the spinal nerve roots. But even invasion of the entrance of an intervertebral foramen will interfere with

There has been considerable discussion in the literature on the subject of brain and spinal cord lesions remote from the focus of trauma and on the absence of histologic changes in cases that clinically showed functional disturbances. On the one side, mechanical theories were advanced. It was suggested that the severe, sudden concussion might have produced a change of the colloidal make-up of the nervous elements, a "shaking up" of the colloidal particles, that resulted in a disturbance of function without necessarily producing microscopic changes. Others assumed changes of the membrane equilibrium of the neuron resulting from such colloidal changes or from changes of the electrical charge of the cellular membrane. The scattered foci of softening and hemorrhage were explained as due to laceration of nervous tissue following the sudden, earthquake-like motion. The histologic findings, however, did not always support such theories. The petechial hemorrhages were produced by diapedesis, not by rupture; and stasis in widened vessels was indicated microscopically by a homogeneous appearance of the blood cells, with disappearance of the outlines of the single cell and a reddish yellow staining of the mass of red blood cells in van Gieson preparations. The walls of such vessels may present a beginning necrosis, with disappearance of the nuclei of the muscular layers and finally hyalinization. Such findings have been cited in support of another theory, attempting to explain the histopathologic changes in concussion on the basis of circulatory disturbances. It is assumed that the sudden extension of vasomotor nerves, especially at the point of entrance of the cerebral and spinal vessels into the skull or the vertebral canal, or in their course through the subarachnoidal spaces, results in irreparable damage. The ensuing vasodilatation with stasis (spasm with ischemia, in the opinion of others) produces focal anemias with resulting softening. These last-named theories of a disturbance in vasomotor regulation would also explain the fact that sudden hemorrhages into the brain may occur many weeks after the concussion, during which time no functional disturbances have been noticed.

COMPRESSION

Compression of the spinal cord may be produced by dislocated or fractured vertebrae or intervertebral disks, by osteomas or chondromas of the vertebrae, by tumors or granulomatous masses invading the spinal canal, and finally by localized inflammatory processes of the meninges, by abscesses, cyst formation, or inflammatory reactions of the vertebral periosteum. In the case of a very slowly growing tumor, the spinal cord tissue may adapt itself to the gradually increased pressure, histologic damage may be very mild, and complete re-establishment of function may follow removal of the cause of compression. In rapidly growing infectious granulomas, a

localized toxic effect may be added to the mechanical compression owing to invasion of the spinal roots.

Macroscopically the spinal cord at the level of the compression may appear swollen, soft, mushy, and of a grayish red color. Microscopically the white matter appears sievelike and contains many empty spaces or meshes filled with compound granular corpuscles and fragments of myelin sheaths and axis-cylinders or cellular debris. In the regions around these foci the myelin sheaths and axons are swollen and partly disintegrated. There is only a mild fibrous gliosis around these foci. The blood vessels may be normal or show a mild hyalinization of their walls. In rare instances, severe hemorrhages or softening is found affecting the gray matter also. The alveolar zones may sometimes assume symmetric form and simulate at first sight a subacute combined degeneration of the pernicious anemia type. The segmental localization, however, and the absence of the typical extensive *Lückenfelder* help to establish the differential diagnosis. In some cases the myelopathy is not confined to the level of the compression. Distributed throughout the spinal cord there may be found isolated meshes filled with compound granular corpuscles, thickened vessel walls, and perivascular glia proliferation. Added to this picture is a secondary ascending and descending degeneration of posterior columns and pyramidal tract fibers, which, however, may be absent in a large number of cases. The neurons may show degenerative changes very early. Different stages of fatty degeneration may be found, without marked progressive glial reaction (figs. 191–93).

In the explanation of compression myelopathy, most authors agree that circulatory disturbances are responsible for the breaking down of the white matter. In the case of an extradural tumor or granuloma, the blood vessels supplying the spinal cord at the level of the invasion, and also the lymphatics of the spinal nerve roots, are compressed. Local anemia and stasis of blood and lymphatic fluid result, producing the edema and the damage of the sensitive myelin sheaths that have been described. This focal process in itself leads to the production of tissue debris, which may irritate the nervous tissue of the adjacent segment and thus be responsible for the microscopic changes reported as being found remote from the level of compression. This process may be compared to the inflammatory reaction in the region of a focus of anemic softening in the brain.

It is a disputed question whether some malignant neoplasms or granulomas (e.g., lymphogranuloma) act destructively upon the spinal cord *par distance* without invading the spinal canal, by producing toxins that invade the spinal cord by way of the lymphatics of the spinal nerve roots. But even invasion of the entrance of an intervertebral foramen will interfere with

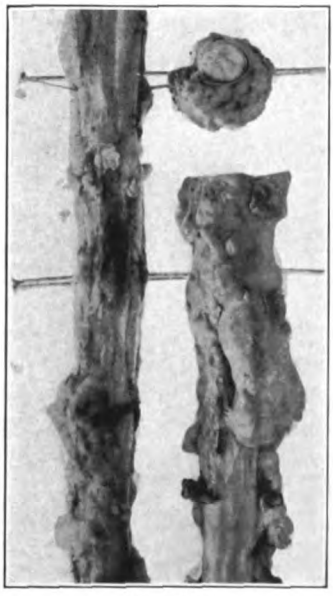


Fig. 191. Spinal cord with transverse section through dorsal segment. Lymphogranulomatous masses are seen outside of dura mater

Fig. 192. Transverse section through dorsal segment. Weil stain. Granulomatous tissue extradural. Myelopathy: edema of spinal cord, with formation of large fluid-filled spaces

FIG. 191

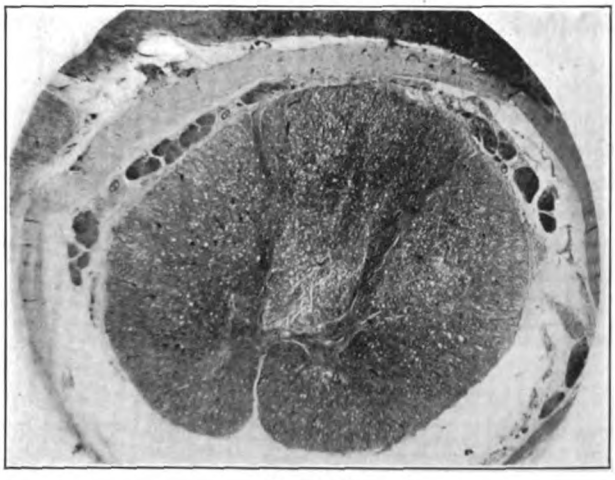


FIG. 192

FIGS. 191, 192. COMPRESSION OF SPINAL CORD: EXTRADURAL GRANULATIONS IN HODGKIN'S DISEASE
(Courtesy Archives of Neurology and Psychiatry)

the blood supply of the corresponding spinal cord segment. Furthermore, an analysis of a relatively large number of cases with concomitant spinal

cord disease has demonstrated that metastases to vertebrae and meninges were mostly responsible for the clinical symptoms and pathologic changes. In more than 80 per cent of cases of lymphogranulomatosis that had shown paraplegia clinically, the granulomatous masses had invaded the spinal canal, and the same applies to corresponding cases of leukemia.

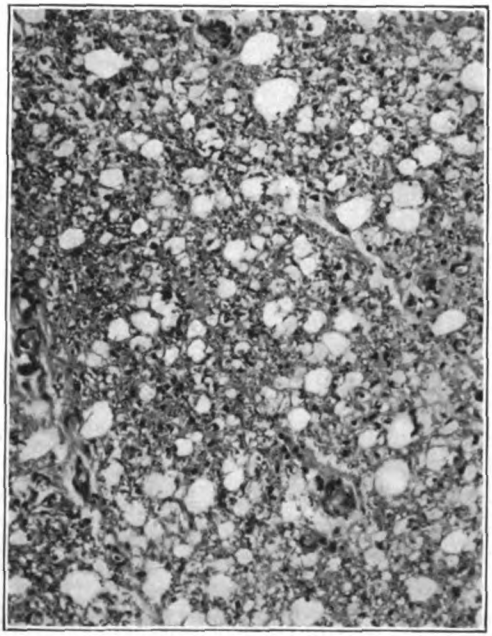


FIG. 193. COMPRESSION OF SPINAL CORD: EXTRADURAL GRANULATIONS IN HODGKIN'S DISEASE

Same case as in figs. 191, 192; longitudinal section through same segment as in fig. 192. Spongy-like appearance of spinal cord

THE PERIPHERAL NERVES

Injury of the peripheral nerves may be produced either by compression (due to tumor, aneurysm, callus formation, abnormal position in sleep, narcosis, or bandages and ligations), by tension with or without disruption (following a heavy fall, abnormal movement, or fracture of a bone), or by severance (as by a knife, a bullet, or bone fragments).

In the first case other, secondary factors, such as alcoholism or cachexia, may precipitate the neuropathy following compression of a peripheral nerve. It seems that long-continued, slowly progressing pressure upon a peripheral nerve, e.g., by a callus formation or an osteoma, produces first a fragmentation of the myelin sheaths and gradual disintegration of the axis-

cylinders without stimulating an active proliferation of the peri- and endoneurium, in a way similar to that demonstrated in animal experimentation by applying pressure of varying degree to peripheral nerves (Denny-Brown). Such mild neuropathies have been reported following long, continuous pressure upon the radial nerve in elderly or cachectic persons confined to bed for a long period of time. Disruption of a peripheral nerve in connection with a bone fracture or overextension has the same effect as severance by a cutting instrument or a bullet. The distal portion of the separated nerve undergoes wallerian degeneration. Regeneration after formation of a connective tissue scar between the two separated ends will depend upon the distance between them and upon the nature of the tissue, which may interfere with the formation of a neuroma (as muscle tissue, bone fragments). The histologic details of this process have been described above (chap. IV). Recovery following compression will depend upon the degree of damage of the axis-cylinders. It seems that when only demyelinization has occurred, repair may follow within a short time. Recovery of function in compressed peripheral nerves when there is complete paralysis of the muscles supplied, has been reported to have taken place within periods of from a few days up to several months.

Effects of X Rays, Heat, and Electrical Current

The ever increasing use of these three methods of physical therapy in the treatment of nervous and mental ailments justifies the addition of a separate section describing their effects upon nervous tissue. It is evident that the intense reactions in the form of shock and fever must produce definite organic changes in the nervous tissues, though we may not be able to demonstrate them under the microscope with our present day technic. Such changes, as has been emphazised above, will depend upon the intensity and duration of the treatment and upon the physical condition of the patient.

The effect of X rays upon the embryonic brain and upon the brains of young children differs from their effect upon adult tissue. It is known from animal experimentation that the growth of very young dogs and rabbits can be inhibited by application of excessive doses of X rays to the skull —an effect that may be due to lesion of the anterior lobe of the hypophysis. In such experiments the cortical neurons present degenerative changes and a diminution in number. Adult neurons and glia cells are resistant to the effect of doses as great as four times the maximal therapeutic dose. The mesenchymal derivatives are more sensitive. The capillary endothelium is damaged, hemorrhages and edema of the surrounding tissue being the result of this damage. Reports on animal experiments have indicated a destruction of the ependymal lining of the choroid plexus, with diminution of secretion of cerebrospinal fluid—an effect that has also been described as

following high dosage X-ray therapy of brain tumors. Radium has an effect upon the blood vessels similar to that of X rays. It has been reported that following implantation of radium in the brain tissue for more than three hours, degeneration of cortical neurons takes place, and longer applications may be followed by damage of the capillary endothelium, with ensuing multiple hemorrhages. Less intense radiation may result in transitory vasodilatation and exudation of red blood cells twenty-four hours later, together with perivascular lymphocytic infiltration and proliferation of capillary endothelium (Colwell and Gladstone).

The damaging effect of heat upon the nervous tissue may be observed in patients in whom excessive temperatures have been induced during short wave diathermy or who after exposure to excessive outside temperatures have suffered heat stroke. It seems that the danger zone is reached in a temperature of about 106 F. A tissue temperature higher than this, even for short periods, leads to severe damage, i.e., breaking down of capillary endothelium, followed by hemorrhages and severe neuronal disease in the form of acute swelling and liquefaction. In man concomitant disease of the vascular system will aggravate such conditions, as is evidenced by meningeal hemorrhages and cortical degeneration in the early stages of high fever treatment of general paresis.

The addition of electrical shock to the methods of treatment of dementia praecox has again raised the question of the damaging effect of this procedure. In animal experimentation (Heilbrunn and Weil; Alpers and Hughes) it could be demonstrated that frequently meningeal and parenchymatous hemorrhages occurred when the current used was just strong enough to produce a convulsive seizure. Similar types of damage have also been reported as following repeated electrical shock treatment in man (Neubürger, Whitehead, Rutledge, and Ebaugh; Alpers and Hughes). Such damage, however, should not be ascribed to the direct effect of the electrical current itself, but rather to excessive stimulation of vago-vasomotor centers of the medulla oblongata and to generalized disturbances of a circulatory and respiratory system that is already damaged owing to preceding disease (Alexander and Loewenbach).

The effect of X rays upon tumors has several different aspects. (1) The tumor cells themselves may be damaged and finally disintegrate. (2) The stimulation of connective tissue growth seems to play an important role in retardation of growth of the tumor cells. In certain gliomas, especially medulloblastomas, this stimulating effect upon the mesenchymal tissues is very pronounced. It seems that the favorable effect of smaller doses of X rays (from 15 to 20 per cent of the erythema dose) upon inflammatory conditions of the brain may also be ascribed to an increase in cellular exudation and to proliferation of fibroblasts and capillaries.

XI

DEGENERATIVE DISEASES

Most of the diseases that traditionally are classified as "degenerative" are represented by clinical symptoms produced by lesions of certain anatomic or physiologic units—lesions of obscure etiology, in which neither an infectious, toxic, or traumatic factor can be detected. The idea of a "defective anlage," of an "abiotrophy" or *Aufbrauch* ("wearing out") of the nervous parenchyma, does not satisfy the student who wants to know the cause of a disease in physical or chemical terms. With the progress of knowledge, some of these obscure diseases have been found to be associated with metabolic disturbances that are also present in other organs of the body. Familial amaurotic idiocy seems to be accompanied by a disturbance of the lipoid metabolism, with accumulation of sphyngomyelin in both neurons and glia cells. At the same time the process may produce similar disturbances in the liver and spleen (Niemann-Pick disease), or the brain and liver may be diseased independently. The muscular dystrophies now seem to be connected with a faulty creatine metabolism. Myotonia congenita and myasthenia gravis are today considered to represent disturbances of the interplay between acetylcholine and the myoneural junction. In Wilson's disease and in pseudosclerosis it is now certain that the liver disease is directly responsible for the pathology of the striatum. The stigma of an inescapable fate has thus been removed from a large group of "degenerative" diseases and it is hoped that with progressing etiologic knowledge others will be added to this group and therapy will become possible.

The histopathology of the degenerative diseases, with the exception perhaps of familial amaurotic idiocy, does not present any specific features that may not also be found in other nervous diseases of known etiology. The disease of the neurons in nuclear atrophies or in amyotrophic lateral sclerosis shows the same pathologic pictures as those seen in retrograde degeneration, in anoxemias, or in toxic processes. The breaking down of the nerve fibers, the removal of the debris, and the process of repair do not differ in Friedreich's disease or in amyotrophic lateral sclerosis from the same process in wallerian degeneration following interruption of a nerve fiber.

We know that certain of these syndromes may be produced or precipitated by infectious or vascular disease. Amyotrophic lateral sclerosis

has been seen following epidemic encephalitis or syphilis; the parkinsonnia syndrome may develop as an "idiopathic" degenerative form or as a disease of the nigra-pallidum system following arteriosclerosis or epidemic encephalitis. But the fact that only a small percentage of cases develop amyotrophic lateral sclerosis in syphilis, or parkinsonism in arteriosclerosis of the diencephalic and mesencephalic systems, compels us to assume a diminished resistance of these anatomic systems in the individual patient with respect to the syphilitic or encephalitic toxin or to the anoxemia (or endogenous toxins) of arteriosclerosis.

Such an inherited endogenous tendency may be limited to one individual of a family or it may occur in several as a familial trait. Different syndromes of degenerative nervous disease combined with degeneration of other organs may be observed in a family in members of different generations or among siblings only. In the latter cases the first manifestation usually occurs at the same age in the several individuals, a phenomenon that is especially striking in homozygous twins. The transmission may be sex-linked

TABLE 16.—*Transmission of Degenerative Diseases*

Dominant	Recessive
Hereditary spastic paralysis	Progressive muscular dystrophy
Hereditary cerebellar ataxia	Friedreich's disease
Hereditary familial spinal muscular atrophies	Myoclonus epilepsy
Myotonia congenita	Familial amaurotic idiocy

in progressive muscular dystrophy, as occurs in hemophilia, or it may be either recessive or dominant. Table 16 lists some examples of the two last-named types (Bauer).

A classification of the degenerative diseases of the nervous system may be based either on the predominant clinical symptoms (muscular atrophy, spasm, ataxia, chorea, athetosis), on the anatomic structures that are chiefly involved (gray matter, white matter, or both combined; peripheral nerves), or on the underlying disturbance of metabolism (lipoid, protein, creatine, acetylcholine, etc.). The last-named classification would be the most satisfactory one from an etiologic point of view, but the state of our knowledge at present is not advanced enough for such a venture. The anatomic classification is not altogether satisfactory because a given disease may begin as a degeneration of either the gray or the white matter (amyotrophic lateral sclerosis), or only the primary degeneration of a peripheral nerve may be apparent, as in some types of familial optic atrophy (Leber's disease), in which frequently a narrow optic foramen in combination with oxycephaly is the essential etiologic factor. Besides, in some diseases that

at present are classified as degenerative and that do not occur in a hereditary form, the etiologic factor is still in doubt.

In accordance with tradition, though with some reluctance on the part of the writer, the section below is based on the grouping of clinical syndromes rather than of disease entities with a common etiology. It should always be remembered that some of these syndromes may also be produced by infection, intoxication, or vascular disease affecting certain groups of nuclei or fiber tracts.

In order to establish the diagnosis of a disease as a heredofamilial condition, the following four points should be established (Londe, Jendrassik, Higier, Bing): (1) homologous heredity—i.e., several members of the same generation show the same type of disease; (2) homochronous heredity—i.e., the disease is found to appear at approximately the same age in different members of the family; (3) absence of endogenous etiology, trauma, intoxication, and infection—i.e., possibility of any of these as a primary factor during intra- or extra-uterine life must be ruled out; (4) steady progression, from the first appearance of the disease.

The Muscular Dystrophies

Because of their close relationship to other clinical forms of muscular atrophy, the primary myopathies or dystrophies are usually included in a textbook on diseases of the nervous system. They are differentiated from the amyotrophies, which represent secondary atrophy and degeneration of muscle fibers following disease of the lower motor neurons.

The three myopathies to be described are: (1) dystrophia musculorum, or progressive muscular dystrophy; (2) dystrophia myotonica (myotonia atrophica); (3) myotonia congenita, or Thomsen's disease. These all occur as heredofamilial diseases, but sporadic cases have also been described.

Though it is generally recognized that the muscular dystrophies are independent of lower motor neuron lesions, there is a division of opinion as to whether the myopathy is really a primary degeneration of striated muscle fibers or whether it is dependent upon disturbance of the vegetative nervous system, which regulates the metabolism of the muscle fibers. That metabolic disturbances play a role is evident from the increase in creatine output and the fact that feeding of glycocoll (amino-acetic acid) seems to increase elimination of creatine. After prolonged adminstration of glycocoll the creatine output falls back to the control level, and at the same time a clinical improvement begins (Band, Sandberg, and Ringer).

DYSTROPHIA MUSCULORUM

There is a definite chemical change in the dystrophic muscles; phosphagen has nearly completely disappeared, and there is a low content of potassium,

glycogen, lactic acid, and water. Macroscopically the diseased muscles may either be atrophic or show increase in size (pseudohypertrophic form) owing to a proliferation of connective tissue and fat. The dystrophic muscles can easily be differentiated from the normal muscles by their pale color, described as that of fish muscle.

The muscles most frequently affected are the pectoralis major (pars sternocostalis) and minor, latissimus dorsi, serratus anterior, rhomboideus, trapezius, sacrospinalis, deltoideus, biceps brachii, brachialis, brachioradialis, glutaei, quadriceps femoris, adductor longus, and peronei. Pseudohypertrophy is frequently seen in the glutaei, gastrocnemius, sartorius, deltoideus, triceps brachii, infraspinatis, and orbicularis oris (Bing).

Microscopically, there is no difference between the diseased muscle fibers in the two forms, the atrophic and the pseudohypertrophic. It seems that in the first stages of the disease a swelling of the muscle fibers takes place. Many large fibers measuring from 100 to 200 microns in transverse diameter are found, while the normal variation is from 20 to 80 microns, with an average of from 20 to 60 microns in 90 per cent of the fibers. Later, with degeneration of the diseased fibers, the muscle becomes atrophic, and in a transverse section most of the fibers measure between 7 and 15 microns. The striatum is well preserved, even in very atrophic fibers. The nuclei are considerably increased in number, both those in the sarcolemma and those within the fibers. According to Heidenhain and Slauck, the increase of the latter (*Binnenkerne*) is characteristic for a dystrophic muscle fiber and is not present in a secondary atrophy (amyotrophy). Finally, the muscle fibers break down, become fragmented, and undergo fatty degeneration. The perimysium internum is increased and contains numerous foci of accumulated nuclei, and its blood vessels show thickening of their walls (fig. 194).

DYSTROPHIA MYOTONICA

The therapeutic effect of quinine upon the myotonic contractions has led to the theory that we are dealing here with a disturbance of the acetylcholine innervation of the striated muscles. Apparently there is either a deficiency in cholinesterase or an abundant production of acetylcholine. Since the content of esterase in the blood is normal, the second possibility is more likely. On the other hand, in myasthenia gravis there is apparently an overproduction of esterase, which destroys the acetylcholine before it has time to act. Consequently, the beneficial effect of prostigmine, which inhibits the esterase action, lends support to such a theory. Though quinine has a favorable influence upon the myotonic reaction, it has no influence upon the atrophy of the muscles involved. The histologic picture of these muscles seems to be essentially the same in progressive

muscular dystrophy and in dystrophia myotonica. The latter is characterized by a combination with endocrine disturbances (testicular atrophy and changes in the thyroid and pituitary), presenile cataract, and disturbances of the vegetative nervous system (hyperhidrosis, increased secretion of tears and saliva, early baldness, and general skeletal atrophy). Progressive muscular dystrophy is relatively often combined with congenital muscular defects and deformities or atrophies of the skull, jaw, or other bones, pointing to a generalization of the defective anlage. It should be added that in some cases mild disease of anterior horn cells and reduction in their number have been reported. However, it seems impossible to decide whether such findings, which are not the rule, may not indicate

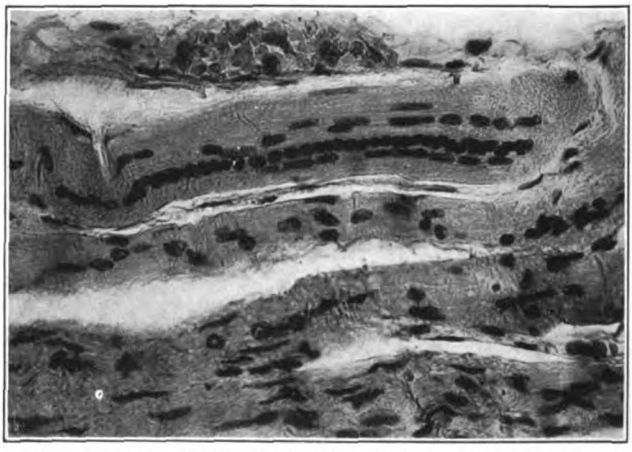


FIG. 194. DYSTROPHIA MYOTONICA (MYOTONIA ATROPHICA)

Longitudinal section through pectoralis major muscle. Hematoxylin-eosin stain. Increase of intrafibrillary nuclei, which form long chains. Beginning degeneration of other muscle fibers, with loss of striation

retrograde degeneration following involvement of the nerve endings and the distal part of the muscular nerve in the process of perimysium proliferation and vascular disease. By some authors, this disease is considered to be the chronic stage of myotonia congenita.

MYOTONIA CONGENITA

In myotonia congenita (Thomsen's disease) the diseased muscles are hypertrophic but not much changed macroscopically as to color, though they may be somewhat paler than usual. Microscopically, hypertrophy of the primitive muscle fibers is the outstanding feature. Their diameter may vary from 30 to 140 microns. The form is round instead of showing the

normal polygonal shapes. In longitudinal sections the transverse striation is indistinct. The sarcolemma nuclei are considerably increased in number, up to four times the normal count. They seem to be enlarged and their outlines are hazy. The perimysium internum shows a mild proliferation. While hypertrophy is the rule, some muscles may show atrophy, which seems to follow the hypertrophy. The primitive muscle fibers become atrophic and their striations disappear. Reports on the condition of the central nervous system in cases that have been more systematically investigated, indicate that no central nervous disease was present.

MYASTHENIA GRAVIS

The etiology of this muscular disease has been discussed above. Not much can be added concerning the pathology. The muscular atrophy may attain varying degrees and may sometimes be absent. In numerous cases, lymphocytic infiltrations are found between the muscle bundles (lymphorrhagia). It has been suggested that this reaction has some connection with the enlargement of the thymus observed in about one-half of the cases. This enlargement may represent either a persistent thymus, a simple hyperplasia, or a tumor.

The Amyotrophies

The clinical entities included in this group are progressive neuropathic (peroneal) muscular atrophy (Charcot-Marie-Tooth), progressive muscular atrophy, and amyotrophic lateral sclerosis. The common feature of the three groups is the muscular atrophy following disease of lower motor neurons. The wasting of the muscles is usually easy to recognize macroscopically. They are flaccid and of a pale color. The microscopic picture shows a marked diminution of muscle fibers, with increase of connective tissue and fat. Most of the remaining fibers are small, the striation is only partly preserved, and some of them present only empty sarcolemma tubes. In Marchi preparations, advanced fatty degeneration is seen. Hypertrophic fibers are encountered occasionally.

The clinical types are differentiated pathologically according to which of the lower motor neurons are involved.

PROGRESSIVE NEUROPATHIC (PERONEAL) MUSCULAR ATROPHY

This type was considered by the first writers on the subject to be a primary neuropathy of the peripheral nerves of heredofamilial type, involving five times as many males as females. With an increasing number of autopsies, many changes in the spinal cord were described—atrophy of anterior horn cells and Clarke's columns, as well as degeneration in posterior and lateral columns and in both anterior and posterior roots and spinal

ganglia. It seems, however, that the degenerative processes in the peripheral nerves, in the form of demyelinization and degeneration of axis-cylinders, together with an increase of the endoneurium, are relatively more prominent (fig. 195). The clinical picture, showing the beginning of the muscular atrophy in the feet and hands and finally involvement of the lower parts of the legs and arms, was not always accompanied by histologic

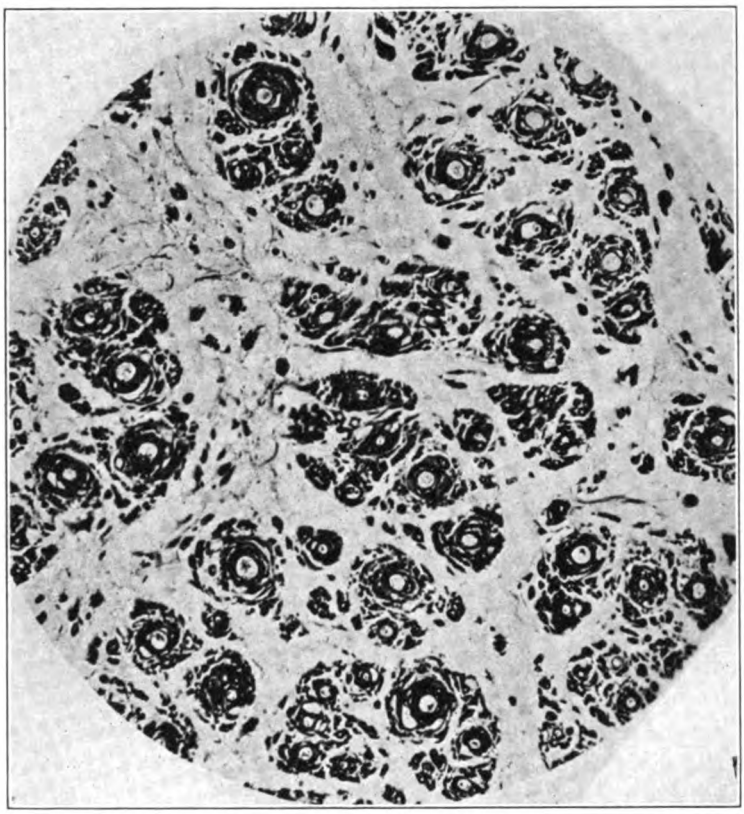


FIG. 195. PROGRESSIVE NEUROPATHIC MUSCULAR ATROPHY (PROGRESSIVE HYPERTROPHIC NEURITIS OF PERIPHERAL NERVE)

"Onion skin" proliferation of endoneurium around nerve fibers: probably proliferation of Schwann sheath cells, together with hyperplasia of mesenchymal endoneurium and production of collagen. Van Gieson stain

changes that might have explained the disturbance of function. Therefore some authors classified this disease with the dystrophies.

PROGRESSIVE MUSCULAR ATROPHIES

The following types are customarily differentiated among the progressive muscular atrophies: (1) spinal progressive muscular atrophy, with two

subdivisions—the Aran-Duchenne classic type and the Werdnig-Hoffmann infantile type; (2) the bulbopontine type, or progressive labioglossopharyngeal paralysis (bulbar palsy); (3) the pontomesencephalic type, or chronic progressive primary nuclear ophthalmoplegia.

Theoretically, manifold combinations of degeneration of motor nuclei in the spinal cord and the brain stem are possible as the bases for a variety of clinical syndromes. Indeed, if the literature on this subject is studied, it will be found that, in addition to pure type forms, many variations have been described—with the reporting neurologist in each instance endeavoring to establish the form as a new clinical entity. Furthermore, the degenerative etiology has not in every case reported been proved beyond any doubt. The classic or Aran-Duchenne type occurs only very rarely as a heredofamilial disease. In the previous history of the patient poliomyelitis is frequently mentioned. Earlier authors assumed that a locus minoris resistentiae had been created in the anterior horn cells after the disease had subsided. But we know from modern experimental investigation (Warburg) that this disease may assume a chronic, slowly progressive character and that the virus perhaps becomes latent over long periods. The second and third groups include cases in which the condition was combined with tabes dorsalis or general paralysis, indicating a syphilitic etiology. On the other hand, there have been reports of instances in which the disease began in early childhood and showed a heredofamilial character. The Werdnig-Hoffman type of progressive muscular atrophy seems to be predominantly of the latter etiology; sporadic cases are the exception. The disease begins in the first years of life. The muscles of the pelvis and the back are first involved. The atrophy affects next the iliopsoas and quadriceps, then the shoulder and neck, and finally the peripheral parts of the extremities. Oppenheim's disease (amyotonia congenita) is now considered another example of this type that occurs at birth or very early in life.

The great variety of the clinical pictures is in contrast to the uniformity of the histologic findings. The anterior horn cells of the spinal cord segments corresponding to the atrophic muscles, or, similarly, the neurons of the corresponding motor nuclei of the brain stem, present different stages of degeneration. Increase of lipofuscin, shrinkage (sclerosis), or complete disappearance of the motor neuron is seen. There is only a mild, progressive glia reaction. Marked perivascular cellular infiltrations, intense proliferation of fibrous glia, and neuronophagia appear; these changes always lead one to suspect an infectious or toxic etiology. This latter histologic picture differentiates amyotrophic lateral aclerosis in combination with myelitis from the degenerative "idiopathic" type. The degeneration of the anterior horn cells in progressive muscular atrophy is combined with degeneration of endogenous fibers in the anterior lateral columns and sometimes of the pyramidal tracts. The close relationship between spinal pro-

gressive muscular atrophy and amyotrophic lateral sclerosis is indicated by cases of the first group that did not show pyramidal tract disease clinically, but in which microscopic examination demonstrated beginning demyelinization in the corticospinal tracts.

AMYOTROPHIC LATERAL SCLEROSIS

In amyotrophic lateral sclerosis the combination of anterior horn cell disease and pyramidal tract degeneration shows a great variety of forms. The degeneration of the anterior horn cells, frequently with central chromatolysis, may dominate the histologic picture, and the pyramidal tract degeneration may be indicated only by a mild Marchi reaction without any marked paling in sections stained for myelin sheaths. In other cases, only one pyramidal tract may be severely affected, while the other may show merely mild swelling of isolated myelin sheaths. Usually, the anterior and crossed pyramidal tracts are involved. Usually the degeneration, if studied in sections stained for myelin sheaths, does not seem to proceed into the medulla oblongata or the pons. In Marchi preparations, however, the evidence of a gradual slight destruction of the myelin sheaths can be followed into the internal capsule or even the precentral area of the cortex. In the spinal cord, the demyelinated area is not sharply defined as in secondary pyramidal tract degeneration, but other fiber tracts in the region (rubrospinal, spinothalamic, and even spinocerebellar) may also be affected. The fibrous glia proliferation in the degenerated areas is only very mild, and the slowly progressive destruction does not stimulate an excessive formation of compound granular corpuscles. Corresponding to the fiber degeneration progressing centrad from distal spinal cord segments, there is a neuronal degeneration that only in the final stages proceeds to the motor nuclei of the medulla oblongata and the pons. The prerolandic area is sometimes distinctly atrophic, in contrast to the well preserved other gyri. The Betz cells may be intact or may present pictures of progressive degeneration similar to that found in the anterior horn cells (figs. 196, 197).

The Heredofamilial Ataxias

The originally well defined entities of this group have suffered the same fate as other disease syndromes of heredofamilial origin. The first of the authors who have described them assumed that a definite pathologic lesion had to be correlated with each different clinical manifestation. Only after many cases had been studied did they find that every schematization was useless, that manifold combinations with other diseases of the group existed. We have already illustrated such a situation in the combinations of the amyotrophies with pyramidal tract disease; the heredofamilial ataxias offer

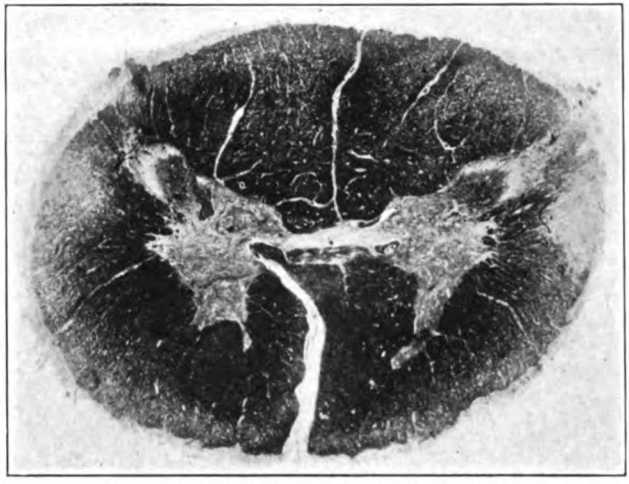


FIG. 196. AMYOTROPHIC LATERAL SCLEROSIS

Transverse section through lumbar segment. Weil stain. Degeneration of both pyramidal tracts and atrophy of anterior horns, more marked on right

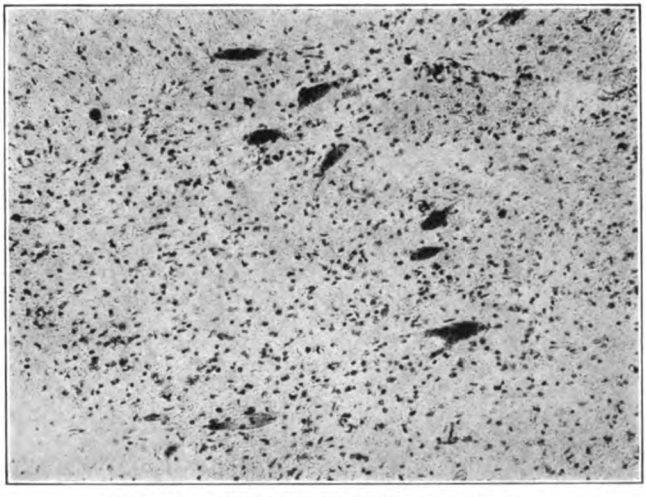


FIG. 197. AMYOTROPHIC LATERAL SCLEROSIS

In case with associated cerebrospinal syphilis. Anterior horn of cervical segment. Cresyl violet stain. Reduction in number of anterior horn cells; mild degenerative changes of remaining ones. Increase in glia nuclei

another example. Originally, two entities were described—spinal hereditary ataxia (Friedreich's disease) and cerebellar hereditary ataxia (Pierre Marie). On the basis of his first 3 cases, Friedreich assumed that degeneration of the posterior columns was responsible for the clinical manifestations he had observed. Later, degeneration of the spinocerebellar tracts, of Clarke's columns, and of the pyramidal tracts was described. In other cases, the whole spinal cord was found to be extremely small, with the main atrophy confined to the white matter. In addition, degenerative

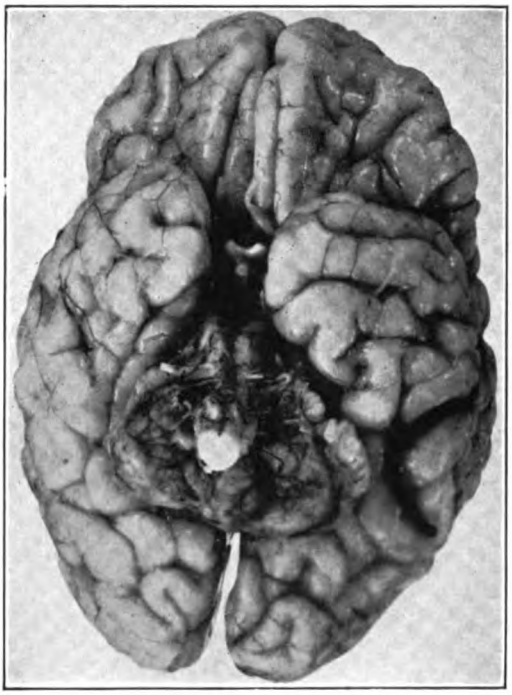


FIG. 198. CONGENITAL CEREBELLAR ATROPHY
Brain of boy aged 1 month. No history of familial disease

processes in peripheral nerves, in combination with progressive muscular atrophy, have been reported.

Cerebellar hereditary ataxia was correlated with cerebellar atrophy and a normal spinal cord in the first descriptions of Pierre Marie. He also described histologic changes in the atrophic cerebellum—diminution in the number of neurons and complete loss of Purkinje cells. Later, however, there were reports of cases in which cerebellar atrophy was combined with the spinal cord condition of Friedreich's disease, or in which the histologic

picture of the cerebellum was normal; or a case that clinically did not show any sign of a cerebellar ataxia was found to present a very small cerebellum, with a 70 per cent reduction in weight. The cause of such atrophy may be hypoplasia, cortical atrophy, total atrophy, systemic atrophy (atrophia olivopontocerebellaris), or sclerosis of the white matter (Scherer). The atrophic process frequently starts at the base of the cerebellum and replaces molecular layer and Purkinje cells by glia proliferation (Aranovich).

Many authors comment on the fact that the amount of fibrous glia reaction in the degenerated posterior and lateral columns in Friedreich's disease exceeds by far that usually seen in other primary degenerations (e.g., amyo-

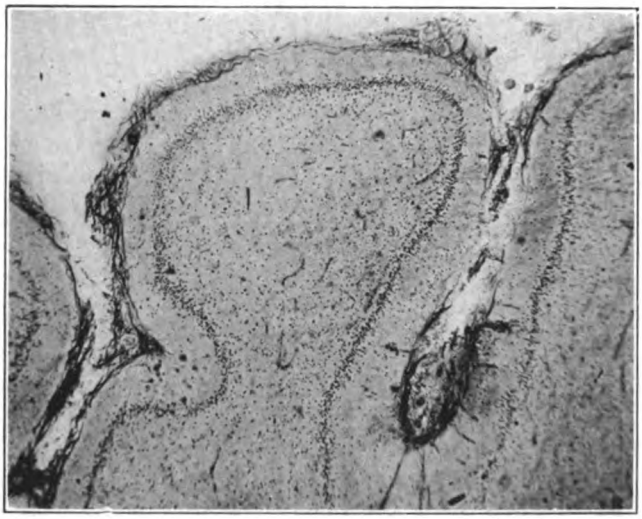


FIG. 199. CONGENITAL CEREBELLAR ATROPHY

Case of hereditary cerebellar ataxia (Marie). Section through cerebellum. Cresyl violet stain. Absence of Purkinje cells. Granular layers poorly developed

trophic lateral sclerosis). French pathologists were the first to describe the dense whorl formations seen in these areas in transverse sections of the spinal cord. It is of interest to mention in this connection that Dejerine and Sottas described two sisters who clinically presented the picture of Friedreich's disease combined with sensory disturbances and muscular atrophy: as found at autopsy, a degeneration of the posterior columns similar to that in tabes dorsalis and a very intense proliferation of the endoneurium in the peripheral nerves, together with degeneration of the nerve fibers, were responsible for the two last-named disturbances. Both the spinal cord glia proliferation of Friedreich's disease, and the endoneurial proliferation of the Dejerine-Sottas "interstitial hypertrophic progressive

neuritis," have been thought by a number of authors to be responsible for the degeneration of nerve fibers.

CHOREA

CHRONIC PROGRESSIVE CHOREA (HUNTINGTON)

The theories concerning the pathology of the hereditary form of chorea have changed considerably. Thirty years ago the atrophy of the brain was considered to be produced by a "chronic hemorrhagic meningo-encephalitis," the glia proliferation being mistaken for lymphocytic infiltration. Later it was recognized that the striatum was essentially involved in the disease process and that those cases in which dyskinesia was combined with progressive mental deterioration showed a marked involvement of the cerebral cortex.

The brain is usually small, with atrophy of the frontal and central convolutions. The cortical atrophy is followed by a secondary internal hydrocephalus. The neo- and paleostriatum are reduced to one-half or less of the normal size (fig. 200). The spinal cord likewise is reduced in size—an indication of the general involvement of the central nervous system in this hereditary degenerative disease. The histologic picture is dominated by a widespread degeneration and disappearance of neurons, combined with a reparative gliosis (neuronophagia and fibrous glia formation). This process is especially marked in the putamen, but the globus pallidus may also be involved. Frequently in cases of Huntington's chorea a marked "calcification" of the walls of the arteries in the striatum has been described. In the adventitia and in the surrounding tissue, granular precipitates may be formed; these stain black with iron hematoxylin and dark blue with cresyl violet. Microchemical reactions speak against the presence of calcium salts; besides, they are not always found in the media and therefore seem to be colloidal precipitates formed in the perivascular spaces. The fact that toward the nervous tissue they gradually disappear may lead one to assume an accumulation of metabolic products, which perhaps indicates a faulty metabolism of neurons or glia cells.

Other nuclei are only mildly involved; the thalamus, the body of Luys, the red nucleus, and the substantia nigra may all show atrophy and diminution in neurons. More severely involved is the dentate nucleus, in some cases with nearly complete elimination of its neurons (fig. 201).

The attempt has been made to correlate anatomic localization with the different clinical manifestations. The choreic dyskinesia was attributed to the affection of the neostriatum, the coordinated rigidity to the involvement of the globus pallidus, and the mental deterioration to the disease of the cerebral cortex. However, there were reports of cases in which, despite a generalized disease process, the clinical manifestations were very well de-

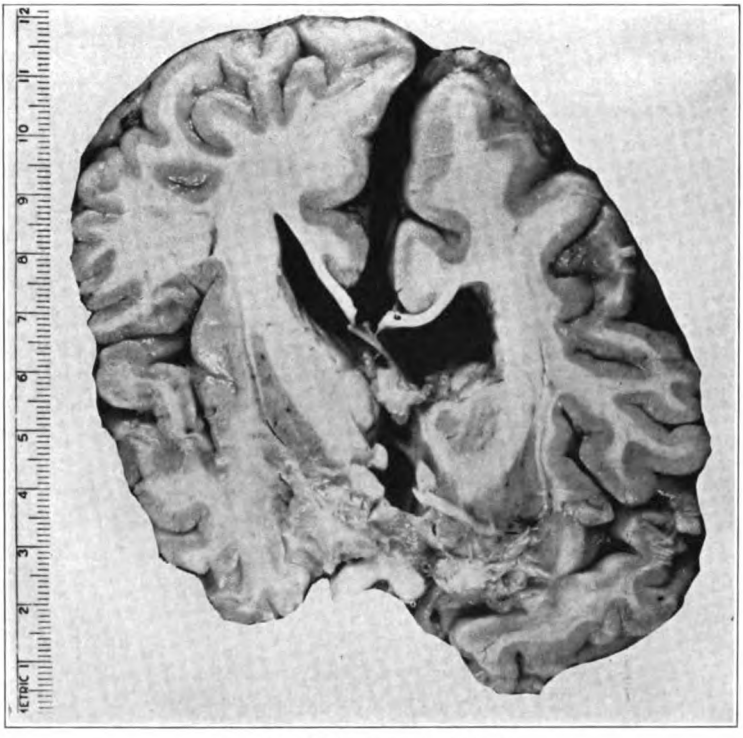


FIG. 200. HUNTINGTON'S CHOREA

Coronal section of brain. Atrophy of caudate nuclei in both hemispheres, with atrophy of cerebral cortex, more marked on right side

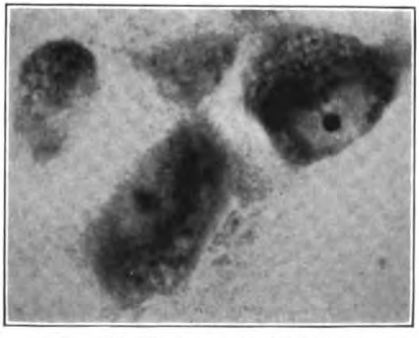


FIG. 201. HUNTINGTON'S CHOREA

Neurons in thalamus. Cresyl violet stain. Vacuolated appearance of cytoplasm. Nuclei eccentric, with folded membranes

fined. On the other hand, similar histopathologic pictures with predominant involvement of the striatum and globus pallidus have been reported in other "extrapyramidal" diseases—parkinsonism (fig. 203), dystonia musculorum progressiva, pseudosclerosis. In brains affected with senile arteriosclerosis, it is not unusual to find a marked diminution of large and small neurons of the neostriatum, with degeneration of the remaining cells, increase in fibrous glia, and pictures of neuronophagia, without any clinical manifestations that might have suggested such an advanced pathologic lesion.

A better support of the hypothesis that disease of the striatum is in some unknown way responsible for choreic or athetoid dyskinesias is offered by

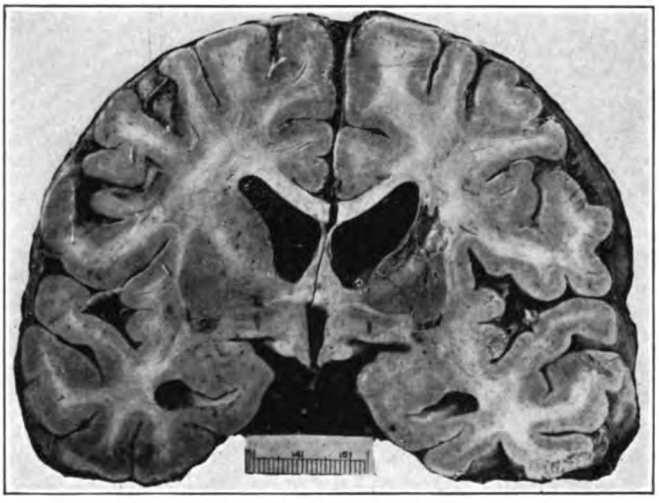


FIG. 202. HEMICHOREA

Hemiatrophy of striatum and of body of Luys, with anemic softening of caudate nucleus of atrophic side

cases of hemichorea. In the few cases that have been reported, there was found an area of softening involving most of the head of the caudate nucleus and part of the putamen and internal capsule. Besides this, there was atrophy of the globus pallidus and of the body of Luys either unilaterally (on the side opposite that of the choreic movements) or bilaterally. In a case personally observed by the writer, the size of the left neostriatum was 58 per cent, that of the left pallidum 66 per cent of that of the corresponding nuclei of the other side. Poor myelination and diminution in the number of neurons appeared, with gliosis in the left neostriatum and the lateral nucleus of the left thalamus. The left body of Luys showed pigment atrophy of its neurons and increase in glia nuclei. In summary, a vascular lesion was

superimposed upon an existing degenerative disease of the neostriatum, probably in combination with disease of the nucleus lateralis thalami and of the corpus Luysii (fig. 202).

INFECTIOUS CHOREA

Infectious chorea (Sydenham) and chorea gravidarum have been well studied as to their etiology and clinical manifestations, but the pathologic anatomy has not been so well investigated. At present there seems to be a tendency to assume a defective anlage of the neostriatum, upon which the infectious or toxic agent acts. Such a point of view is supported by the fact that in infectious chorea, encephalitic reactions were found in only 10 per cent of cases; in the rest a degenerative neuronal disease, with predilection for the striatum, was present. Such a hypothesis would invalidate those theories that assume a specific micro-organism (streptococcus, virus) with special affinity for the striatum. The idea that Sydenham's chorea is mainly a postrheumatic manifestation has been abandoned. Histories of chorea gravidarum have frequently revealed instances of previous infectious chorea or chorea among relatives.

In order to explain such a selective vulnerability of the neostriatum, the selective permeability of the blood vessels of this structure should be remembered, as discussed above in relation to the hemato-encephalic barrier. Just as bile pigments may penetrate this barrier in young children but not in adults, other toxic products (e.g., in rheumatic inflammation of the heart) may filter into the neostriatum, being prevented from penetrating through the blood vessels of other areas of the brain.

PARKINSONISM

It has been emphasized above that different pathologic processes affecting the same anatomic structure may give rise to identical clinical syndromes. There are three main pathologic factors giving rise to the parkinsonian syndrome—arteriosclerosis (p. 90), epidemic encephalitis (p. 137), and the degenerative type of paralysis agitans. The structures most frequently involved are the substantia nigra and the globus pallidus. Next in importance are the neostriatum, the motor cortex, and the inferior olives. In the arteriosclerotic form, the outstanding histopathologic feature are multiple areas of anemic softening with cyst formation; in the postencephalitic form, death of ganglion cells with neuronophagia and glia foci. In the latter form of parkinsonism, the substantia nigra is affected in nearly 90 per cent of all cases. It has been suggested that destruction of the pigmented zone gives rise to tremor, while rigidity predominates when the zona compacta (red zone) is affected (Kohnstamm). Inflammatory reaction and softening are absent in the "idiopathic" type of paralysis agitans. Here we find

homogenization of the pigmented cells of the substantia nigra; the granular appearance of the black pigment is lost, and the cells stain homogeneously light black, or they disintegrate and their pigment is found in the environment in small granules. Glial scavenger function or scar formation is very minute and barely detectable (fig. 203).

Familial Amaurotic Idiocy

The research on familial amaurotic idiocy is an interesting example of the mode of scientific progress in medicine. First described in 1881 by Tay, English ophthalmologist, and in 1887 by Sachs, American neurologist, it was up to 1905 considered to be a familial heredodegenerative disease occurring in children of Jewish descent not older than 3 years. Its main characteristics

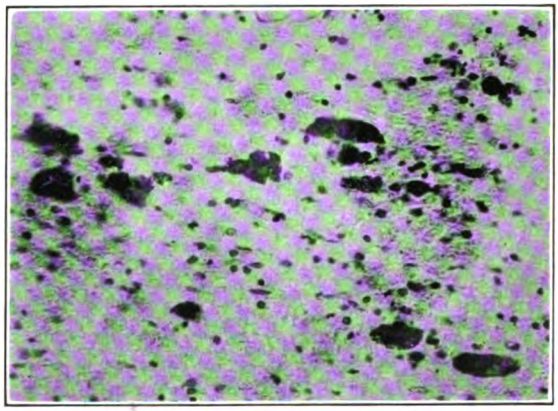


Fig. 203. Parkinsonian Syndrome (Idiopathic Type)
Substantia nigra. Cresyl violet stain. Loss of pigment. Severe neuronal disease. (Cf. fig. 125)

were described as the typical cherry red spot in the macula and the diffuse swelling of the neurons of the central nervous system. In 1905 Spielmeyer and H. Vogt simultaneously described the juvenile type, occurring mostly in gentile children, with the first onset between the seventh and the eighth year of life. The macula in such cases might be normal and only atrophy of the optic nerve, retinitis pigmentosa, or small isolated spots might be present. Finally in 1908 Jansky and in 1913 Bielschowsky described a late infantile form beginning in children between the ages of 4 and 7 years. The optic changes noted were just as variable as those in the second group. Degenerative changes in the white matter, besides the typical neuronal disease, were described in 1914 by Brodman.

With increase in the number of case reports, it was soon recognized that these different groups were identical as to anatomic substratum and that

many combinations of the ocular and central nervous system changes might occur. Up to 1908 Apert had registered 106 cases. From 1908 to 1931, approximately 150 more cases were published. Table 17 shows the age distribution and racial differentiation of those patients in the latter group for whom complete records were available. Of these 143 verified cases, 49 per cent were male and 51 per cent female.

The hereditary and familial character of the disease is emphasized by the fact that, besides the idiocy, isolated forms of macular or optic atrophy occur in the same family and among the nonidiotic brothers and sisters.

There has been a great number of publications theorizing on the origin of the disease process. According to Schaffer, the typical swelling of the neurons is produced by a decomposition of the hyaloplasm—the undifferentiated part of the cytoplasm—into its basic components, proteins and lipoids. The latter can be stained with fat stains. According to Bielschowsky, the process of swelling is produced by an accumulation of lipoid substances, originating in a faulty metabolism of the cell. This theory was

TABLE 17.—*Age and Race Incidence of Familial Amaurotic Idiocy*

Type	Total No. of Cases	No. of Cases		Percentage	
		Jewish	Gentile	Jewish	Gentile
Infantile	86	64	13	83	17
Late infantile	27	4	17	25	63
Juvenile	30	2	24	7	80

very strongly supported by the discovery (1928) that the nervous changes in familial amaurotic idiocy may be only one phase of a syndrome including a generalized disturbance of the phospholipid metabolism, Niemann-Pick disease, or lipoid-cellular splenohepatomegaly.

Epstein has tried to classify the different disturbances of lipoid metabolism into three lipoidoses: (1) phosphatide (lecithin) lipoidosis (Niemann-Pick disease); (2) cerebroside (kerasin) lipoidosis (Gaucher's disease); (3) cholesterol lipoidosis (Schüller-Christian-Hand disease). It should be of interest to give more attention to the pathology of the central nervous system in the different manifestations of disturbance of the lipoid metabolism.

While in Niemann-Pick disease the phosphatides of the liver and spleen are increased by about 50 per cent, and those of the brain by about 25 per cent, increase in brain phosphatides is negligible in familial amaurotic idiocy (E.Epstein). However, in the latter disease the free cholesterol and the sphingomyelin of the brain are increased at the expense of galactolipids and cholesterol esters (Baumann, Klenk, and Scheidegger).

Any of numerous congenital malformations of the brain may be combined with the typical histologic picture. Very small and very large brains have been found, with extremes ranging in weight between 430 and 1600 Gm. Defects of the cortical configuration have frequently been described—microgyria, wide fissures, and sulcus lunatus, besides atrophy of the cerebellum, pons, or medulla oblongata. The consistency of the brain varies from toughness offering resistance to the cutting knife to extreme softness, in some cases with transformation of the white matter into a gelatinous mass.

The microscopic changes are generalized, involving neurons and glia cells alike. The typical changes of the neurons may be described as follows: In sections stained with cresyl violet, one can barely recognize the outlines of the diseased cells. They are extremely swollen, balloon-like. The nucleus, with a well staining nucleolus, is frequently pushed to one side of the cell; it may be surrounded by the remains of the Nissl bodies (figs. 204, 205). In sections stained for myelin sheaths (Weil), the interior of the cell stains diffusely with a bluish color or shows a fine granulation (fig. 24). Sudan III stains the same area more or less intensely red; the Marchi method often has no staining effect or may develop a brownish color. Fat solvents sometimes remove these fatty substances; in cases of the juvenile type, the extraction is accomplished only with difficulty (Hurst). Glycogen is frequently found within the cells, with a corresponding decrease in the amount of oxydase. In preparations by the Bielschowsky method, the area deprived of Nissl bodies is also free of neurofibrils. On the outer surface of the diseased neuron there may be detected with higher magnifications a darker-staining, basket-like meshwork. The axis-cylinders are surprisingly intact; sometimes, however, they show globular swelling and distortions. Swelling of the main dendrite may frequently be seen, especially at the place of a bifurcation. Severe degeneration of the myelin sheaths is not the rule. In some cases complete demyelinization of the white matter has been described, in others it was confined to the U fibers.

Astrocytes and oligodendroglia are involved in the process of cellular degeneration, but the intensity of their disease does not always parallel the changes of the neuron. There may be severe swelling and lipoid accumulation in the neuron without any marked changes in the neighboring glia. In other cases the neurons stain diffusely and lightly with sudan III, while the glia cells contain granular masses that stain a brilliant red. There is no progressive glia reaction in many cases; in others, a marked sclerosis, with formation of monstrous astrocytes, has been described. The neurons of the spinal cord and of the spinal ganglia are just as frequently involved in the disease process as those of the cerebral cortex.

Reactive processes of the mesodermal tissues do not belong to the classic picture of the disease. Those cases in which the condition is combined with marked meningitis are suggestive of addition of a second morbid factor

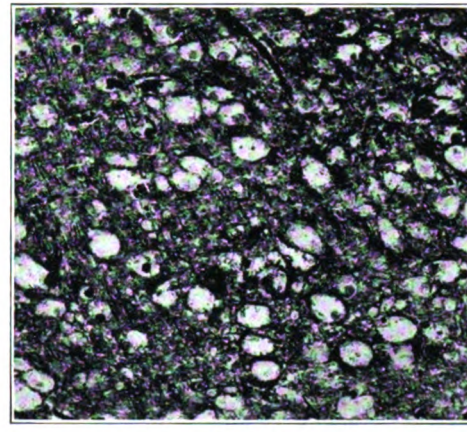


FIG. 204

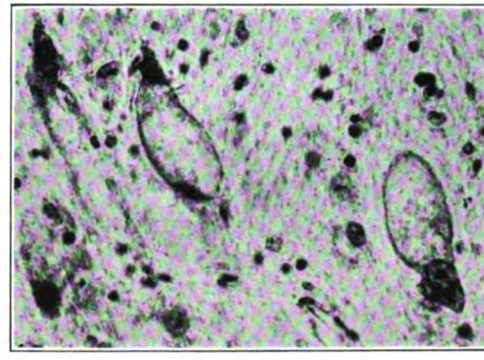


FIG. 205

FIGS. 204, 205. FAMILIAL AMAUROTIC IDIOCY

Fig. 204. Occipital cortex. Weil stain. Both neurons and glia cells are swollen, unstained. (Cf. fig. 24)

Fig. 205. Thalamus. Cresyl violet stain. Balloon-like swelling of neurons, disappearance of Nissl bodies, eccentric position of nucleus in main dendrite

in the degenerative process. Thickening of the piarachnoid has been described. In cases of Niemann-Pick disease presenting at the same time familial amaurotic idiocy, infiltration of the typical lipoids may also be

seen in the cells of the piarachnoid, the tela chorioidea, and along the adventitial sheaths of the cerebral vessels.

Cases of cholesterol lipoidosis combined with brain disease are rare. If the brain is involved in the process of the metabolic disturbances, large cholesterol-filled foamy cells are found within the cortex, giving rise to a mild reactive gliosis (Davison).

Cerebral Cortical Degeneration

It had been suggested that there should be added to this chapter a detailed description of the brain pathology in the more common psychoses. However, as regards the organic reaction types, descriptions of their pathology will be found in the chapters on vascular disease, infections, intoxications, and tumors. As to the manic-depressive psychosis and the schizophrenic reaction types, one is obliged to agree with Peters and others that at present there is no pathologic histology of these diseases.

There is a restricted literature concerning the neuropathology of mental disorders associated with endocrine disturbances. But the results of these investigations are so meager, aspecific, and contradictory that not much attention can be paid to them. Animal experiments have yielded little more information than has study of the human pathology. But it seems that chemical investigation of the different thyroid, gonadal, and adrenal disorders will yield more definite results than microscopic studies (Weil).

To round off the discussion of degenerative diseases, a few instances of senile changes of the brain may be added. These are represented by Alzheimer's disease, senile dementia, and Pick's disease.

SENILE CORTICAL DEGENERATION

The high rate of incidence of arteriosclerotic changes after the sixth decade of life makes it difficult to decide whether the organic changes of the aging brain are due to nutritive disturbances or to the process of aging itself. It has been mentioned above that macroscopic changes of the larger atherosclerotic vessels may be absent, while the capillary fibrosis may nevertheless be intense and widespread and responsible for the cortical atrophy. Even without any vascular pathology, the aging brain loses weight—as much as 10 per cent, as compared with its peak weight (cf. table 25). This is due mainly to a change in its chemical composition, to loss of water, and to increase of meso- and fibroglia at the expense of the neurons themselves, which are reduced in number and also disappear in large areas of the cerebral cortex. Colloidal chemical changes are revealed by appearance of the senile plaques—argyrophile areas within the gray matter that present either an amorphous appearance or radiating figures (figs. 25, 39). These are not confined to the cortex but appear within

the basal ganglia as well. The statement that their presence indicates a senile dementia during life should be corrected. They are seen in the brains of old persons who never developed any senile psychosis; they are found likewise in cases of presenile dementia—Alzheimer's disease—and it has been claimed that they may even be absent in characteristic cases of this group. They apparently indicate a disintegration of the nervous parenchyma, a colloidal aging—"hysteresis" (von Braunmühl)—that leads to the affinity for silver. The glia also is involved in this process; in sections stained for microglia, one may see attempted encapsulation of a

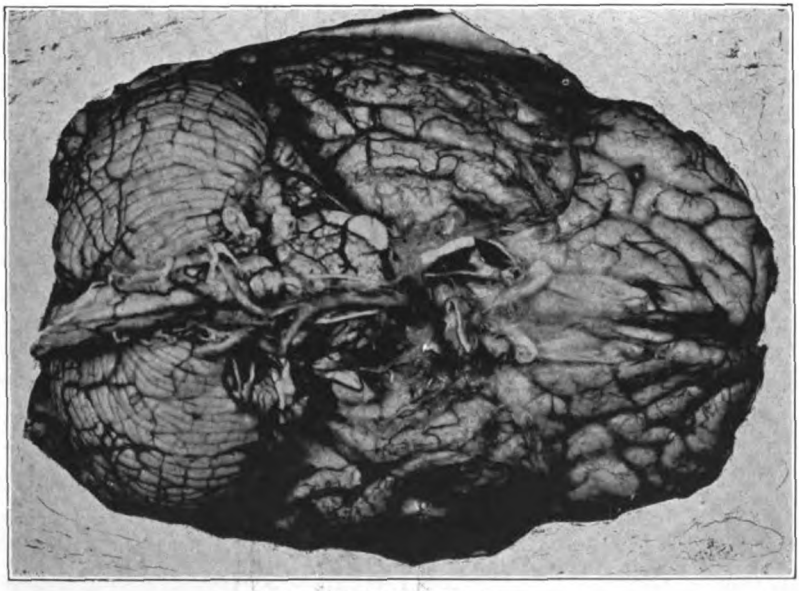


FIG. 206. PICK'S DISEASE
Bilateral atrophy of temporal lobes

plaque frustrated by breaking down of the processes of microgliocytes that have invaded it (fig. 39). In the nonaffected areas one sees hypertrophy and hyperplasia of both astroglia and microglia; this change, however, in senile atrophy not complicated by vascular disease, does not seem to attain the intense degree of fibrous gliosis seen in the latter condition. In Alzheimer's disease peculiar changes of the neurofibrils have been described. They are either fragmented into numerous globules or show formation of spirals or loops (fig. 25). However, it is now recognized that these changes are not specific for presenile dementia, since they have been observed in the brains of older, nonpsychotic persons. Some authors even consider them arte-

facts, produced during fixation (Alexander). The number of neurons within the cerebral cortex is markedly diminished. In advanced cases this may lead to complete loss of the typical cyto-architecture. Especially in silver-stained preparations, this distortion of the cellular arrangement is impressive and emphasized by the large number of shrunken, dark-staining neurons.

PICK'S DISEASE (LOBAR SCLEROSIS)

While in senile brain degeneration and in Alzheimer's disease the atrophy of the cortex is generalized, it is confined in Pick's disease to certain lobes of the cerebral hemispheres. The predilection with respect to the lobes is in the order of frontal, temporal, parietal. Affections of these different sites in combination are not infrequent (fig. 206), and a generalized atrophy of the brain has been described in cases with the typical histopathologic changes. In contrast to the histologic changes in the senile dementia group, both the gray and the white matter are involved in Pick's disease. In the gray matter the upper layers seem to be affected first. In early cases one may see a peculiar swelling of these cells, and argyrophile globules and fatty substances staining with sudan III appear in their cytoplasm. In later stages one sees more shrunken, dark-staining cell types, vacuolated forms, or mere cell shadows—changes that now involve also the deeper cortical layers. At the same time axis-cylinders and myelin sheaths are severely diseased. The former show fragmentation and loop formation—pictures that may be seen in axonal degeneration of other etiology. The myelin sheaths show globulation and fragmentation. However, in contrast to other pictures of myelin sheath degeneration, these fragments in Pick's disease do not stain with fat stains and there is no increase in the number of compound granular corpuscles. In contrast to the findings in senile dementia, the glia undergoes active proliferation and forms a dense fibrous meshwork in the white matter, which has led to designation of the condition as lobar "sclerosis."

This pathologic process is not confined to the cortex but spreads to the striatum, cerebellum, and brain stem nuclei. The question of its etiology is still unsolved. The rapid progression, the spread to both cortex and subcortex, and the absence of severe vascular disease, suggest disturbances of metabolism, perhaps of the nutritive function of the glia, as was suggested by some authors who were impressed by the intense progressive changes of both astroglia and microglia.

XII

TUMORS

THE DIFFERENT theories that have been advanced to explain tumor growth in general have also been applied to the neoplasms of the nervous system. One of the more generally recognized theories is that of Cohnheim, which assumes that tumors arise from misplacement of embryonic cellular remains that preserve their original undifferentiated condition in the differentiated adult environment and may be stimulated to excessive growth by certain still unknown stimuli. In the central nervous system, sites of such embryonic cell survival are the closing line of the neural tube at the posterior median fissure of the spinal cord, which hypothetically retains nests of spongioblasts that may give rise to glioma and syrinx formation. Another center seems to be the roof of the fourth ventricle, above which in young persons the medulloblastomas take their origin. At the anterior surface of the infundibulum two different types of remains of the craniopharyngeal duct—the squamous epithelium and the pars tuberalis—may give rise to various neoplasms.

Another group of theories assumed regression of adult cells to embryonic stages. The stimuli producing such transformation may be chemical ones, as in the coal tar carcinomas of the skin, or toxins of nematodes (Spiroptera), which produce malignant papillomas in the stomach of the rat. This chemical theory received very strong support during the last decade following the synthesis of anthracene derivatives, which are capable of inducing neoplasms of different tissues following their implantation. This principle has also been applied to the brain and has led to experimental production of manifold tumors. First a styryl compound was implanted in rat brain; this had only a very mild carcinogenic action, but transformation of adult glia cells into unipolar spongioblasts could be demonstrated (Weil). The next step was injection of emulsions of dibenzanthracene in lard into the rat brain, which led to production of an astrocytoma in combination with an epithelioma. It could be proved that the latter was formed by a metaplasia of mesothelial lining cells of the arachnoidal membrane (Weil). The final step was implantation of pure crystals of methylcholanthrene in brains of rats and mice (Weil; Seligman and Shear; Zimmerman). Mesenchymal cells formed sarcomas; glial cells formed different types of gliomas; mesothelial lining cells produced epithelial cysts, and in one instance cells of the anterior lobe of the pituitary formed an adeno-

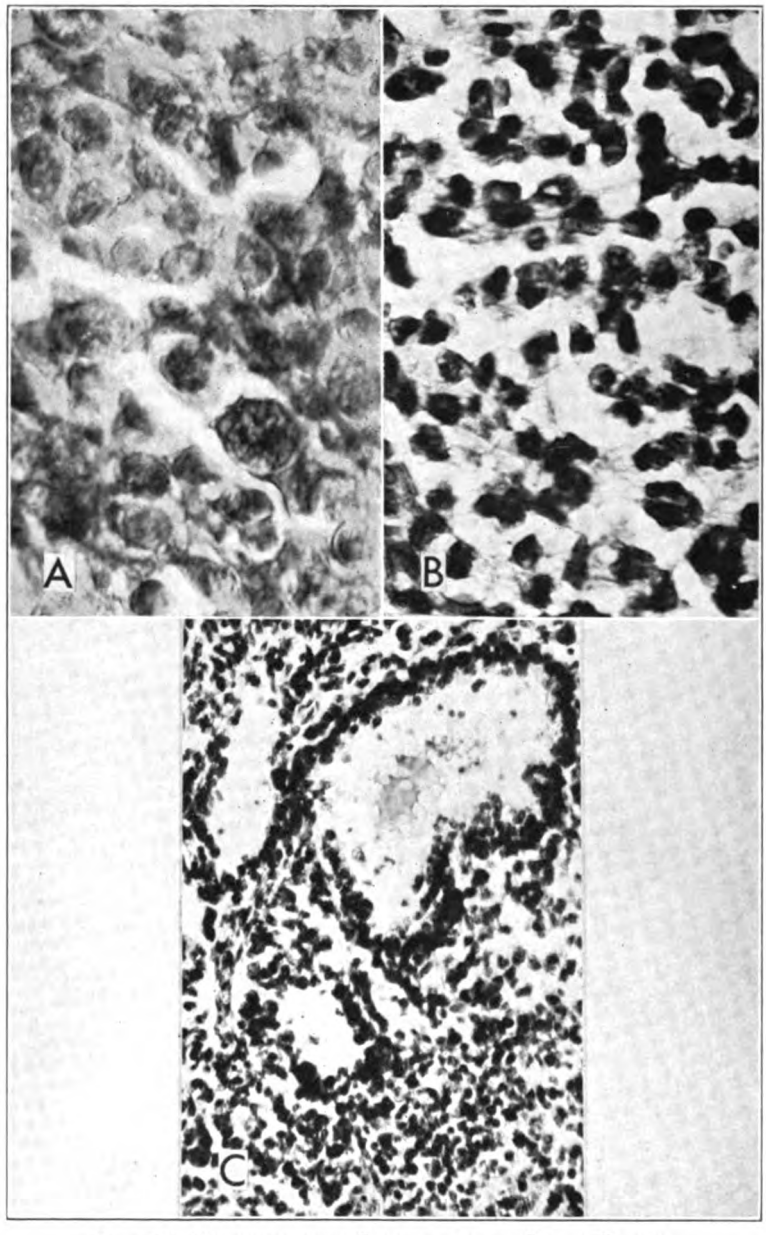


FIG. 207. EXPERIMENTAL PRODUCTION OF BRAIN TUMORS WITH METHYLCHOLANTHRENE

Methylcholanthrene crystals were implanted into infundibular region of rat brain. After 12 months both hypophysis and median eminence had been transformed into tumors. Each cell had produced its own specific neoplasm: A, adenoma of anterior lobe; B, glioma of pars nervosa of hypophysis; C, glioma of median eminence, with cyst formation in region of pars tuberalis. A, triple stain, Haterius modification; B, C, Davenport stain for gliomas

carcinoma (Weil) (fig. 207). On the basis of these findings it may now be postulated that *"each cell is potentially neoplastic and forms its adequate tumor under the stimulating influence of the proper chemical substance."* Such a hypothesis is a great advance as compared with the limited theory of Cohnheim.

At the same time such a theory will explain why tumors of the meninges, for example, not only are neoplastic transformations of mesothelial cells but at the same time contain neoplastic mesenchymal tissue, and why tumors of peripheral nerves may be combinations of neoplastic Schwann sheath cells and neoplastic fibroblasts.

Besides such a stimulating chemical factor producing neoplastic disease of a cell, we must also assume a certain "disposition" of a cell that makes it sensitive to the stimulus and changes its adult metabolism to that of an embryonic cell. The example of the production of liver carcinoma by feeding of butter yellow suggests that upset of endocellular oxidative processes, or lack of certain vitamins (B_1), may bring about such predisposition. Such a disposition in the central nervous system is convincingly demonstrated in those rare cases in which the whole medulla or the upper spinal cord undergoes neoplastic transformation, with different types of tumors arising from the ependyma, the glia, and the endoneurium of the cranial nerve roots. Other examples of the presence of such disposition are multiple primary brain tumors of mesenchymal and glial origin, or cases of congenital malformation of the brain in which the glia of a given area suddenly undergoes neoplastic proliferation or in which gliomatosis of the brain is combined with multiple neurinomas of peripheral nerves.

A natural classification of tumors of the nervous system may be formulated, if we assume that each type of cell in the various tissues may form its particular type of tumor. We then may differentiate between tumors (1) of the meninges, (2) of the glia, (3) of the neuron, (4) of the ependyma, (5) of the choroidal epithelium, (6) of the blood vessels, (7) of the hypophysis and epiphysis, and (8) of the peripheral nerves.

Tumors of the Meninges

The different structures of the dura mater and piarachnoid that may undergo neoplastic transformation are (*a*) the endothelial (mesothelial) cells lining the inner surface of the dura mater and of the arachnoidea and its trabeculae, (*b*) the pigment-containing cells of the piarachnoid (melanophores), (*c*) the connective tissue, and (*d*) the blood vessels.

The problem of classifying the different tumors arising in the meninges may be simplified by combining them into a single group—*meningiomas*. Most of them are encapsulated, benign tumors that do not infiltrate the brain or spinal cord but only compress the tissues. Their slow growth gives the underlying structures time to adapt themselves to the gradually

increased pressure. A mild fibrous glia reaction develops in the underlying outer cortical zones; severe degenerative changes seem to be the exception, a fact that explains the speedy recovery after early removal of such a tumor.

The most frequent type of this group is the *dural endothelioma*, characterized by the whorl formation of the tumor cells. The type cell is elongated, somewhat spindle-shaped, with scanty cytoplasm and vesicular nucleus. The cells form long strands or whorls around capillaries or other cells (fig. 208). Frequently the center of a whorl is calcified or the whole whorl is transformed into concentric calcified layers (psammoma bodies). The whorls are separated by connective tissue, but no intercellular collagenous or argyrophile fibers are found. Usually these tumors

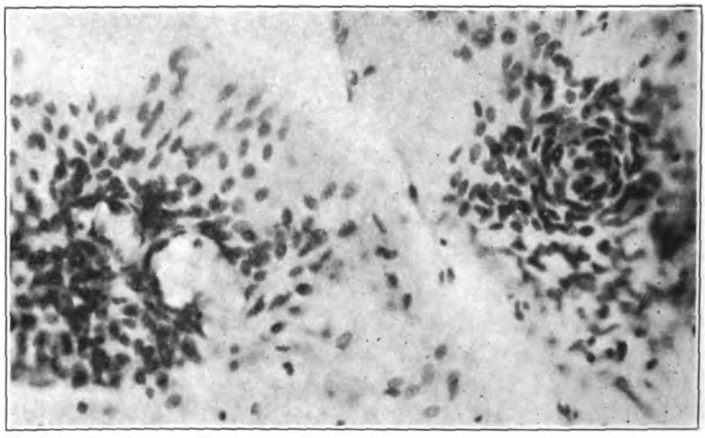


FIG. 208. WHORL FORMATION OF ARACHNOIDAL MESOTHELIAL CELLS
Case of dementia alcoholica. Hematoxylin-eosin stain

are very vascular, and not infrequently membranous bone formation is present (figs. 209–13).

Bailey and Bucy have attempted to classify the different types of meningeal tumors according to the predominant type cell. They oppose the idea of certain French neuropathologists who consider them to be of neuroepithelial origin and who speak of "peripheral gliomas." They do not accept the theories of Mallory and Penfield, who consider them generally as fibroblastomas. They differentiate nine types: (1) mesenchymal; (2) angioblastic; (3) meningotheliomatous; (4) psammomatous; (5) osteoblastic; (6) fibroblastic; (7) melanoblastic; (8) sarcomatous; and (9) lipomatous.

As in the case of every other type of brain tumor, it is sometimes difficult to classify a given meningioma in comformity with a standardization based on the occurrence and arrangement of the above-named groups of type

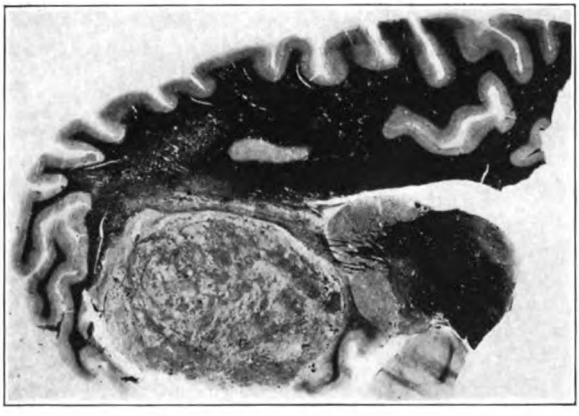


FIG. 209. MENINGIOMA (PSAMMOMATOUS TYPE)
Invading sylvian fissure and compressing frontal and temporal lobe. Sagittal section through brain. Loyez stain

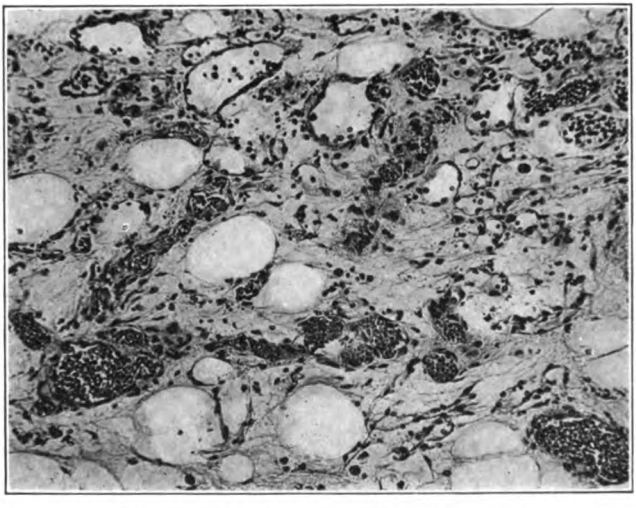


FIG. 210. MENINGIOMA OF SPINAL CORD
With telangiectasis and lipomatous formation. Hematoxylin-eosin stain

cells. In analogy with the manifold cellular variations found in the gliomas, one finds, in a careful examination of a single meningioma, different regions in which either the meningotheliomatous, the psam-

momatous, or the angiomatous formation predominates (fig. 212). The same combinations may occur in the fibroblastic type, which sometimes is difficult to differentiate from a neurinoma of the cranial nerves (fig. 213). The mesenchymal type is described as a loose tumor formed by bipolar cells with long processes and a few stellate cells. The cells are surrounded by fine fibers of reticulin. Fibrous glia has also been demonstrated. The meningotheliomatous type has cells similar to those of the dural endothelioma; they show no definite arrangement, however, but form large lobules with evenly distributed vesicular nuclei. In normal persons, formation of small bony platelets in the piarachnoid of the spinal cord may be noticed.

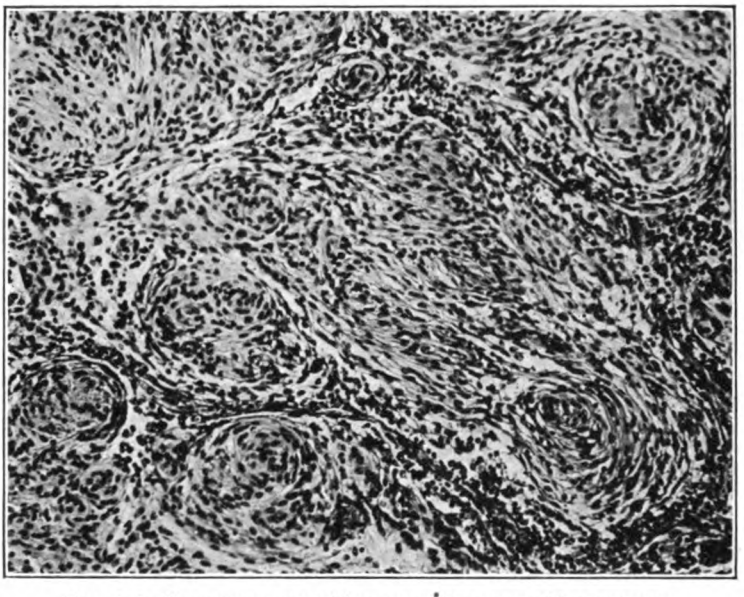


FIG. 211. PSAMMOMATOUS TYPE OF CEREBRAL MENINGIOMA
Van Gieson stain

Neoplastic membranous bone formation in the dura mater of the falx cerebri has frequently been reported. This occurrence in meningiomas has led Bailey and Bucy to differentiate an osteoblastic type; to this, however, one may apply the qualification made above regarding the possibility of variant predominance of cell types.

Occasionally, sarcomatous transformation of the meningioma has been reported. Primary neoplasms of mesenchymal origin are the *melanoblastoma*, the *diffuse sarcomatosis of the meninges*, and the *lipoma*.

The melanophores of the piarachnoid, which have already been described, seem to be the origin of the melanoblastic type. Unlike the benign, encap-

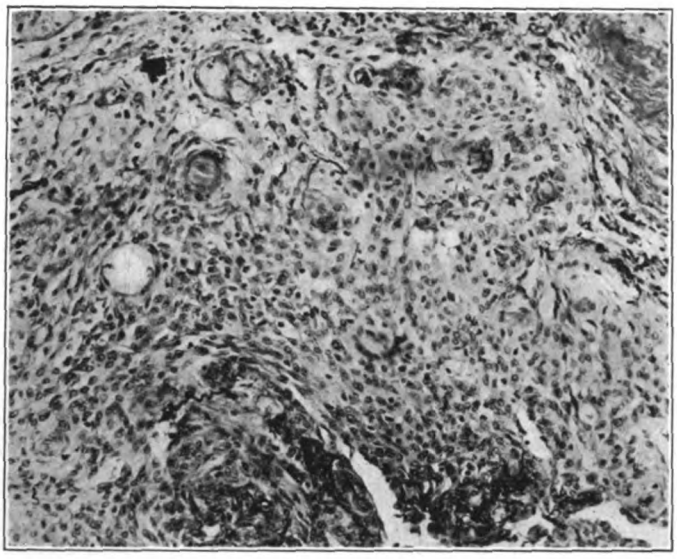


FIG. 212. MENINGOTHELIOMATOUS TYPE OF CEREBRAL MENINGIOMA
Hematoxylin-eosin stain

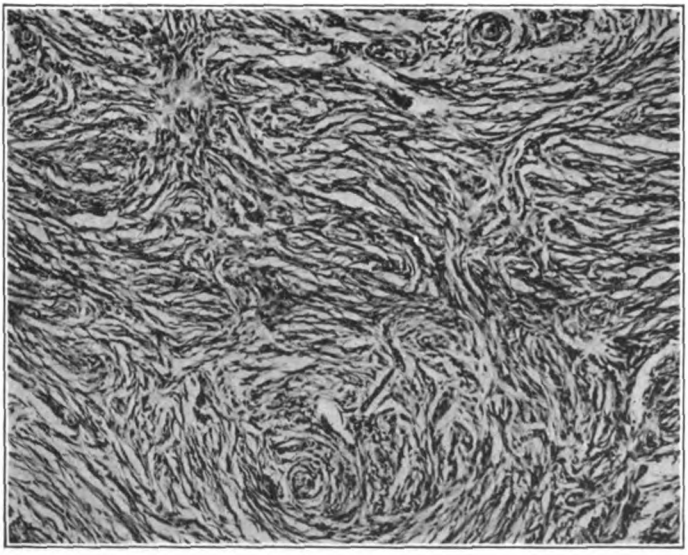


FIG. 213. FIBROBLASTIC TYPE OF CEREBRAL MENINGIOMA
Meningioma of falx cerebri. Van Gieson stain

momatous, or the angiomatous formation predominates (fig. 212). The same combinations may occur in the fibroblastic type, which sometimes is difficult to differentiate from a neurinoma of the cranial nerves (fig. 213). The mesenchymal type is described as a loose tumor formed by bipolar cells with long processes and a few stellate cells. The cells are surrounded by fine fibers of reticulin. Fibrous glia has also been demonstrated. The meningotheliomatous type has cells similar to those of the dural endothelioma; they show no definite arrangement, however, but form large lobules with evenly distributed vesicular nuclei. In normal persons, formation of small bony platelets in the piarachnoid of the spinal cord may be noticed.

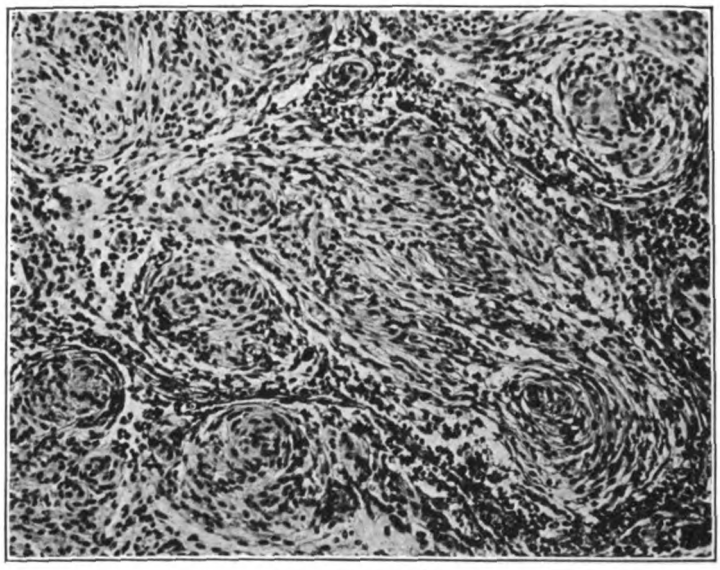


FIG. 211. PSAMMOMATOUS TYPE OF CEREBRAL MENINGIOMA
Van Gieson stain

Neoplastic membranous bone formation in the dura mater of the falx cerebri has frequently been reported. This occurrence in meningiomas has led Bailey and Bucy to differentiate an osteoblastic type; to this, however, one may apply the qualification made above regarding the possibility of variant predominance of cell types.

Occasionally, sarcomatous transformation of the meningioma has been reported. Primary neoplasms of mesenchymal origin are the *melanoblastoma*, the *diffuse sarcomatosis of the meninges*, and the *lipoma*.

The melanophores of the piarachnoid, which have already been described, seem to be the origin of the melanoblastic type. Unlike the benign, encap-

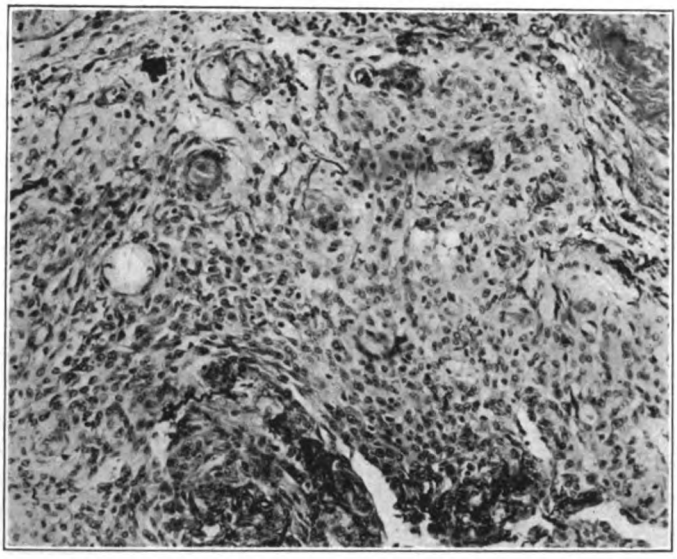


FIG. 212. MENINGOTHELIOMATOUS TYPE OF CEREBRAL MENINGIOMA
Hematoxylin-eosin stain

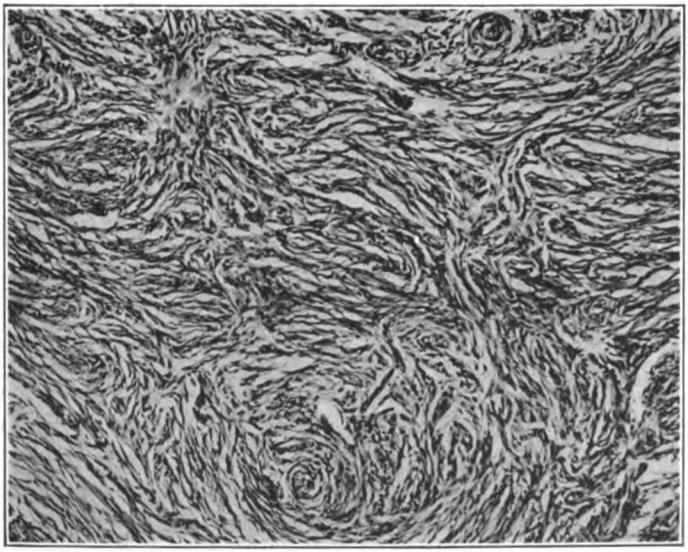


FIG. 213. FIBROBLASTIC TYPE OF CEREBRAL MENINGIOMA
Meningioma of falx cerebri. Van Gieson stain

momatous, or the angiomatous formation predominates (fig. 212). The same combinations may occur in the fibroblastic type, which sometimes is difficult to differentiate from a neurinoma of the cranial nerves (fig. 213). The mesenchymal type is described as a loose tumor formed by bipolar cells with long processes and a few stellate cells. The cells are surrounded by fine fibers of reticulin. Fibrous glia has also been demonstrated. The meningotheliomatous type has cells similar to those of the dural endothelioma; they show no definite arrangement, however, but form large lobules with evenly distributed vesicular nuclei. In normal persons, formation of small bony platelets in the piarachnoid of the spinal cord may be noticed.

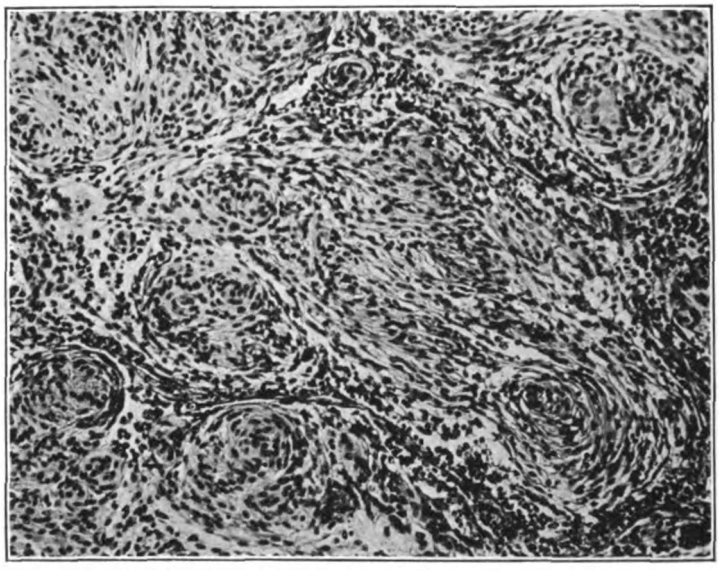


FIG. 211. PSAMMOMATOUS TYPE OF CEREBRAL MENINGIOMA
Van Gieson stain

Neoplastic membranous bone formation in the dura mater of the falx cerebri has frequently been reported. This occurrence in meningiomas has led Bailey and Bucy to differentiate an osteoblastic type; to this, however, one may apply the qualification made above regarding the possibility of variant predominance of cell types.

Occasionally, sarcomatous transformation of the meningioma has been reported. Primary neoplasms of mesenchymal origin are the *melanoblastoma*, the *diffuse sarcomatosis of the meninges*, and the *lipoma*.

The melanophores of the piarachnoid, which have already been described, seem to be the origin of the melanoblastic type. Unlike the benign, encap-

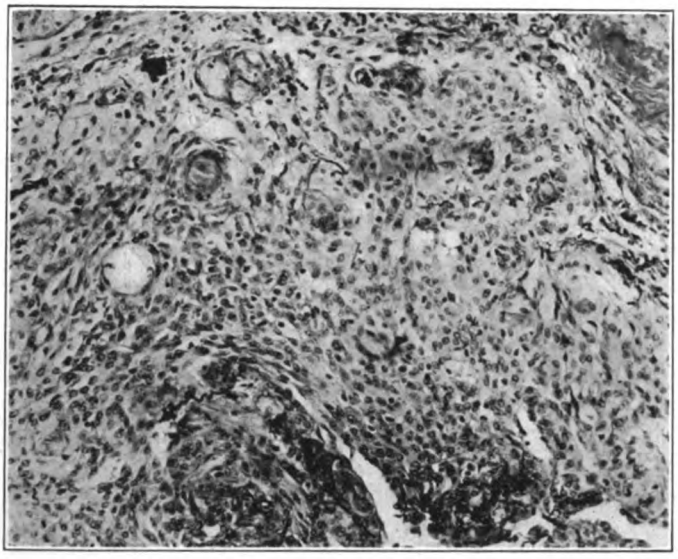


FIG. 212. MENINGOTHELIOMATOUS TYPE OF CEREBRAL MENINGIOMA
Hematoxylin-eosin stain

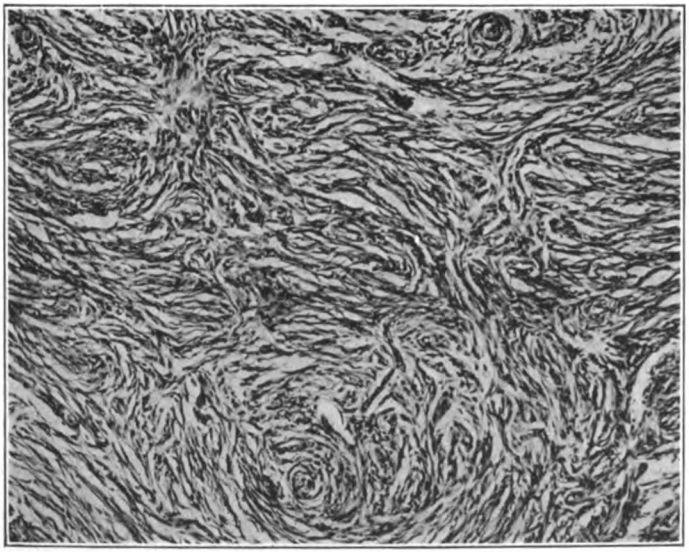


FIG. 213. FIBROBLASTIC TYPE OF CEREBRAL MENINGIOMA
Meningioma of falx cerebri. Van Gieson stain

sulated tumors of groups 1 to 6, they may invade the brain and become malignant growths. They may then show combinations of melanin-containing polyhedral cells with more elongated cells of a sarcomatous arrangement. The pigment is found in the form of small granules in the tumor cells, staining dark brown or black under Hortega's method.

Sarcomas may arise from the connective tissue fibroblasts of the cerebral blood vessels, in the form of peritheliomas. Diffuse spreading throughout the piarachnoid is a rare occurrence. Bailey and Bucy state that this lesion is found in adults as a primary tumor, while in children such a diffuse, neoplastic meningeal disease follows primary sarcoma of the brain. The cell types are manifold: most numerous are the round or polyhedral eosinophilic cells with eccentric nuclei, which are embedded in a stroma of reticular connective tissue.

Lipomas may be found in rare instances as accidental autopsy disclosures, most of them on the superior surface of the corpus callosum, others about the tuber cinereum or the corpora quadrigemina. Figures showing the relative frequency of meningeal tumors are given in table 20. Guttmann found 47 meningiomas (in 38 females, 9 males) in 11,000 autopsies at the hospital in München-Schwabing in the period from 1913 to 1922.

Tumors of the Glia

The lack of a uniform nomenclature for classification of the gliomas is regrettable because it renders difficult a mutual understanding among pathologists of different countries. Fortunately, the photomicrographs published in monographs and in the standard works facilitate identification of a given tumor (Bailey and Cushing, *Tumors of the Glioma Group;* Roussy and Oberling, *Les tumeurs des centres nerveux et des nerfs périphériques*).

The gliomas may be subdivided into two groups. In the first group the type cell is the adult glia cell, astrocyte, or oligodendrocyte. In the second group the type cells imitate, more or less closely, embryonic types of glia cells. They are designated in each case by addition of the suffix "-oma" to the name of the main type cell.

Group 1

1. *Astrocytoma* (*Astrocytome, Gliome Astrocytaire*).—Four different forms have been described—the protoplasmic, the fibrillary, the piloidal, and the giant cell type. Cushing suggested the probability that the protoplasmic astrocyte represents a degenerative or undeveloped form of the fibrillary astrocyte. Furthermore, a single given tumor may present considerably varying aspects. In some areas one may find densely accumulated large fibrillary astrocytes intermingled with the piloidal ("hairlike," on account of their numerous fine, hairlike fibers); in others the cells are more

widely spaced, small, and embedded in a dense meshwork of glia fibers. The tumors may undergo cystic degeneration, especially those found in the cerebellum; in such a case the tumor cells are small, or they may become calcified (figs. 216, 217). Tumors of the giant cell type

TABLE 18.—*Synonyms of Brain Tumors*

Bailey and Cushing	Roussy and Oberling		Other Authors
Name	Name	Plate*	Name
Astroblastoma	astrocytome	IV-A	neuroblastoma
Astrocytoma	astrocytome	II	astroma; glioma; Sternzellengliom
Ependymoma	épendymocytome épendymoblastome	VII-D, E	ependymal glioma
Ganglioneuroma	ganglioneurome	IX-C, D	glioneuroma; gliogangliome; neuroglioma ganglionare; spongioneuroblastoma
Glioblastoma multiforme	glioblastome	III-A IV-D, G	gliosarcoma; gliome polymorphe; spongioblastoma multiforme
Medulloblastoma	neurospongiome	X, XI-A, B	neuroblastoma; neurocytome embryonnaire
Medullo-epithelioma	neuroépithéliome sacrococcygien	XI-D	
Neuro-epithelioma	épendymogliome	IX-B	blastome épendymale; retinocytome à stéphanocytes
Oligodendroglioma	oligodendrocytome	III-D V-A, B	gliome à petites cellules
Spongioblastoma polare	astrocytome or oligodendrocytome à cellules fusiformes	III-C V-C	gliome sous-épendymaire; central neurinoma
Neurinoma	neurinome	XII-A, C	perineurial fibroblastoma; schwannoma; solitary neurofibroma; gliome périphérique

* Numerals refer to plates in Roussy, G., and Oberling, C.: Atlas du cancer, pts. 9 and 10.

frequently present a picture of fattened glia, a condition that has been described as "ameboid transformation." Some astrocytomas, such as those arising in the subependymal tissue of the ventricles, are extremely fibrillary and of a dense consistency. Sometimes one may have difficulty in differentiating such tumors, which are rich in fibers and poor in cells,

sulated tumors of groups 1 to 6, they may invade the brain and become malignant growths. They may then show combinations of melanin-containing polyhedral cells with more elongated cells of a sarcomatous arrangement. The pigment is found in the form of small granules in the tumor cells, staining dark brown or black under Hortega's method.

Sarcomas may arise from the connective tissue fibroblasts of the cerebral blood vessels, in the form of peritheliomas. Diffuse spreading throughout the piarachnoid is a rare occurrence. Bailey and Bucy state that this lesion is found in adults as a primary tumor, while in children such a diffuse, neoplastic meningeal disease follows primary sarcoma of the brain. The cell types are manifold: most numerous are the round or polyhedral eosinophilic cells with eccentric nuclei, which are embedded in a stroma of reticular connective tissue.

Lipomas may be found in rare instances as accidental autopsy disclosures, most of them on the superior surface of the corpus callosum, others about the tuber cinereum or the corpora quadrigemina. Figures showing the relative frequency of meningeal tumors are given in table 20. Guttmann found 47 meningiomas (in 38 females, 9 males) in 11,000 autopsies at the hospital in München-Schwabing in the period from 1913 to 1922.

Tumors of the Glia

The lack of a uniform nomenclature for classification of the gliomas is regrettable because it renders difficult a mutual understanding among pathologists of different countries. Fortunately, the photomicrographs published in monographs and in the standard works facilitate identification of a given tumor (Bailey and Cushing, *Tumors of the Glioma Group;* Roussy and Oberling, *Les tumeurs des centres nerveux et des nerfs périphériques*).

The gliomas may be subdivided into two groups. In the first group the type cell is the adult glia cell, astrocyte, or oligodendrocyte. In the second group the type cells imitate, more or less closely, embryonic types of glia cells. They are designated in each case by addition of the suffix "-oma" to the name of the main type cell.

GROUP 1

1. *Astrocytoma* (*Astrocytome, Gliome Astrocytaire*).—Four different forms have been described—the protoplasmic, the fibrillary, the piloidal, and the giant cell type. Cushing suggested the probability that the protoplasmic astrocyte represents a degenerative or undeveloped form of the fibrillary astrocyte. Furthermore, a single given tumor may present considerably varying aspects. In some areas one may find densely accumulated large fibrillary astrocytes intermingled with the piloidal ("hairlike," on account of their numerous fine, hairlike fibers); in others the cells are more

widely spaced, small, and embedded in a dense meshwork of glia fibers. The tumors may undergo cystic degeneration, especially those found in the cerebellum; in such a case the tumor cells are small, or they may become calcified (figs. 216, 217). Tumors of the giant cell type

TABLE 18.—*Synonyms of Brain Tumors*

Bailey and Cushing	Roussy and Oberling		Other Authors
Name	Name	Plate*	Name
Astroblastoma	astrocytome	IV-A	neuroblastoma
Astrocytoma	astrocytome	II	astroma; glioma; Sternzellengliom
Ependymoma	épendymocytome épendymoblastome	VII-D, E	ependymal glioma
Ganglioneuroma	ganglioneurome	IX-C, D	glioneuroma; gliogangliome; neuroglioma ganglionare; spongioneuroblastoma
Glioblastoma multiforme	glioblastome	III-A IV-D, G	gliosarcoma; gliome polymorphe; spongioblastoma multiforme
Medulloblastoma	neurospongiome	X, XI-A, B	neuroblastoma; neurocytome embryonnaire
Medullo-epithelioma	neuroépithéliome sacrococcygien	XI-D	
Neuro-epithelioma	épendymogliome	IX-B	blastome épendymale; retinocytome à stéphanocytes
Oligodendroglioma	oligodendrocytome	III-D V-A, B	gliome à petites cellules
Spongioblastoma polare	astrocytome or oligodendrocytome à cellules fusiformes	III-C V-C	gliome sous-épendymaire; central neurinoma
Neurinoma	neurinome	XII-A, C	perineurial fibroblastoma; schwannoma; solitary neurofibroma; gliome périphérique

* Numerals refer to plates in Roussy, G., and Oberling, C.: Atlas du cancer, pts. 9 and 10.

frequently present a picture of fattened glia, a condition that has been described as "ameboid transformation." Some astrocytomas, such as those arising in the subependymal tissue of the ventricles, are extremely fibrillary and of a dense consistency. Sometimes one may have difficulty in differentiating such tumors, which are rich in fibers and poor in cells,

sulated tumors of groups 1 to 6, they may invade the brain and become malignant growths. They may then show combinations of melanin-containing polyhedral cells with more elongated cells of a sarcomatous arrangement. The pigment is found in the form of small granules in the tumor cells, staining dark brown or black under Hortega's method.

Sarcomas may arise from the connective tissue fibroblasts of the cerebral blood vessels, in the form of peritheliomas. Diffuse spreading throughout the piarachnoid is a rare occurrence. Bailey and Bucy state that this lesion is found in adults as a primary tumor, while in children such a diffuse, neoplastic meningeal disease follows primary sarcoma of the brain. The cell types are manifold: most numerous are the round or polyhedral eosinophilic cells with eccentric nuclei, which are embedded in a stroma of reticular connective tissue.

Lipomas may be found in rare instances as accidental autopsy disclosures, most of them on the superior surface of the corpus callosum, others about the tuber cinereum or the corpora quadrigemina. Figures showing the relative frequency of meningeal tumors are given in table 20. Guttmann found 47 meningiomas (in 38 females, 9 males) in 11,000 autopsies at the hospital in München-Schwabing in the period from 1913 to 1922.

Tumors of the Glia

The lack of a uniform nomenclature for classification of the gliomas is regrettable because it renders difficult a mutual understanding among pathologists of different countries. Fortunately, the photomicrographs published in monographs and in the standard works facilitate identification of a given tumor (Bailey and Cushing, *Tumors of the Glioma Group;* Roussy and Oberling, *Les tumeurs des centres nerveux et des nerfs périphériques*).

The gliomas may be subdivided into two groups. In the first group the type cell is the adult glia cell, astrocyte, or oligodendrocyte. In the second group the type cells imitate, more or less closely, embryonic types of glia cells. They are designated in each case by addition of the suffix "-oma" to the name of the main type cell.

Group 1

1. *Astrocytoma* (*Astrocytome, Gliome Astrocytaire*).—Four different forms have been described—the protoplasmic, the fibrillary, the piloidal, and the giant cell type. Cushing suggested the probability that the protoplasmic astrocyte represents a degenerative or undeveloped form of the fibrillary astrocyte. Furthermore, a single given tumor may present considerably varying aspects. In some areas one may find densely accumulated large fibrillary astrocytes intermingled with the piloidal ("hairlike," on account of their numerous fine, hairlike fibers); in others the cells are more

widely spaced, small, and embedded in a dense meshwork of glia fibers. The tumors may undergo cystic degeneration, especially those found in the cerebellum; in such a case the tumor cells are small, or they may become calcified (figs. 216, 217). Tumors of the giant cell type

TABLE 18.—*Synonyms of Brain Tumors*

Bailey and Cushing	Roussy and Oberling		Other Authors
Name	Name	Plate*	Name
Astroblastoma	astrocytome	IV-A	neuroblastoma
Astrocytoma	astrocytome	II	astroma; glioma; Sternzellengliom
Ependymoma	épendymocytome épendymoblastome	VII-D, E	ependymal glioma
Ganglioneuroma	ganglioneurome	IX-C, D	glioneuroma; gliogangliome; neuroglioma ganglionare; spongioneuroblastoma
Glioblastoma multiforme	glioblastome	III-A IV-D, G	gliosarcoma; gliome polymorphe; spongioblastoma multiforme
Medulloblastoma	neurospongiome	X, XI-A, B	neuroblastoma; neurocytome embryonnaire
Medullo-epithelioma	neuroépithéliome sacrococcygien	XI-D	
Neuro-epithelioma	épendymogliome	IX-B	blastome épendymale; retinocytome à stéphanocytes
Oligodendroglioma	oligodendrocytome	III-D V-A, B	gliome à petites cellules
Spongioblastoma polare	astrocytome or oligodendrocytome à cellules fusiformes	III-C V-C	gliome sous-épendymaire; central neurinoma
Neurinoma	neurinome	XII-A, C	perineurial fibroblastoma; schwannoma; solitary neurofibroma; gliome périphérique

* Numerals refer to plates in Roussy, G., and Oberling, C.: Atlas du cancer, pts. 9 and 10.

frequently present a picture of fattened glia, a condition that has been described as "ameboid transformation." Some astrocytomas, such as those arising in the subependymal tissue of the ventricles, are extremely fibrillary and of a dense consistency. Sometimes one may have difficulty in differentiating such tumors, which are rich in fibers and poor in cells,

sulated tumors of groups 1 to 6, they may invade the brain and become malignant growths. They may then show combinations of melanin-containing polyhedral cells with more elongated cells of a sarcomatous arrangement. The pigment is found in the form of small granules in the tumor cells, staining dark brown or black under Hortega's method.

Sarcomas may arise from the connective tissue fibroblasts of the cerebral blood vessels, in the form of peritheliomas. Diffuse spreading throughout the piarachnoid is a rare occurrence. Bailey and Bucy state that this lesion is found in adults as a primary tumor, while in children such a diffuse, neoplastic meningeal disease follows primary sarcoma of the brain. The cell types are manifold: most numerous are the round or polyhedral eosinophilic cells with eccentric nuclei, which are embedded in a stroma of reticular connective tissue.

Lipomas may be found in rare instances as accidental autopsy disclosures, most of them on the superior surface of the corpus callosum, others about the tuber cinereum or the corpora quadrigemina. Figures showing the relative frequency of meningeal tumors are given in table 20. Guttmann found 47 meningiomas (in 38 females, 9 males) in 11,000 autopsies at the hospital in München-Schwabing in the period from 1913 to 1922.

Tumors of the Glia

The lack of a uniform nomenclature for classification of the gliomas is regrettable because it renders difficult a mutual understanding among pathologists of different countries. Fortunately, the photomicrographs published in monographs and in the standard works facilitate identification of a given tumor (Bailey and Cushing, *Tumors of the Glioma Group;* Roussy and Oberling, *Les tumeurs des centres nerveux et des nerfs périphériques*).

The gliomas may be subdivided into two groups. In the first group the type cell is the adult glia cell, astrocyte, or oligodendrocyte. In the second group the type cells imitate, more or less closely, embryonic types of glia cells. They are designated in each case by addition of the suffix "-oma" to the name of the main type cell.

Group 1

1. *Astrocytoma* (*Astrocytome, Gliome Astrocytaire*).—Four different forms have been described—the protoplasmic, the fibrillary, the piloidal, and the giant cell type. Cushing suggested the probability that the protoplasmic astrocyte represents a degenerative or undeveloped form of the fibrillary astrocyte. Furthermore, a single given tumor may present considerably varying aspects. In some areas one may find densely accumulated large fibrillary astrocytes intermingled with the piloidal ("hairlike," on account of their numerous fine, hairlike fibers); in others the cells are more

widely spaced, small, and embedded in a dense meshwork of glia fibers. The tumors may undergo cystic degeneration, especially those found in the cerebellum; in such a case the tumor cells are small, or they may become calcified (figs. 216, 217). Tumors of the giant cell type

TABLE 18.—*Synonyms of Brain Tumors*

Bailey and Cushing	Roussy and Oberling		Other Authors
Name	Name	Plate*	Name
Astroblastoma	astrocytome	IV-A	neuroblastoma
Astrocytoma	astrocytome	II	astroma; glioma; Sternzellengliom
Ependymoma	épendymocytome épendymoblastome	VII-D, E	ependymal glioma
Ganglioneuroma	ganglioneurome	IX-C, D	glioneuroma; gliogangliome; neuroglioma ganglionare; spongioneuroblastoma
Glioblastoma multiforme	glioblastome	III-A IV-D, G	gliosarcoma; gliome polymorphe; spongioblastoma multiforme
Medulloblastoma	neurospongiome	X, XI-A, B	neuroblastoma; neurocytome embryonnaire
Medullo-epithelioma	neuroépithéliome sacrococcygien	XI-D	
Neuro-epithelioma	épendymogliome	IX-B	blastome épendymale; retinocytome à stéphanocytes
Oligodendroglioma	oligodendrocytome	III-D V-A, B	gliome à petites cellules
Spongioblastoma polare	astrocytome or oligodendrocytome à cellules fusiformes	III-C V-C	gliome sous-épendymaire; central neurinoma
Neurinoma	neurinome	XII-A, C	perineurial fibroblastoma; schwannoma; solitary neurofibroma; gliome périphérique

* Numerals refer to plates in Roussy, G., and Oberling, C.: Atlas du cancer, pts. 9 and 10.

frequently present a picture of fattened glia, a condition that has been described as "ameboid transformation." Some astrocytomas, such as those arising in the subependymal tissue of the ventricles, are extremely fibrillary and of a dense consistency. Sometimes one may have difficulty in differentiating such tumors, which are rich in fibers and poor in cells,

sulated tumors of groups 1 to 6, they may invade the brain and become malignant growths. They may then show combinations of melanin-containing polyhedral cells with more elongated cells of a sarcomatous arrangement. The pigment is found in the form of small granules in the tumor cells, staining dark brown or black under Hortega's method.

Sarcomas may arise from the connective tissue fibroblasts of the cerebral blood vessels, in the form of peritheliomas. Diffuse spreading throughout the piarachnoid is a rare occurrence. Bailey and Bucy state that this lesion is found in adults as a primary tumor, while in children such a diffuse, neoplastic meningeal disease follows primary sarcoma of the brain. The cell types are manifold: most numerous are the round or polyhedral eosinophilic cells with eccentric nuclei, which are embedded in a stroma of reticular connective tissue.

Lipomas may be found in rare instances as accidental autopsy disclosures, most of them on the superior surface of the corpus callosum, others about the tuber cinereum or the corpora quadrigemina. Figures showing the relative frequency of meningeal tumors are given in table 20. Guttmann found 47 meningiomas (in 38 females, 9 males) in 11,000 autopsies at the hospital in München-Schwabing in the period from 1913 to 1922.

Tumors of the Glia

The lack of a uniform nomenclature for classification of the gliomas is regrettable because it renders difficult a mutual understanding among pathologists of different countries. Fortunately, the photomicrographs published in monographs and in the standard works facilitate identification of a given tumor (Bailey and Cushing, *Tumors of the Glioma Group;* Roussy and Oberling, *Les tumeurs des centres nerveux et des nerfs périphériques*).

The gliomas may be subdivided into two groups. In the first group the type cell is the adult glia cell, astrocyte, or oligodendrocyte. In the second group the type cells imitate, more or less closely, embryonic types of glia cells. They are designated in each case by addition of the suffix "-oma" to the name of the main type cell.

Group 1

1. *Astrocytoma* (*Astrocytome, Gliome Astrocytaire*).—Four different forms have been described—the protoplasmic, the fibrillary, the piloidal, and the giant cell type. Cushing suggested the probability that the protoplasmic astrocyte represents a degenerative or undeveloped form of the fibrillary astrocyte. Furthermore, a single given tumor may present considerably varying aspects. In some areas one may find densely accumulated large fibrillary astrocytes intermingled with the piloidal ("hairlike," on account of their numerous fine, hairlike fibers); in others the cells are more

widely spaced, small, and embedded in a dense meshwork of glia fibers. The tumors may undergo cystic degeneration, especially those found in the cerebellum; in such a case the tumor cells are small, or they may become calcified (figs. 216, 217). Tumors of the giant cell type

TABLE 18.—*Synonyms of Brain Tumors*

Bailey and Cushing	Roussy and Oberling		Other Authors
Name	Name	Plate*	Name
Astroblastoma	astrocytome	IV-A	neuroblastoma
Astrocytoma	astrocytome	II	astroma; glioma; Sternzellengliom
Ependymoma	épendymocytome épendymoblastome	VII-D, E	ependymal glioma
Ganglioneuroma	ganglioneurome	IX-C, D	glioneuroma; gliogangliome; neuroglioma ganglionare; spongioneuroblastoma
Glioblastoma multiforme	glioblastome	III-A IV-D, G	gliosarcoma; gliome polymorphe; spongioblastoma multiforme
Medulloblastoma	neurospongiome	X, XI-A, B	neuroblastoma; neurocytome embryonnaire
Medullo-epithelioma	neuroépithéliome sacrococcygien	XI-D	
Neuro-epithelioma	épendymogliome	IX-B	blastome épendymale; retinocytome à stéphanocytes
Oligodendroglioma	oligodendrocytome	III-D V-A, B	gliome à petites cellules
Spongioblastoma polare	astrocytome or oligodendrocytome à cellules fusiformes	III-C V-C	gliome sous-épendymaire; central neurinoma
Neurinoma	neurinome	XII-A, C	perineurial fibroblastoma; schwannoma; solitary neurofibroma; gliome périphérique

* Numerals refer to plates in Roussy, G., and Oberling, C.: Atlas du cancer, pts. 9 and 10.

frequently present a picture of fattened glia, a condition that has been described as "ameboid transformation." Some astrocytomas, such as those arising in the subependymal tissue of the ventricles, are extremely fibrillary and of a dense consistency. Sometimes one may have difficulty in differentiating such tumors, which are rich in fibers and poor in cells,

sulated tumors of groups 1 to 6, they may invade the brain and become malignant growths. They may then show combinations of melanin-containing polyhedral cells with more elongated cells of a sarcomatous arrangement. The pigment is found in the form of small granules in the tumor cells, staining dark brown or black under Hortega's method.

Sarcomas may arise from the connective tissue fibroblasts of the cerebral blood vessels, in the form of peritheliomas. Diffuse spreading throughout the piarachnoid is a rare occurrence. Bailey and Bucy state that this lesion is found in adults as a primary tumor, while in children such a diffuse, neoplastic meningeal disease follows primary sarcoma of the brain. The cell types are manifold: most numerous are the round or polyhedral eosinophilic cells with eccentric nuclei, which are embedded in a stroma of reticular connective tissue.

Lipomas may be found in rare instances as accidental autopsy disclosures, most of them on the superior surface of the corpus callosum, others about the tuber cinereum or the corpora quadrigemina. Figures showing the relative frequency of meningeal tumors are given in table 20. Guttmann found 47 meningiomas (in 38 females, 9 males) in 11,000 autopsies at the hospital in München-Schwabing in the period from 1913 to 1922.

Tumors of the Glia

The lack of a uniform nomenclature for classification of the gliomas is regrettable because it renders difficult a mutual understanding among pathologists of different countries. Fortunately, the photomicrographs published in monographs and in the standard works facilitate identification of a given tumor (Bailey and Cushing, *Tumors of the Glioma Group;* Roussy and Oberling, *Les tumeurs des centres nerveux et des nerfs périphériques*).

The gliomas may be subdivided into two groups. In the first group the type cell is the adult glia cell, astrocyte, or oligodendrocyte. In the second group the type cells imitate, more or less closely, embryonic types of glia cells. They are designated in each case by addition of the suffix "-oma" to the name of the main type cell.

Group 1

1. *Astrocytoma* (*Astrocytome, Gliome Astrocytaire*).—Four different forms have been described—the protoplasmic, the fibrillary, the piloidal, and the giant cell type. Cushing suggested the probability that the protoplasmic astrocyte represents a degenerative or undeveloped form of the fibrillary astrocyte. Furthermore, a single given tumor may present considerably varying aspects. In some areas one may find densely accumulated large fibrillary astrocytes intermingled with the piloidal ("hairlike," on account of their numerous fine, hairlike fibers); in others the cells are more

widely spaced, small, and embedded in a dense meshwork of glia fibers. The tumors may undergo cystic degeneration, especially those found in the cerebellum; in such a case the tumor cells are small, or they may become calcified (figs. 216, 217). Tumors of the giant cell type

TABLE 18.—*Synonyms of Brain Tumors*

Bailey and Cushing	Roussy and Oberling		Other Authors
Name	Name	Plate*	Name
Astroblastoma	astrocytome	IV-A	neuroblastoma
Astrocytoma	astrocytome	II	astroma; glioma; Sternzellengliom
Ependymoma	épendymocytome épendymoblastome	VII-D, E	ependymal glioma
Ganglioneuroma	ganglioneurome	IX-C, D	glioneuroma; gliogangliome; neuroglioma ganglionare; spongioneuroblastoma
Glioblastoma multiforme	glioblastome	III-A IV-D, G	gliosarcoma; gliome polymorphe; spongioblastoma multiforme
Medulloblastoma	neurospongiome	X, XI-A, B	neuroblastoma; neurocytome embryonnaire
Medullo-epithelioma	neuroépithéliome sacrococcygien	XI-D	
Neuro-epithelioma	épendymogliome	IX-B	blastome épendymale; retinocytome à stéphanocytes
Oligodendroglioma	oligodendrocytome	III-D V-A, B	gliome à petites cellules
Spongioblastoma polare	astrocytome or oligodendrocytome à cellules fusiformes	III-C V-C	gliome sous-épendymaire; central neurinoma
Neurinoma	neurinome	XII-A, C	perineurial fibroblastoma; schwannoma; solitary neurofibroma; gliome périphérique

* Numerals refer to plates in Roussy, G., and Oberling, C.: Atlas du cancer, pts. 9 and 10.

frequently present a picture of fattened glia, a condition that has been described as "ameboid transformation." Some astrocytomas, such as those arising in the subependymal tissue of the ventricles, are extremely fibrillary and of a dense consistency. Sometimes one may have difficulty in differentiating such tumors, which are rich in fibers and poor in cells,

sulated tumors of groups 1 to 6, they may invade the brain and become malignant growths. They may then show combinations of melanin-containing polyhedral cells with more elongated cells of a sarcomatous arrangement. The pigment is found in the form of small granules in the tumor cells, staining dark brown or black under Hortega's method.

Sarcomas may arise from the connective tissue fibroblasts of the cerebral blood vessels, in the form of peritheliomas. Diffuse spreading throughout the piarachnoid is a rare occurrence. Bailey and Bucy state that this lesion is found in adults as a primary tumor, while in children such a diffuse, neoplastic meningeal disease follows primary sarcoma of the brain. The cell types are manifold: most numerous are the round or polyhedral eosinophilic cells with eccentric nuclei, which are embedded in a stroma of reticular connective tissue.

Lipomas may be found in rare instances as accidental autopsy disclosures, most of them on the superior surface of the corpus callosum, others about the tuber cinereum or the corpora quadrigemina. Figures showing the relative frequency of meningeal tumors are given in table 20. Guttmann found 47 meningiomas (in 38 females, 9 males) in 11,000 autopsies at the hospital in München-Schwabing in the period from 1913 to 1922.

Tumors of the Glia

The lack of a uniform nomenclature for classification of the gliomas is regrettable because it renders difficult a mutual understanding among pathologists of different countries. Fortunately, the photomicrographs published in monographs and in the standard works facilitate identification of a given tumor (Bailey and Cushing, *Tumors of the Glioma Group;* Roussy and Oberling, *Les tumeurs des centres nerveux et des nerfs périphériques*).

The gliomas may be subdivided into two groups. In the first group the type cell is the adult glia cell, astrocyte, or oligodendrocyte. In the second group the type cells imitate, more or less closely, embryonic types of glia cells. They are designated in each case by addition of the suffix "-oma" to the name of the main type cell.

Group 1

1. *Astrocytoma* (*Astrocytome, Gliome Astrocytaire*).—Four different forms have been described—the protoplasmic, the fibrillary, the piloidal, and the giant cell type. Cushing suggested the probability that the protoplasmic astrocyte represents a degenerative or undeveloped form of the fibrillary astrocyte. Furthermore, a single given tumor may present considerably varying aspects. In some areas one may find densely accumulated large fibrillary astrocytes intermingled with the piloidal ("hairlike," on account of their numerous fine, hairlike fibers); in others the cells are more

widely spaced, small, and embedded in a dense meshwork of glia fibers. The tumors may undergo cystic degeneration, especially those found in the cerebellum; in such a case the tumor cells are small, or they may become calcified (figs. 216, 217). Tumors of the giant cell type

TABLE 18.—*Synonyms of Brain Tumors*

Bailey and Cushing	Roussy and Oberling		Other Authors
Name	Name	Plate*	Name
Astroblastoma	astrocytome	IV-A	neuroblastoma
Astrocytoma	astrocytome	II	astroma; glioma; Sternzellengliom
Ependymoma	épendymocytome épendymoblastome	VII-D, E	ependymal glioma
Ganglioneuroma	ganglioneurome	IX-C, D	glioneuroma; gliogangliome; neuroglioma ganglionare; spongioneuroblastoma
Glioblastoma multiforme	glioblastome	III-A IV-D, G	gliosarcoma; gliome polymorphe; spongioblastoma multiforme
Medulloblastoma	neurospongiome	X, XI-A, B	neuroblastoma; neurocytome embryonnaire
Medullo-epithelioma	neuroépithéliome sacrococcygien	XI-D	
Neuro-epithelioma	épendymogliome	IX-B	blastome épendymale; retinocytome à stéphanocytes
Oligodendroglioma	oligodendrocytome	III-D V-A, B	gliome à petites cellules
Spongioblastoma polare	astrocytome or oligodendrocytome à cellules fusiformes	III-C V-C	gliome sous-épendymaire; central neurinoma
Neurinoma	neurinome	XII-A, C	perineurial fibroblastoma; schwannoma; solitary neurofibroma; gliome périphérique

* Numerals refer to plates in Roussy, G., and Oberling, C.: Atlas du cancer, pts. 9 and 10.

frequently present a picture of fattened glia, a condition that has been described as "ameboid transformation." Some astrocytomas, such as those arising in the subependymal tissue of the ventricles, are extremely fibrillary and of a dense consistency. Sometimes one may have difficulty in differentiating such tumors, which are rich in fibers and poor in cells,

sulated tumors of groups 1 to 6, they may invade the brain and become malignant growths. They may then show combinations of melanin-containing polyhedral cells with more elongated cells of a sarcomatous arrangement. The pigment is found in the form of small granules in the tumor cells, staining dark brown or black under Hortega's method.

Sarcomas may arise from the connective tissue fibroblasts of the cerebral blood vessels, in the form of peritheliomas. Diffuse spreading throughout the piarachnoid is a rare occurrence. Bailey and Bucy state that this lesion is found in adults as a primary tumor, while in children such a diffuse, neoplastic meningeal disease follows primary sarcoma of the brain. The cell types are manifold: most numerous are the round or polyhedral eosinophilic cells with eccentric nuclei, which are embedded in a stroma of reticular connective tissue.

Lipomas may be found in rare instances as accidental autopsy disclosures, most of them on the superior surface of the corpus callosum, others about the tuber cinereum or the corpora quadrigemina. Figures showing the relative frequency of meningeal tumors are given in table 20. Guttmann found 47 meningiomas (in 38 females, 9 males) in 11,000 autopsies at the hospital in München-Schwabing in the period from 1913 to 1922.

Tumors of the Glia

The lack of a uniform nomenclature for classification of the gliomas is regrettable because it renders difficult a mutual understanding among pathologists of different countries. Fortunately, the photomicrographs published in monographs and in the standard works facilitate identification of a given tumor (Bailey and Cushing, *Tumors of the Glioma Group;* Roussy and Oberling, *Les tumeurs des centres nerveux et des nerfs périphériques*).

The gliomas may be subdivided into two groups. In the first group the type cell is the adult glia cell, astrocyte, or oligodendrocyte. In the second group the type cells imitate, more or less closely, embryonic types of glia cells. They are designated in each case by addition of the suffix "-oma" to the name of the main type cell.

Group 1

1. *Astrocytoma* (*Astrocytome, Gliome Astrocytaire*).—Four different forms have been described—the protoplasmic, the fibrillary, the piloidal, and the giant cell type. Cushing suggested the probability that the protoplasmic astrocyte represents a degenerative or undeveloped form of the fibrillary astrocyte. Furthermore, a single given tumor may present considerably varying aspects. In some areas one may find densely accumulated large fibrillary astrocytes intermingled with the piloidal ("hairlike," on account of their numerous fine, hairlike fibers); in others the cells are more

widely spaced, small, and embedded in a dense meshwork of glia fibers. The tumors may undergo cystic degeneration, especially those found in the cerebellum; in such a case the tumor cells are small, or they may become calcified (figs. 216, 217). Tumors of the giant cell type

TABLE 18.—*Synonyms of Brain Tumors*

Bailey and Cushing	Roussy and Oberling		Other Authors
Name	Name	Plate*	Name
Astroblastoma	astrocytome	IV-A	neuroblastoma
Astrocytoma	astrocytome	II	astroma; glioma; Sternzellengliom
Ependymoma	épendymocytome épendymoblastome	VII-D, E	ependymal glioma
Ganglioneuroma	ganglioneurome	IX-C, D	glioneuroma; gliogangliome; neuroglioma ganglionare; spongioneuroblastoma
Glioblastoma multiforme	glioblastome	III-A IV-D, G	gliosarcoma; gliome polymorphe; spongioblastoma multiforme
Medulloblastoma	neurospongiome	X, XI-A, B	neuroblastoma; neurocytome embryonnaire
Medullo-epithelioma	neuroépithéliome sacrococcygien	XI-D	
Neuro-epithelioma	épendymogliome	IX-B	blastome épendymale; retinocytome à stéphanocytes
Oligodendroglioma	oligodendrocytome	III-D V-A, B	gliome à petites cellules
Spongioblastoma polare	astrocytome or oligodendrocytome à cellules fusiformes	III-C V-C	gliome sous-épendymaire; central neurinoma
Neurinoma	neurinome	XII-A, C	perineurial fibroblastoma; schwannoma; solitary neurofibroma; gliome périphérique

* Numerals refer to plates in Roussy, G., and Oberling, C.: Atlas du cancer, pts. 9 and 10.

frequently present a picture of fattened glia, a condition that has been described as "ameboid transformation." Some astrocytomas, such as those arising in the subependymal tissue of the ventricles, are extremely fibrillary and of a dense consistency. Sometimes one may have difficulty in differentiating such tumors, which are rich in fibers and poor in cells,

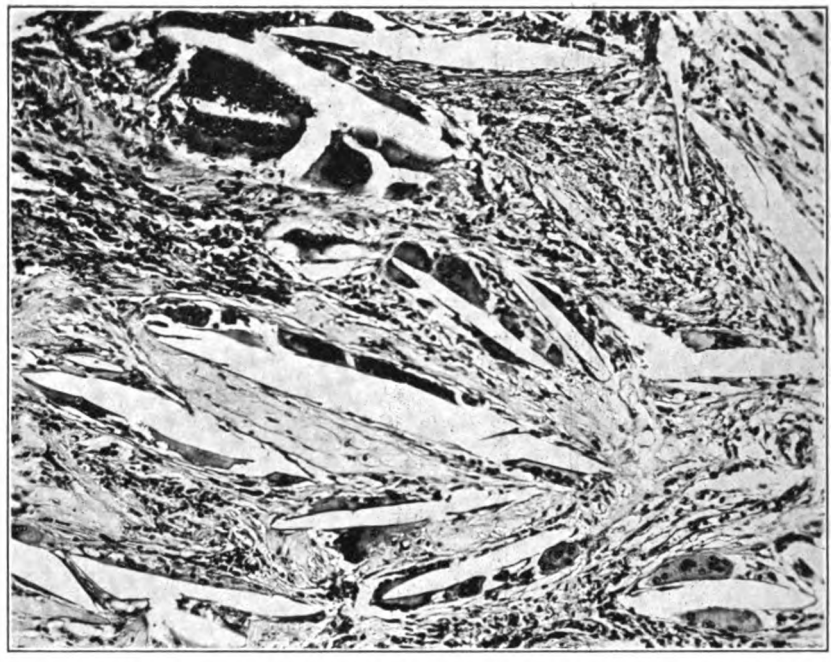


FIG. 214. CYST AT BASE OF BRAIN

Tumor-like, encapsulated mass of granulomatous tissue, containing numerous acicular slits surrounded by multinuclear giant cells. Van Gieson stain. Similar formations can be produced experimentally by injecting fats into animal brains. Liberated fatty acid crystals act as foreign bodies and induce granuloma formation

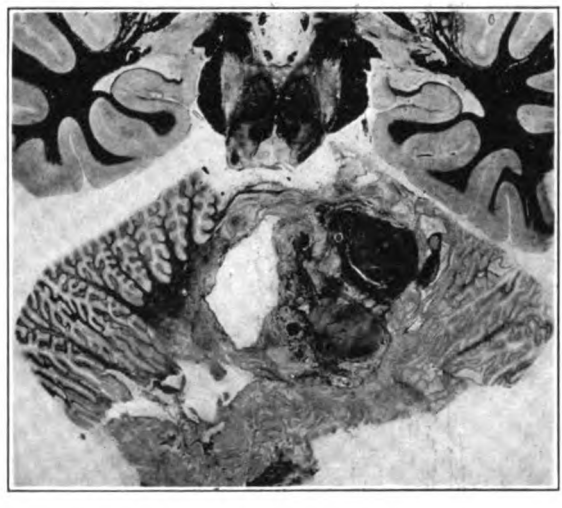


FIG. 215. CEREBELLAR CYST AND ASTROCYTOMA

Horizontal section of brain. Loyez stain

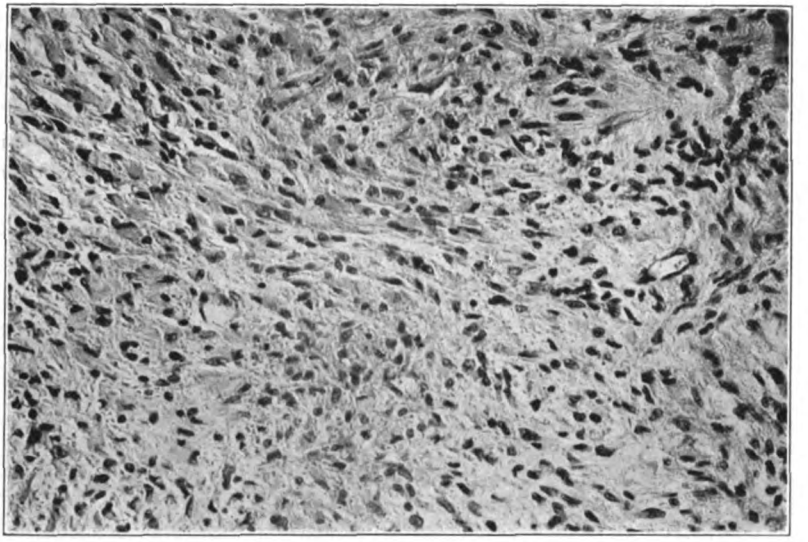


FIG. 216

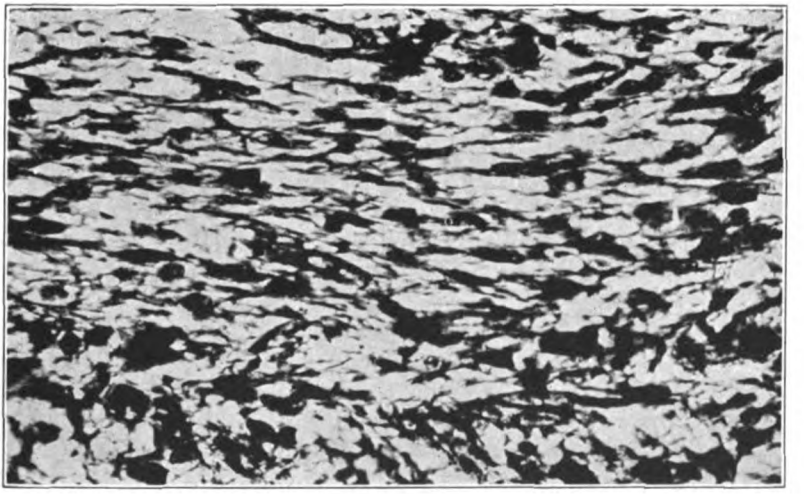


FIG. 217

FIGS. 216, 217. ASTROCYTOMA PILIFORME

Fig. 216. Van Gieson stain.

Fig. 217. Formation of numerous fine hairlike fibrillary processes of neoplastic astrocytes. Davenport stain for gliomas

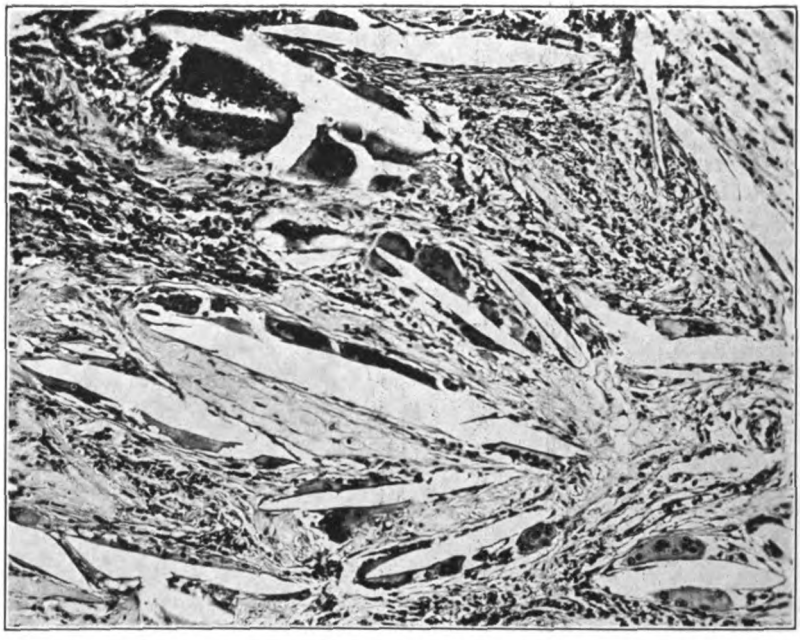


FIG. 214. CYST AT BASE OF BRAIN

Tumor-like, encapsulated mass of granulomatous tissue, containing numerous acicular slits surrounded by multinuclear giant cells. Van Gieson stain. Similar formations can be produced experimentally by injecting fats into animal brains. Liberated fatty acid crystals act as foreign bodies and induce granuloma formation

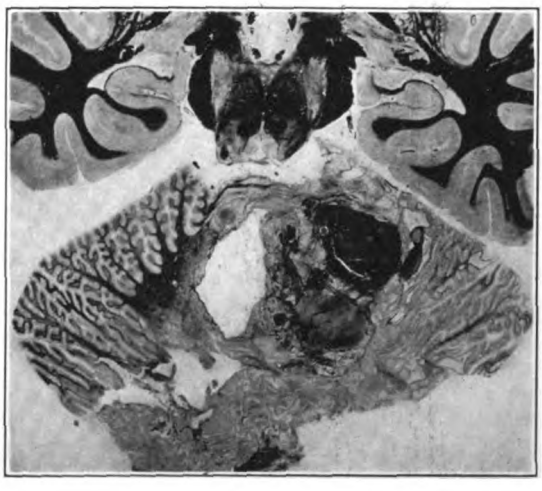


FIG. 215. CEREBELLAR CYST AND ASTROCYTOMA

Horizontal section of brain. Loyez stain

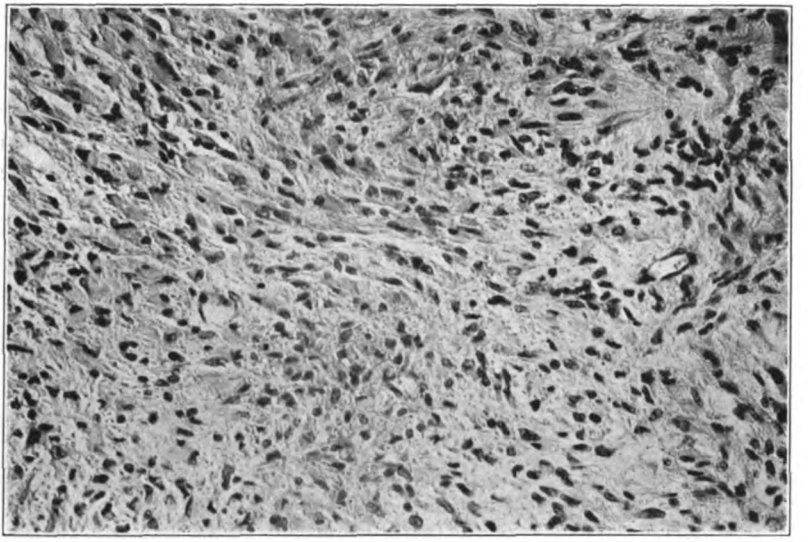


FIG. 216

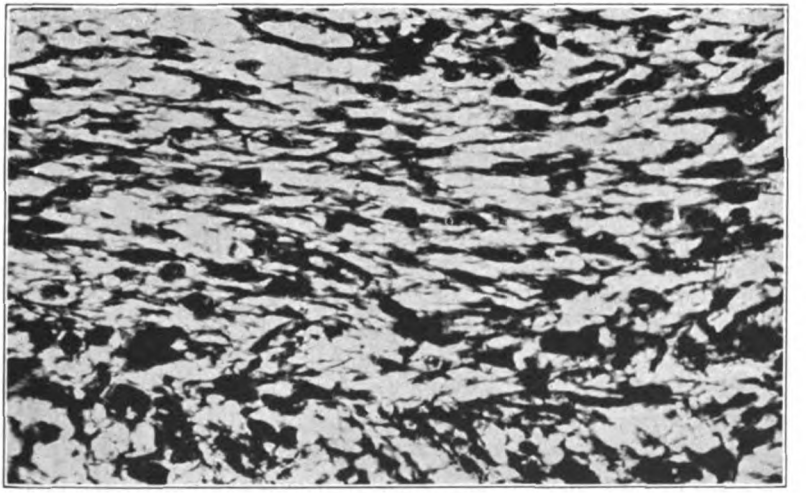


FIG. 217

FIGS. 216, 217. ASTROCYTOMA PILIFORME

Fig. 216. Van Gieson stain.

Fig. 217. Formation of numerous fine hairlike fibrillary processes of neoplastic astrocytes. Davenport stain for gliomas

from sclerotic areas that develop after softening or inflammatory reactions (figs. 218, 219). According to the orthodox theory, astrocytomas are slowly growing tumors and relatively benign. However, Scherer claims that in his material most of the astrocytomas underwent transformation into glioblastomas. He doubts that the astrocytic proliferation found in the periphery of glioblastomas represents an attempt at encapsulation, regarding it rather as a preliminary step in the neoplastic transformation of glia cells. Alpers and Rowe found in a material of 128 astrocytomas a distribution as follows: 75 per cent, fibrillary; 12 per cent, cystic; 8 per cent, giant cell type; 5 per cent, small cell type.

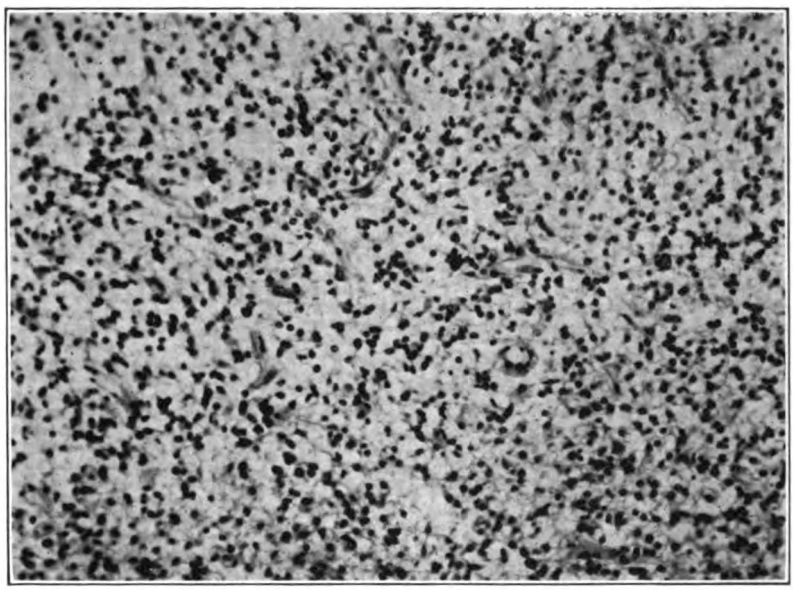


FIG. 218. ASTROCYTOMA FIBRILLARE
Hematoxylin-eosin stain

2. *Oligodendroglioma (Oligodendrocytome).*—In preparations stained with hematoxylin-eosin, this tumor may easily be recognized by the uniform appearance of the round, densely accumulated nuclei, measuring from 10 to 20 microns. They are surrounded by a small zone of cytoplasm, sometimes staining distinctly with eosin, but usually forming a pale halo. In silver preparations different forms may be seen, the relative number varying in different tumors. Forms that resemble the normal oligodendroglia, with short processes radiating to all sides, are frequently encountered. Other cells, which are larger, send out one massive fiber to the one pole and a few fine fibers to the other pole, thus resembling the embryonic oligodendro-

blast. Besides these, there appear transitional forms that are difficult to differentiate from astrocytes (figs. 220, 221). In the region surrounding the tumor, an intense proliferation of satellites around neurons may be seen, increasing toward the tumor. Such pictures, as well as proliferation of astrocytes and transformation of fasicular glia into bipolar cells, as seen in the outer zones of glioblastomas, favor decidedly the assumption of a neoplastic transformation of adult glia cells rather than of a proliferation of pre-existing germ centers.

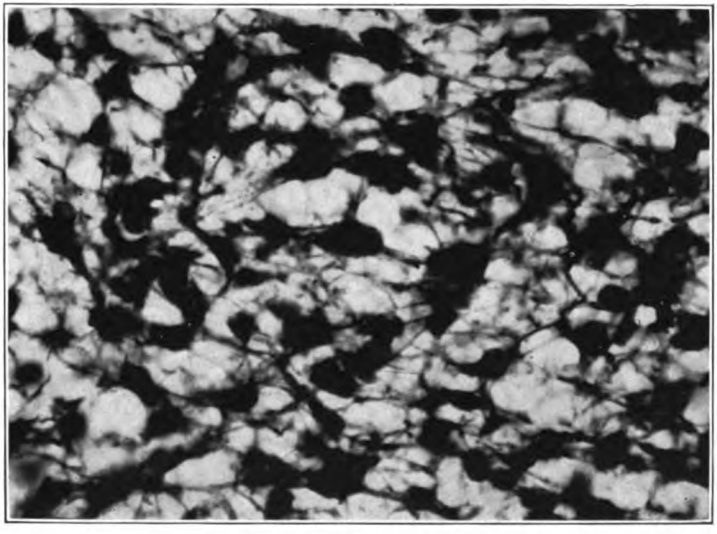


FIG. 219. ASTROCYTOMA FIBRILLARE
Davenport stain for gliomas. Higher magnification than in fig. 218

Oligodendrogliomas are not very vascular. Intense capillary hyperplasia seems to be an exception. The tumor cells may be swollen and undergo fatty degeneration. Necrotic areas within the tumor and incrustation with calcium salts, producing a shadow on the roentgen ray plate, are frequently found. Like the astrocytoma, this glioma grows slowly and is relatively benign. It is most frequently found within the cerebral hemispheres.

It appears strange that no tumors arising from microglia have been described; it may be that the lack of special staining methods prevents disclosure of the neoplastic transformation of microglia in the early stages of glioblastoma formation. It is also possible that the tumor described as "polar spongioblastoma" is a derivative of this element. There is further

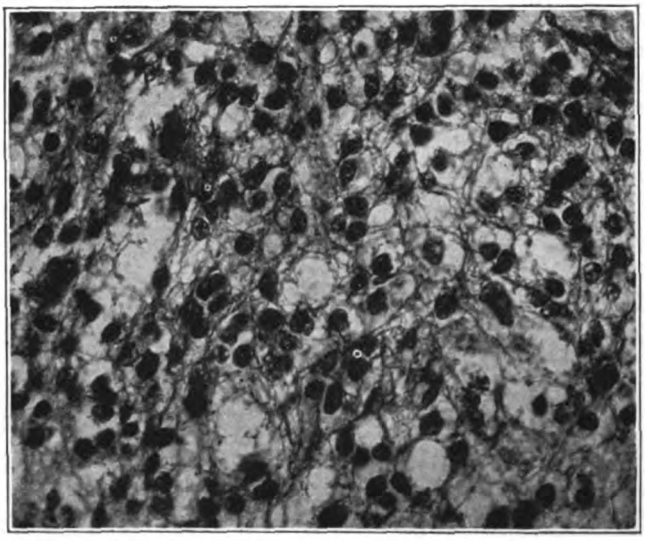


FIG. 220

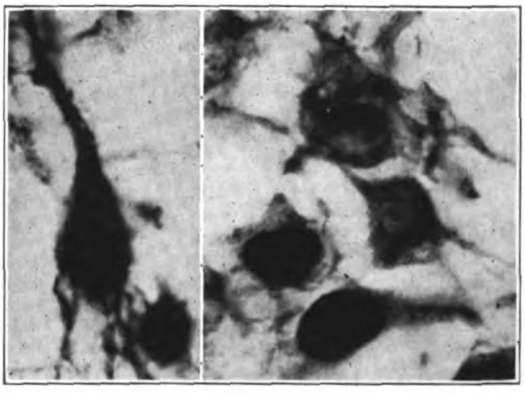


FIG. 221

FIGS. 220, 221. OLIGODENDROGLIOMA

Fig. 220. Hematoxylin-eosin stain.

Fig. 221. Davenport stain. One large elongated oligodendroblast with several more adult forms, oligodendrocytes

the possibility that tumors described as "mesogliomas" belong to this group (Belezky, Anzen).

GROUP 2

Six different tumors may be classified within this group.

1. *Glioblastoma Multiforme (Glioblastome).*—This tumor is described in the older literature as "gliosarcoma." The resemblance of its cells to the embryonic spongioblasts has been emphasized by Ribbert, and by Globus and Strauss in their term "spongioblastoma multiforme"—indicating the polymorphous nature of these gliomas, which makes impossible any more detailed classification. The more of these tumors one studies, the more one is surprised at the number of variations that occur. The type of tumor that was described by Globus and Strauss is characterized by the presence of multinuclear giant cells, by a palisade arrangement of unipolar spongioblasts, the processes of which radiate to a common center, and by necrotic areas surrounded by rows of more densely accumulated tumor cells. In hematoxylin-eosin preparations the closely arranged nuclei of different form and size, the typical arrangement described above, and the multinuclear giant cells, make diagnosis easy. In silver-impregnated sections, cells resembling unipolar spongioblasts are seen intermingled with more elongated bipolar forms and various transitional forms of astrocytes (figs. 222–29).

Other tumors of this group do not contain the multinuclear giant cells, and their aspect is more uniform, owing to the absence of necrotic areas. The cell types are just as variable as in the first-mentioned type. In the outer zone, a more fibrillary structure may be seen, brought about by the arrangement of elongated bipolar cells in long chains. One is under the impression that these cells arise from the interfascicular glia, especially if they are studied in sections stained for myelin sheaths or axis-cylinders (fig. 228).

In many of the multiform glioblastomas an abundance of vascular spaces is present. These are lined with endothelial cells, which may proliferate, and they may be surrounded by a connective tissue stroma undergoing hyaline transformation. The hemorrhages frequently found in these tumors are easily explained by reason of ruptures of these numerous thin-walled vessels (figs. 224, 243). French pathologists assume neoplastic disease of the blood vessels accompanying the glia transformation; they speak of an *angiogliome.* About 40 per cent of such hemorrhages occur in lesion of the midline or of the midline structures (Oberg).

2. *Spongioblastoma Polare.*—This type of tumor has been described as "central neurinoma" (Josephy) and also as "diffuse lemmoblastosis" (von Santha), because of its elongated cells streaming out in long rows and imitating an acoustic neurinoma. In silver-impregnated sections the long processes of the unipolar or bipolar cells, resembling spongioblasts, may be

recognized. Similar neoplastic forms have been described as occurring in combination with tuberous sclerosis (Globus), or they may be seen in rare cases of generalized glioblastomatosis involving large areas of the brain

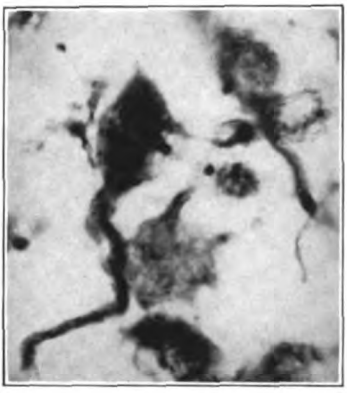


FIG. 222

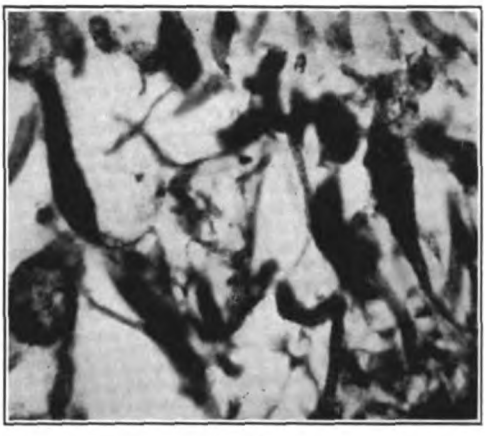


FIG. 223

FIGS. 222, 223. SPONGIOBLASTS

From glioblastoma multiforme. Davenport stain

Fig. 222. Unipolar spongioblasts.

Fig. 223. Bipolar spongioblasts

stem. In the series of Bailey and Cushing, 6 out of 9 growths were found in the cerebellum. They may undergo cystic degeneration (figs. 229, 279).

3. *Astroblastoma.*—These tumors could also be classified as a transitional group between astrocytomas and glioblastomas, because their type cell,

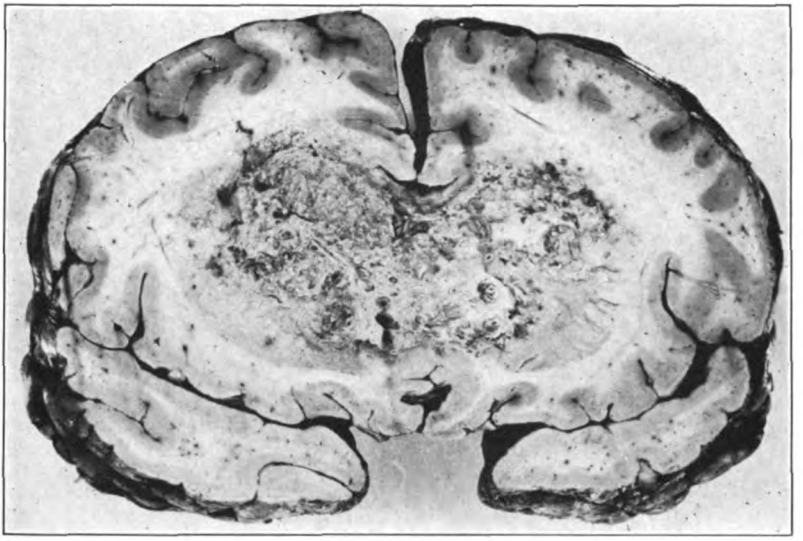


FIG. 224. GLIOBLASTOMA MULTIFORME
Neoplastic transformation of corpus callosum and white matter of cerebral cortex

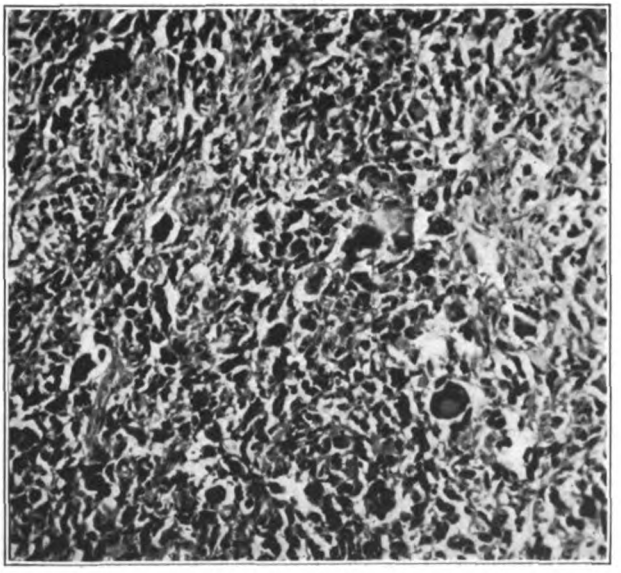


FIG. 225. GLIOBLASTOMA MULTIFORME (SPONGIOBLASTOMA MULTIFORME)
Demonstrating polymorphous type of tumor cells and formation of multinuclear giant cells. Hematoxylin-eosin stain

recognized. Similar neoplastic forms have been described as occurring in combination with tuberous sclerosis (Globus), or they may be seen in rare cases of generalized glioblastomatosis involving large areas of the brain

FIG. 222

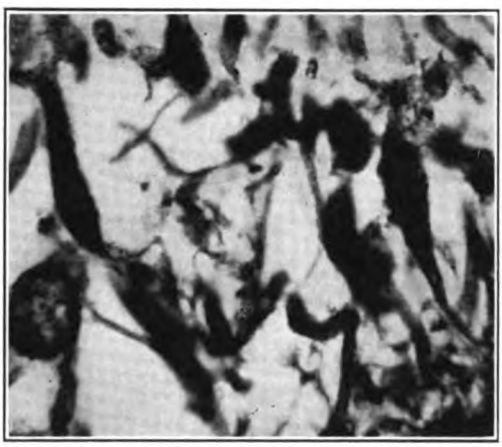


FIG. 223

FIGS. 222, 223. SPONGIOBLASTS

From glioblastoma multiforme. Davenport stain

Fig. 222. Unipolar spongioblasts.

Fig. 223. Bipolar spongioblasts

stem. In the series of Bailey and Cushing, 6 out of 9 growths were found in the cerebellum. They may undergo cystic degeneration (figs. 229, 279).

3. *Astroblastoma.*—These tumors could also be classified as a transitional group between astrocytomas and glioblastomas, because their type cell,

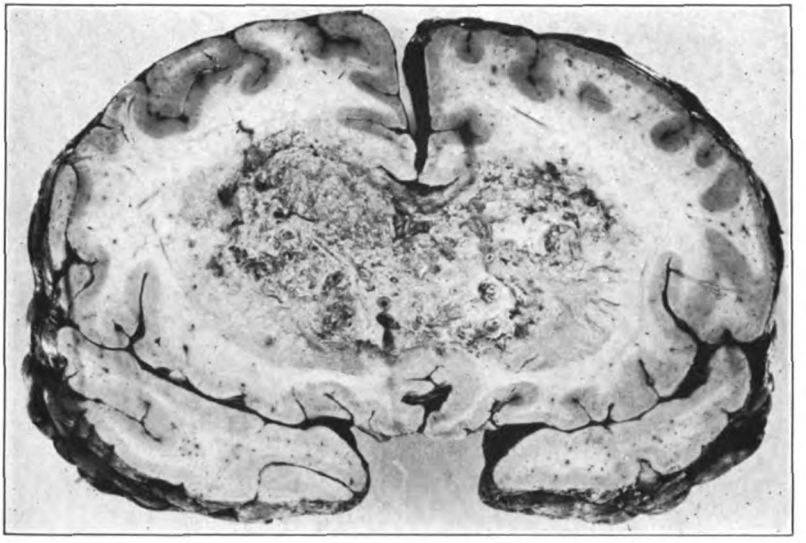


FIG. 224. GLIOBLASTOMA MULTIFORME
Neoplastic transformation of corpus callosum and white matter of cerebral cortex

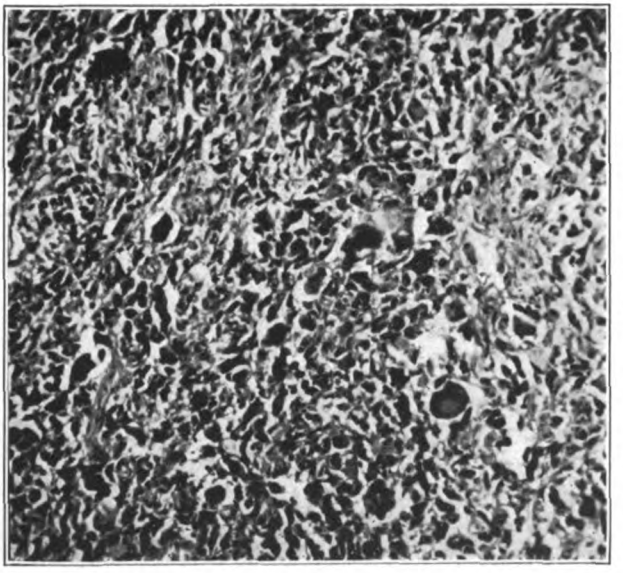


FIG. 225. GLIOBLASTOMA MULTIFORME (SPONGIOBLASTOMA MULTIFORME)
Demonstrating polymorphous type of tumor cells and formation of multinuclear giant cells. Hematoxylin-eosin stain

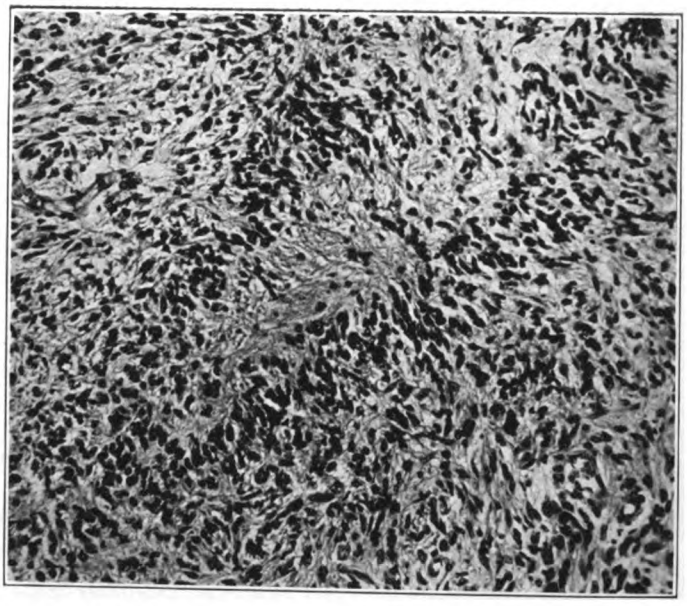


FIG. 226. GLIOBLASTOMA MULTIFORME (SPONGIOBLASTOMA MULTIFORME)
Formation of necrotic areas surrounded by palisading tumor cells that send processes toward center of these areas. Van Gieson stain

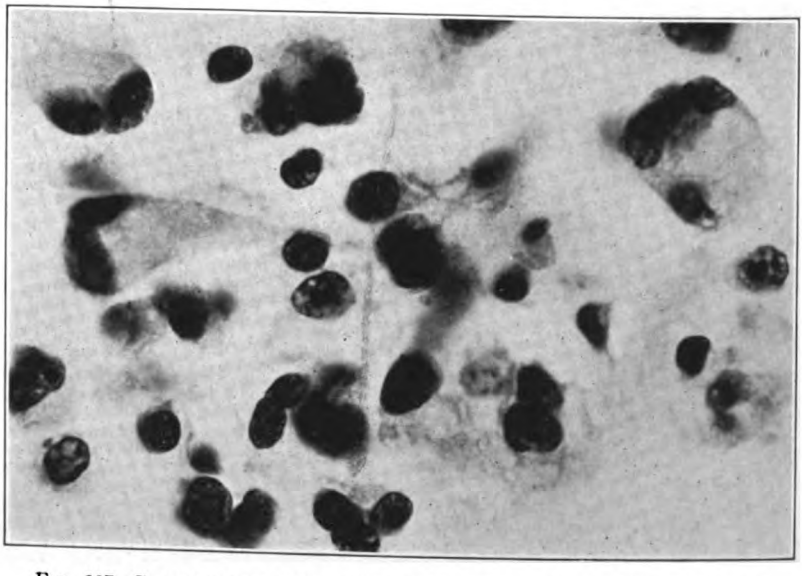


FIG. 227. GLIOBLASTOMA MULTIFORME (SPONGIOBLASTOMA MULTIFORME)
Tumor was characterized by formation of numerous multinuclear giant cells. Processes of some smaller spongioblasts are seen in center. Van Gieson stain

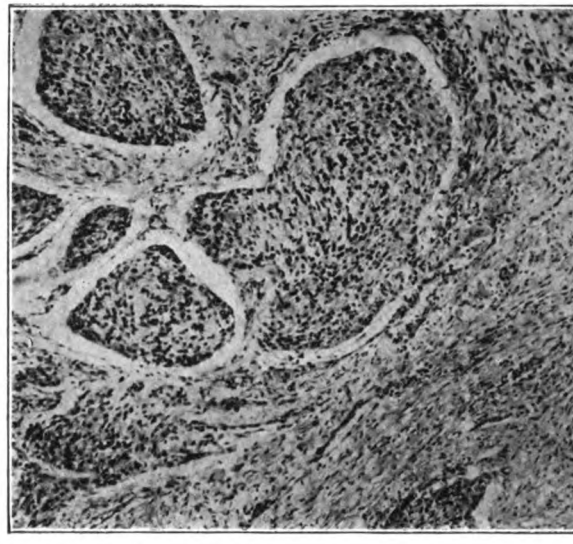


FIG. 228. GLIOBLASTOMA MULTIFORME

Tumor was composed of islands of formation of glioblastoma multiforme, surrounded by polar spongioblasts. Hematoxylin-eosin stain

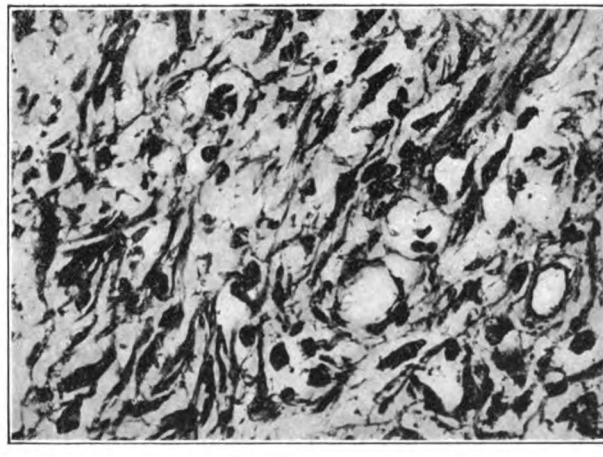


FIG. 229. SPONGIOBLASTOMA POLARE

Most of tumor cells are bipolar spongioblasts. Davenport stain

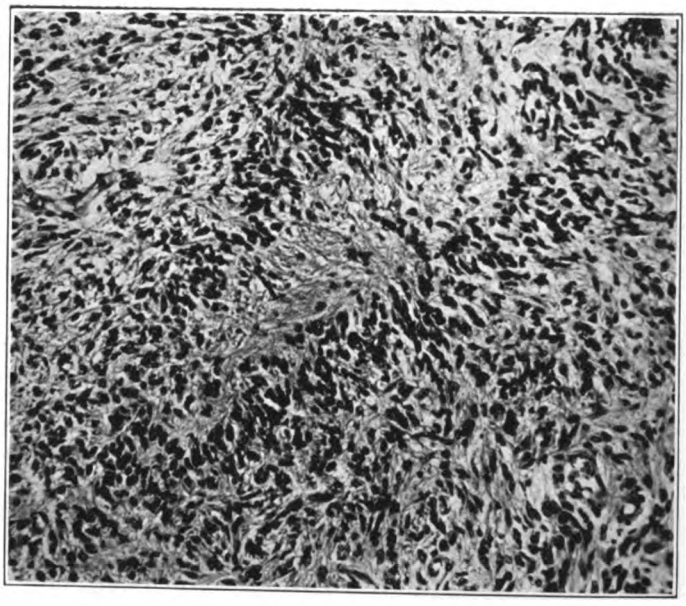


FIG. 226. GLIOBLASTOMA MULTIFORME (SPONGIOBLASTOMA MULTIFORME)
Formation of necrotic areas surrounded by palisading tumor cells that send processes toward center of these areas. Van Gieson stain

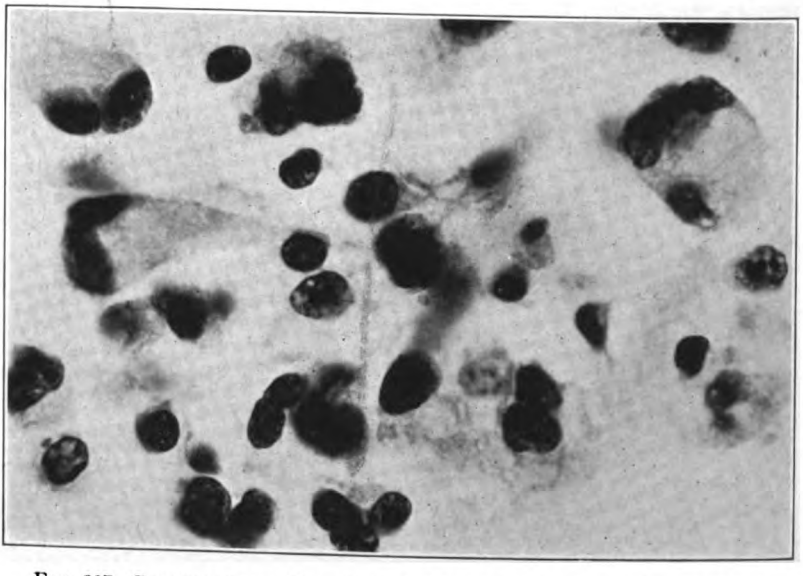


FIG. 227. GLIOBLASTOMA MULTIFORME (SPONGIOBLASTOMA MULTIFORME)
Tumor was characterized by formation of numerous multinuclear giant cells. Processes of some smaller spongioblasts are seen in center. Van Gieson stain

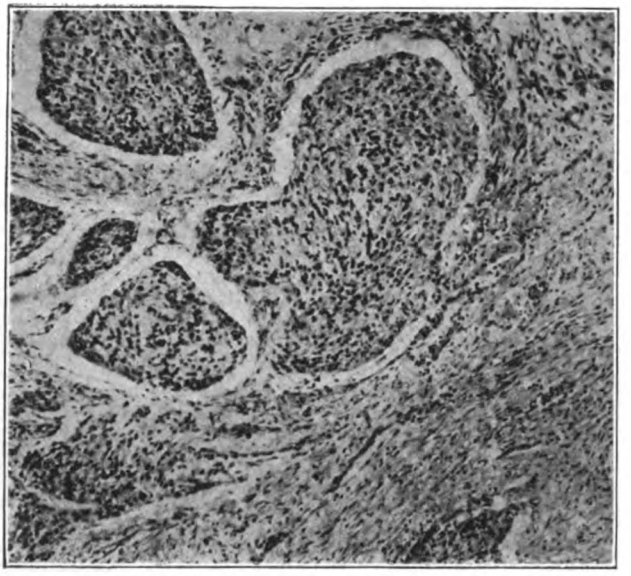


FIG. 228. GLIOBLASTOMA MULTIFORME

Tumor was composed of islands of formation of glioblastoma multiforme, surrounded by polar spongioblasts. Hematoxylin-eosin stain

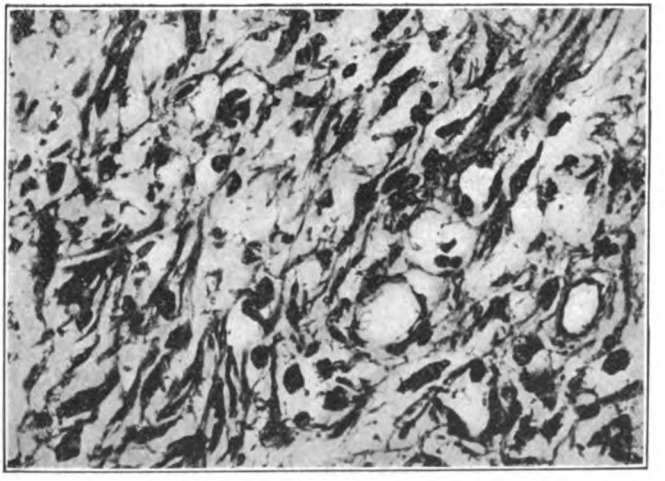


FIG. 229. SPONGIOBLASTOMA POLARE

Most of tumor cells are bipolar spongioblasts. Davenport stain

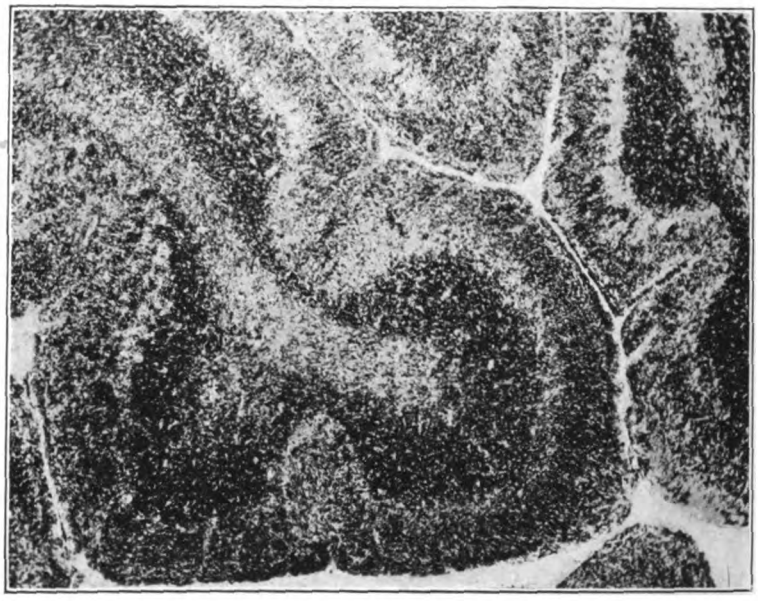


FIG. 230. DIFFUSE GLIOBLASTOMATOSIS

Case of megalencephalia in boy aged 7 years. Cerebellum. Entire brain stem and cerebellum showed neoplastic transformation. Cresyl violet stain

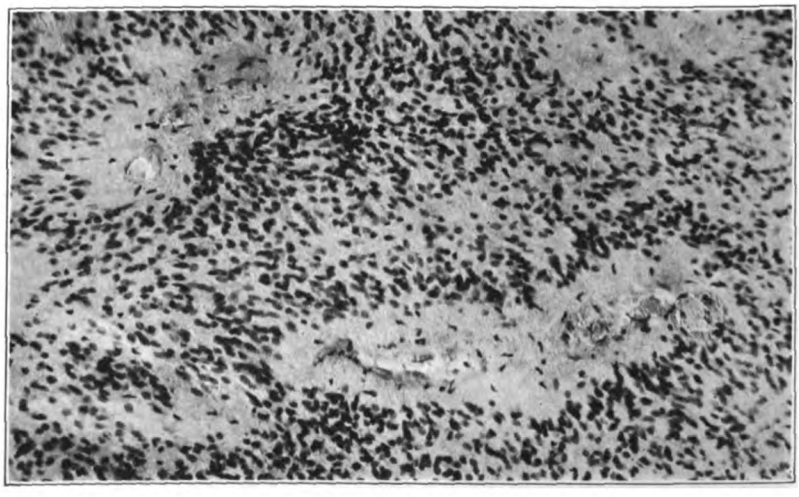


FIG. 231. ASTROBLASTOMA

Van Gieson stain, to demonstrate empty spaces around blood vessels, which are surrounded by wall of centrally radiating tumor cells

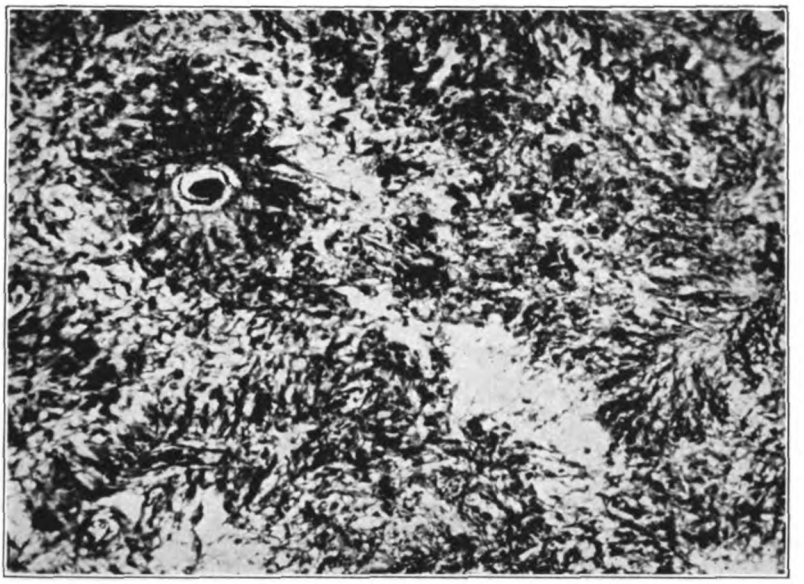


FIG. 232. ASTROBLASTOMA

Same tumor as in fig. 231. Davenport stain, to demonstrate fibrillary processes of tumor cells, which radiate toward blood vessels and fill out apparently empty spaces seen in fig. 231.

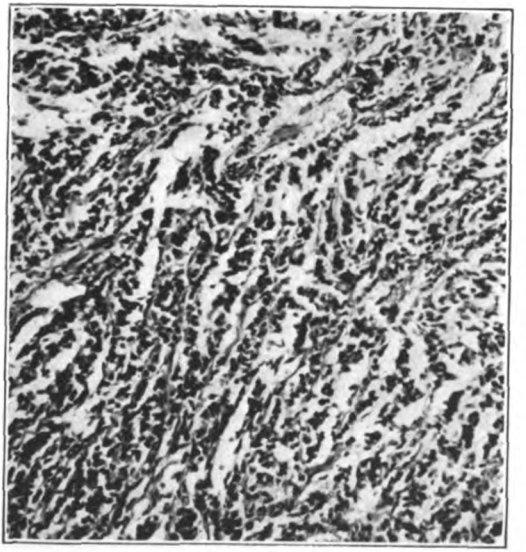


FIG. 233. MEDULLOBLASTOMA

Hematoxylin-eosin stain

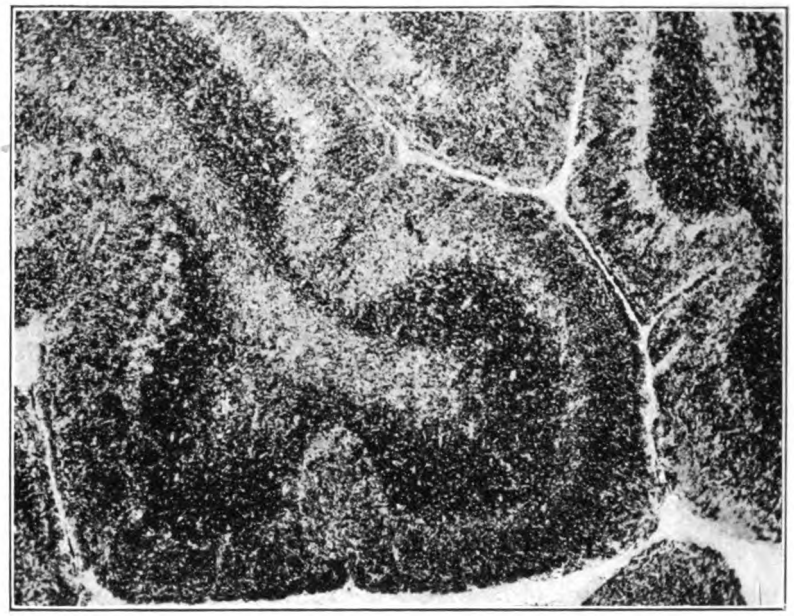


FIG. 230. DIFFUSE GLIOBLASTOMATOSIS

Case of megalencephalia in boy aged 7 years. Cerebellum. Entire brain stem and cerebellum showed neoplastic transformation. Cresyl violet stain

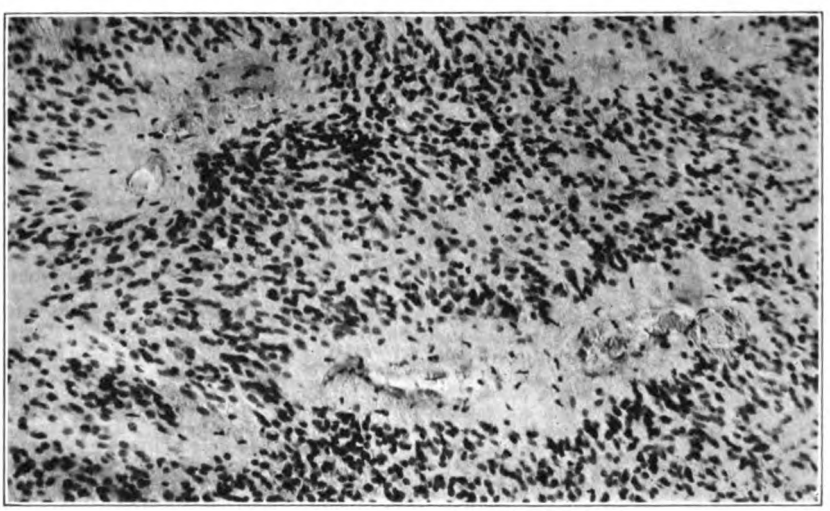


FIG. 231. ASTROBLASTOMA

Van Gieson stain, to demonstrate empty spaces around blood vessels, which are surrounded by wall of centrally radiating tumor cells

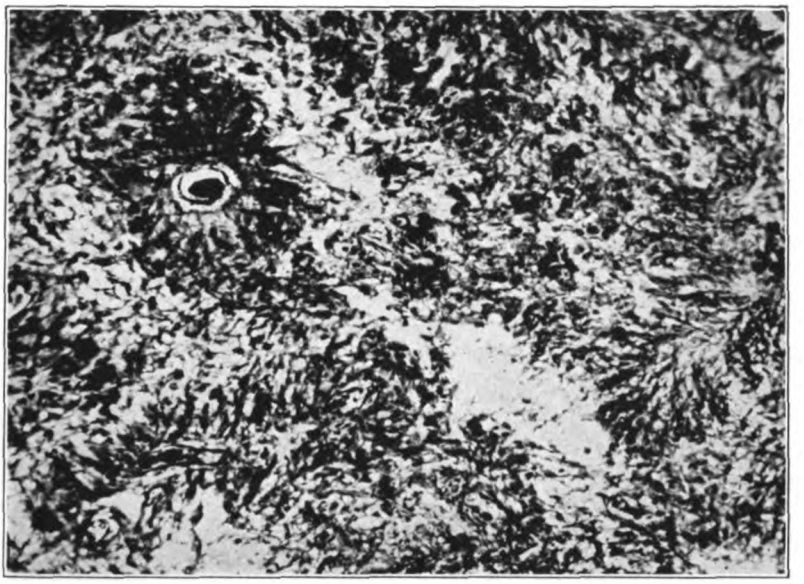


FIG. 232. ASTROBLASTOMA

Same tumor as in fig. 231. Davenport stain, to demonstrate fibrillary processes of tumor cells, which radiate toward blood vessels and fill out apparently empty spaces seen in fig. 231.

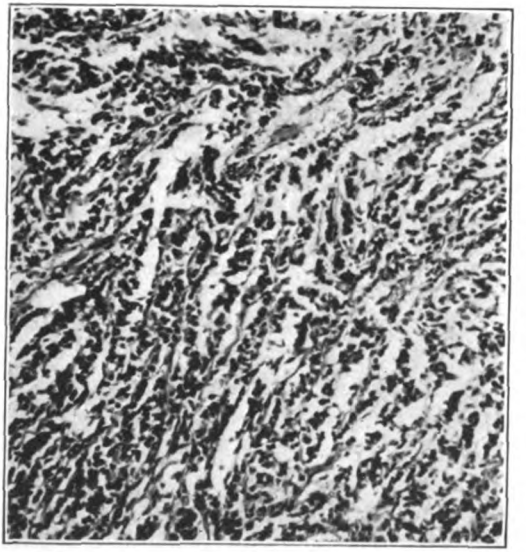


FIG. 233. MEDULLOBLASTOMA

Hematoxylin-eosin stain

the astroblast, ranks embryologically between astrocyte and unipolar spongioblast. They are found in the cerebral hemispheres, growing slowly and infiltrating the surrounding tissue. They may show cystic degeneration. Microscopically, they present a loose structure of large cells, with abundant cytoplasm, the triangular form of which may simulate a cortical neuron. The cell may contain two or three nuclei. In silver-impregnated sections, long, thick processes are seen streaming to thin-walled blood vessels, where they end with sucker feet like adult astrocytes (figs. 231, 232).

4. *Medulloblastoma (Neurospongiome).*—This tumor was originally described by Bailey and Cushing as "spongioblastoma multiforme." In order to avoid confusion with the tumor described by Globus and Strauss under this name, the first-named authors gave to the tumor they described, which was usually found in children, and arising in the cerebellum, the name "medulloblastoma." They wanted to indicate by this term that the type cell was the medulloblast, a bipotential embryonic cell, which may give rise to neuroblasts or spongioblasts. Roussy and Oberling thought that the type cell resembled polar and apolar neuroblasts, but they too found spongioblasts in many of these tumors, and therefore differentiate, in agreement with Bailey and Cushing's proposal, between *neurospongiomes* that are essentially *neuroblastiques* (medulloblastoma neuromatosum) and those that are *neurospongioblastiques* (medulloblastoma glioneuromatosum) (fig. 233).

The common site of these tumors is over the roof of the fourth ventricle; they usually arise in the vermis of the cerebellum. At an early stage they present soft, grayish red masses, without sharp outlines, that are attached to the overlying, very vascular piarachnoid. Growing rapidly, they invade the cerebellar hemispheres and the fourth ventricle, destroying the choroid plexus and producing internal hydrocephalus by occlusion of its foramina. As they grow, they extend into the subarachnoidal spaces along the cervical spinal cord, which they invade by growing into the outer surface. This latter fact has led to the opinion that medulloblastomas represent sarcomas of mesenchymal origin endowed with metastatic potentiality (Nishii). The presence of neuroblasts and spongioblasts and the confinement of the implantation metastases to the central nervous system, however, speak strongly in favor of assumption of an ectodermal origin.

Histologically also these tumors are diagnosed by the inexperienced as sarcomas. In sections stained with hematoxylin-eosin they present a dense accumulation of round or slightly oval nuclei that stain intensively and that are surrounded by a small zone of cytoplasm that may form a short process at one pole. With use of special methods, spongioblasts and neuroblasts may be seen in varying proportions, intermingled with undifferentiated round cells or even with astrocytes. The tumor cells may be

seen in densely packed groups, arranged grapelike along strands of connective tissue, or forming pseudorosette-like or adenomatous structures around blood vessels.

Following roentgen ray treatment, there seems to be a reduction in number and size of the nuclei, together with a marked increase of collagenous connective tissue. Because of its rapid and destructive growth and the tendency to implantation in the fourth ventricle and in the subarachnoidal spaces, the tumor is to be classified as malignant. Tumors of similar structure are found in the retina (retinal glioma, retinoblastoma), and

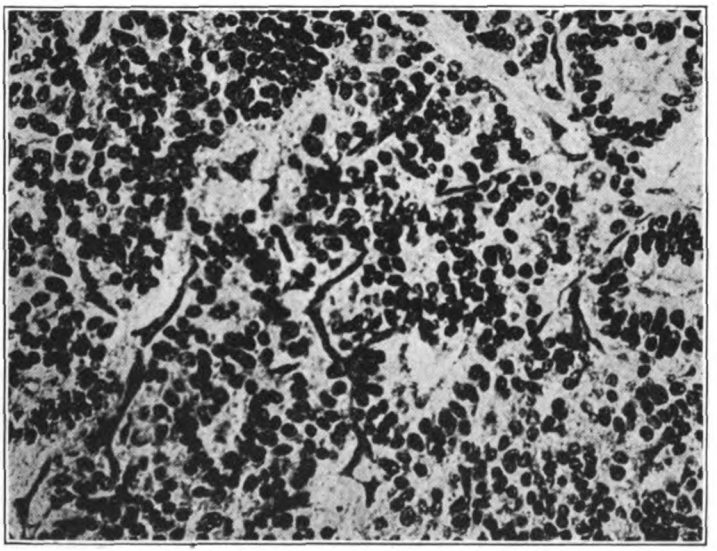


FIG. 234. NEURO-EPITHELIOMA
Hematoxylin-eosin stain
(*P. Bailey. Courtesy Archives of Pathology*)

arising from the sympathetic nervous system (neurocytoma, sympathicoblastoma).

5. *Neuro-epithelioma* (*Neuroépithéliome*).—Neuro-epitheliomas are formed by cells similar to primitive spongioblasts. They have a tendency to form canals or tubular cavities by a rosette-like arrangement of their columnar bodies. The inner lining is formed by a cuticular membrane, to which cilia may be attached; the latter contain small blepharoplasts. (The name "blepharoplast" has been given to a small granular body surrounded by a pale halo, in order to indicate its probable homology with the kinetonucleus in certain flagellates (trypanosomes) from which the cilium

the astroblast, ranks embryologically between astrocyte and unipolar spongioblast. They are found in the cerebral hemispheres, growing slowly and infiltrating the surrounding tissue. They may show cystic degeneration. Microscopically, they present a loose structure of large cells, with abundant cytoplasm, the triangular form of which may simulate a cortical neuron. The cell may contain two or three nuclei. In silver-impregnated sections, long, thick processes are seen streaming to thin-walled blood vessels, where they end with sucker feet like adult astrocytes (figs. 231, 232).

4. *Medulloblastoma* (*Neurospongiome*).—This tumor was originally described by Bailey and Cushing as "spongioblastoma multiforme." In order to avoid confusion with the tumor described by Globus and Strauss under this name, the first-named authors gave to the tumor they described, which was usually found in children, and arising in the cerebellum, the name "medulloblastoma." They wanted to indicate by this term that the type cell was the medulloblast, a bipotential embryonic cell, which may give rise to neuroblasts or spongioblasts. Roussy and Oberling thought that the type cell resembled polar and apolar neuroblasts, but they too found spongioblasts in many of these tumors, and therefore differentiate, in agreement with Bailey and Cushing's proposal, between *neurospongiomes* that are essentially *neuroblastiques* (medulloblastoma neuromatosum) and those that are *neurospongioblastiques* (medulloblastoma glioneuromatosum) (fig. 233).

The common site of these tumors is over the roof of the fourth ventricle; they usually arise in the vermis of the cerebellum. At an early stage they present soft, grayish red masses, without sharp outlines, that are attached to the overlying, very vascular piarachnoid. Growing rapidly, they invade the cerebellar hemispheres and the fourth ventricle, destroying the choroid plexus and producing internal hydrocephalus by occlusion of its foramina. As they grow, they extend into the subarachnoidal spaces along the cervical spinal cord, which they invade by growing into the outer surface. This latter fact has led to the opinion that medulloblastomas represent sarcomas of mesenchymal origin endowed with metastatic potentiality (Nishii). The presence of neuroblasts and spongioblasts and the confinement of the implantation metastases to the central nervous system, however, speak strongly in favor of assumption of an ectodermal origin.

Histologically also these tumors are diagnosed by the inexperienced as sarcomas. In sections stained with hematoxylin-eosin they present a dense accumulation of round or slightly oval nuclei that stain intensively and that are surrounded by a small zone of cytoplasm that may form a short process at one pole. With use of special methods, spongioblasts and neuroblasts may be seen in varying proportions, intermingled with undifferentiated round cells or even with astrocytes. The tumor cells may be

seen in densely packed groups, arranged grapelike along strands of connective tissue, or forming pseudorosette-like or adenomatous structures around blood vessels.

Following roentgen ray treatment, there seems to be a reduction in number and size of the nuclei, together with a marked increase of collagenous connective tissue. Because of its rapid and destructive growth and the tendency to implantation in the fourth ventricle and in the subarachnoidal spaces, the tumor is to be classified as malignant. Tumors of similar structure are found in the retina (retinal glioma, retinoblastoma), and

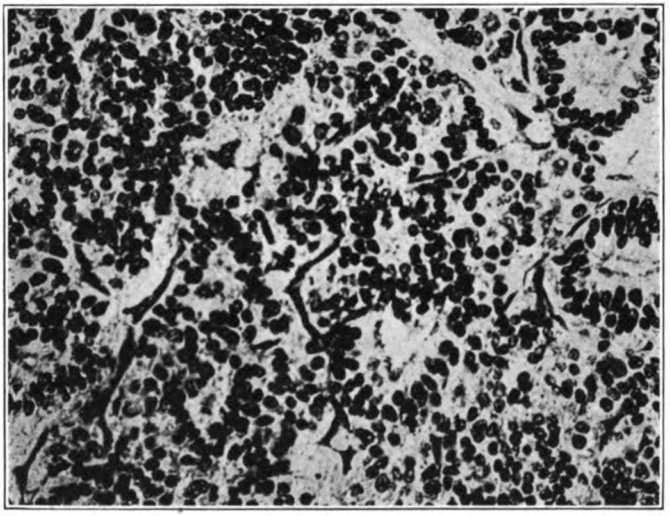


FIG. 234. NEURO-EPITHELIOMA
Hematoxylin-eosin stain
(*P. Bailey. Courtesy Archives of Pathology*)

arising from the sympathetic nervous system (neurocytoma, sympathicoblastoma).

5. *Neuro-epithelioma* (*Neuroépithéliome*).—Neuro-epitheliomas are formed by cells similar to primitive spongioblasts. They have a tendency to form canals or tubular cavities by a rosette-like arrangement of their columnar bodies. The inner lining is formed by a cuticular membrane, to which cilia may be attached; the latter contain small blepharoplasts. (The name "blepharoplast" has been given to a small granular body surrounded by a pale halo, in order to indicate its probable homology with the kinetonucleus in certain flagellates (trypanosomes) from which the cilium

arises.) The opposite free surface in these cells extends into a long process that may be impregnated by the Golgi method. These processes end free, or (as in an illustration published by Roussy and Oberling) form another membrane similar to the formation of the embryonic spinal cord at a very early stage. Though most of these tumors occur in the spinal cord, the neuro-epithelioma retinae, in which similar rosettes are found, also belongs in this group. Bailey and Cushing, therefore, propose to differentiate between "spongioblastoma primitivum medullae spinalis" and "spongioblastoma primitivum retinae" (fig. 234).

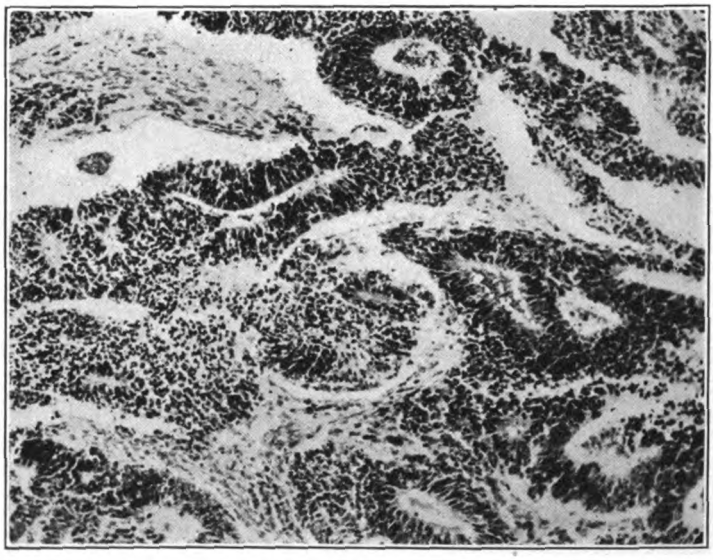


FIG. 235. MEDULLO-EPITHELIOMA
Phosphotungstic acid-hematoxylin stain
(*P. Bailey. Courtesy Archives of Pathology*)

6. *Medullo-epithelioma* (*Neuroépithéliome Sacrococcygien, Roussy and Oberling*)—These rare tumors are formed by cells resembling the most primitive cells of the neural tube, the medullary epithelium. They arise from sites where these cells are not differentiated in the adult brain, i.e., the roof and floor plates. In the eye a similar tumor originates from the pars ciliaris retinae. The epithelium-like cells are arranged in bands with two limiting membranes, and do not contain blepharoplasts, or they may form medullary tubes. Numerous mitotic figures and a rapid growth characterize this embryonic tumor (fig. 235).

TUMORS OF THE NEURON

As in the subdivision of the gliomas, we may classify this group into tumors composed of adult neurons, i.e., ganglioneuromas, and those of more primitive, embryonic type, i.e., neuroblastomas.

1. GANGLIONEUROMA

This type of tumor seems to occur with exceeding rarity within the brain. Those cases in which nests of neurons are found within the white matter, or in the outer layer of the cerebellar cortex, should not be classified as tumors if expansive growth cannot be proved. They should be called heterotopias (misplacements). Outside the central nervous system, gang-

TABLE 19.—*Gliomas of the Brain and Spinal Cord*

Type	Intramedullary (Kernohan et al.)			Intracerebral (Cushing)			Brain and Spinal Cord (Roussy and Oberling)	
	No.	Per-centage	Symp-toms (Mo.)*	No.	Per-centage	Sur-vival (Mo.)†	No.	Per-centage
Astroblastoma	2	5.0	66	35	5.0	32		
Astrocytoma				255	38.0	78	119	52.0
Ependymoma	21	50.0	59	25	4.0	36	26	11.0
Ganglioneuroma	2	5.0	48	3	0.4		1	0.4
Glioblastoma multiforme	11	26.0	41	208	31.0	13	43	19.0
Medulloblastoma	4	9.0	54	86	13.0	19	20	10.0
Neuro-epithelioma				2	0.3		2	1.0
Oligodendroglioma				27	4.0	75	16	7.0
Spongioblastoma	2	5.0	48	32	5.0	45		
Total no.	42			673			227	

* Duration of symptoms in months prior to operation.

† Average period of survival in months from time of earliest known symptoms.

lioneuromas seem to be more frequent. Both extra- and intracerebral tumors grow slowly; the former are well encapsulated (fig. 273).

The tumors found in the brain contain a varying amount of neuroglia in different phases of neoplastic transformation. Accordingly, one may diagnose them as ganglioglioneuromas or spongioneuroblastomas (Globus). The tumors of the periphery contain cells resembling the elongated forms of tumor cells that are found in the neurinomas. The neurons contain well defined Nissl bodies, a vesicular nucleus, and a darkly stained nucleolus. They form processes extending in different directions. In certain types of peripheral tumors, small satellites may be seen surrounding the neurons (fig. 236). Many abnormal forms are present forms with two nuclei,

arises.) The opposite free surface in these cells extends into a long process that may be impregnated by the Golgi method. These processes end free, or (as in an illustration published by Roussy and Oberling) form another membrane similar to the formation of the embryonic spinal cord at a very early stage. Though most of these tumors occur in the spinal cord, the neuro-epithelioma retinae, in which similar rosettes are found, also belongs in this group. Bailey and Cushing, therefore, propose to differentiate between "spongioblastoma primitivum medullae spinalis" and "spongioblastoma primitivum retinae" (fig. 234).

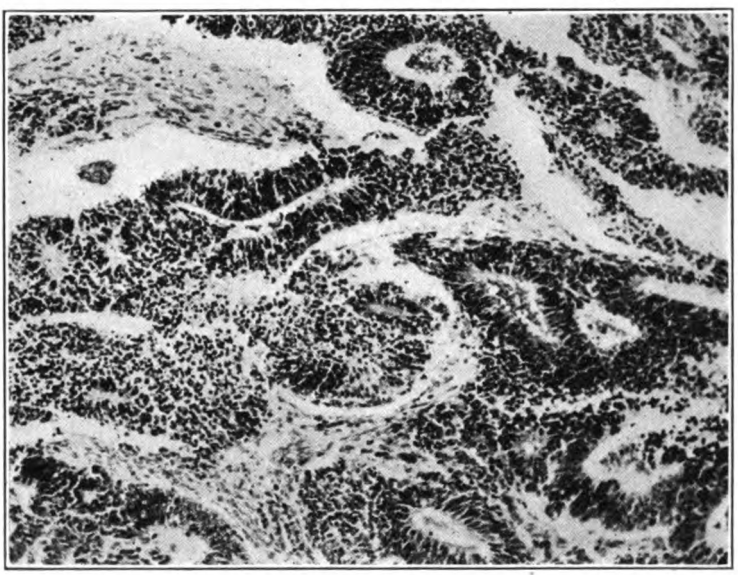


FIG. 235. MEDULLO-EPITHELIOMA
Phosphotungstic acid-hematoxylin stain
(*P. Bailey. Courtesy Archives of Pathology*)

6. *Medullo-epithelioma* (*Neuroépithéliome Sacrococcygien, Roussy and Oberling*)—These rare tumors are formed by cells resembling the most primitive cells of the neural tube, the medullary epithelium. They arise from sites where these cells are not differentiated in the adult brain, i.e., the roof and floor plates. In the eye a similar tumor originates from the pars ciliaris retinae. The epithelium-like cells are arranged in bands with two limiting membranes, and do not contain blepharoplasts, or they may form medullary tubes. Numerous mitotic figures and a rapid growth characterize this embryonic tumor (fig. 235).

Tumors of the Neuron

As in the subdivision of the gliomas, we may classify this group into tumors composed of adult neurons, i.e., ganglioneuromas, and those of more primitive, embryonic type, i.e., neuroblastomas.

1. GANGLIONEUROMA

This type of tumor seems to occur with exceeding rarity within the brain. Those cases in which nests of neurons are found within the white matter, or in the outer layer of the cerebellar cortex, should not be classified as tumors if expansive growth cannot be proved. They should be called heterotopias (misplacements). Outside the central nervous system, gang-

TABLE 19.—*Gliomas of the Brain and Spinal Cord*

Type	Intramedullary (Kernohan et al.)			Intracerebral (Cushing)			Brain and Spinal Cord (Roussy and Oberling)	
	No.	Per-centage	Symp-toms (Mo.)*	No.	Per-centage	Sur-vival (Mo.)†	No.	Per-centage
Astroblastoma	2	5.0	66	35	5.0	32		
Astrocytoma				255	38.0	78	119	52.0
Ependymoma	21	50.0	59	25	4.0	36	26	11.0
Ganglioneuroma	2	5.0	48	3	0.4		1	0.4
Glioblastoma multiforme	11	26.0	41	208	31.0	13	43	19.0
Medulloblastoma	4	9.0	54	86	13.0	19	20	10.0
Neuro-epithelioma				2	0.3		2	1.0
Oligodendroglioma				27	4.0	75	16	7.0
Spongioblastoma	2	5.0	48	32	5.0	45		
Total no.	42			673			227	

* Duration of symptoms in months prior to operation.

† Average period of survival in months from time of earliest known symptoms.

lioneuromas seem to be more frequent. Both extra- and intracerebral tumors grow slowly; the former are well encapsulated (fig. 273).

The tumors found in the brain contain a varying amount of neuroglia in different phases of neoplastic transformation. Accordingly, one may diagnose them as ganglioglioneuromas or spongioneuroblastomas (Globus). The tumors of the periphery contain cells resembling the elongated forms of tumor cells that are found in the neurinomas. The neurons contain well defined Nissl bodies, a vesicular nucleus, and a darkly stained nucleolus. They form processes extending in different directions. In certain types of peripheral tumors, small satellites may be seen surrounding the neurons (fig. 236). Many abnormal forms are present—forms with two nuclei,

with absence of or agglutinated Nissl bodies, with extremely large cells. Degeneration occurs, in that the nuclei may be fragmented, the cytoplasm may be vacuolated, and fatty degeneration may be present, or neuronophagia takes place. In silver-impregnated sections a more or less dense meshwork of nerve fibers can be made out; in the peripheral tumors these are interwoven with the chains of elongated cells of the neurinoma type. The stroma of collagenous fibers may be excessive in some of the peripheral

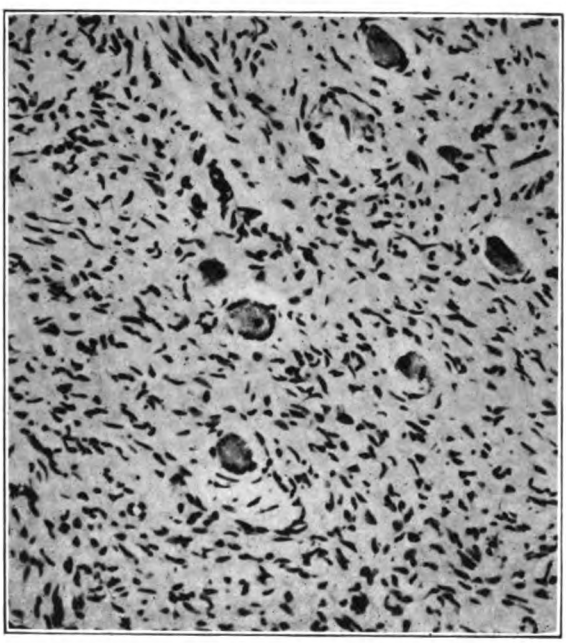


FIG. 236. GANGLIONEUROMA

Multiple tumors in neck and retroperitoneal region. Neurons resembling those found in sympathetic ganglia are surrounded by capsule of satellite cells and unmyelinated nerve fibers. Tissue between neurons is filled with fibroblasts and with unmyelinated nerve fibers. Cresyl violet stain

tumors. It contains nests of densely packed, lymphocyte-like round cells, the origin of which is disputed, and which are considered by some authors to be primitive neuroblasts. Multiple occurrence of such tumors has been reported.

2. NEUROBLASTOMA

Roussy and Oberling include this tumor in their group of *neurospongiomes essentiéllement neuroblastiques*, while Bailey and Cushing separate the

medulloblastoma with its bipotential medulloblast from tumors that are composed of more highly differentiated, unipolar neuroblasts. Such tumors are very cellular and are embedded in a connective tissue stroma formed by bridges between the numerous small blood vessels. From the unipolar cells, with their vesicular nuclei and their argyrophile cytoplasm condensed at one pole, there emanate long processes united in long bands and frequently ending with bulblike processes in the neighborhood of blood vessels. Rosettes formed by circles of tumor cells around a central cavity have been described (fig. 237).

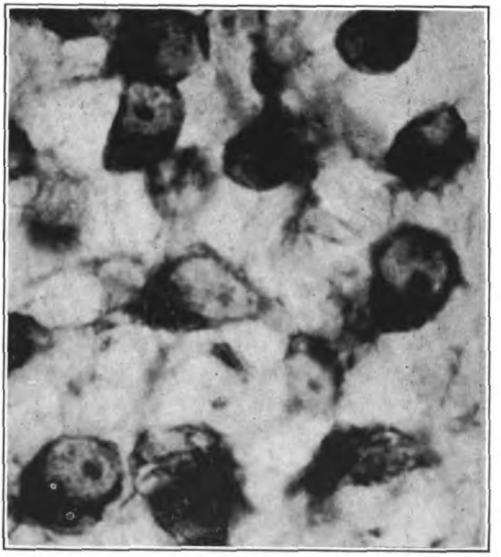


FIG. 237. NEUROBLASTOMA IN GASSERIAN GANGLION

Large neuroblasts with vesicular nucleus and deeply staining cytoplasm that occupies cell's single pole. Cresyl violet stain

Of especial interest are those tumors that arise in the adrenal medulla. In early childhood neuroblastomas prevail and are frequently bilateral; most of the tumor cells are small cells with scanty cytoplasm, arranged in rosettes. In addition, manifold stages of transition to the form of the adult neuron are seen. The ganglioneuroma is found in older persons and is a relatively rare tumor. The same is true of the chromaffinoma or pheochromocytoma. It is usually a benign, encapsulated tumor, the cells of which show affinity for chrome salts and stain an intense yellow. They resemble very malignant carcinoma cells, containing large nuclei and mitotic figures surrounded by abundant cytoplasm.

with absence of or agglutinated Nissl bodies, with extremely large cells. Degeneration occurs, in that the nuclei may be fragmented, the cytoplasm may be vacuolated, and fatty degeneration may be present, or neuronophagia takes place. In silver-impregnated sections a more or less dense meshwork of nerve fibers can be made out; in the peripheral tumors these are interwoven with the chains of elongated cells of the neurinoma type. The stroma of collagenous fibers may be excessive in some of the peripheral

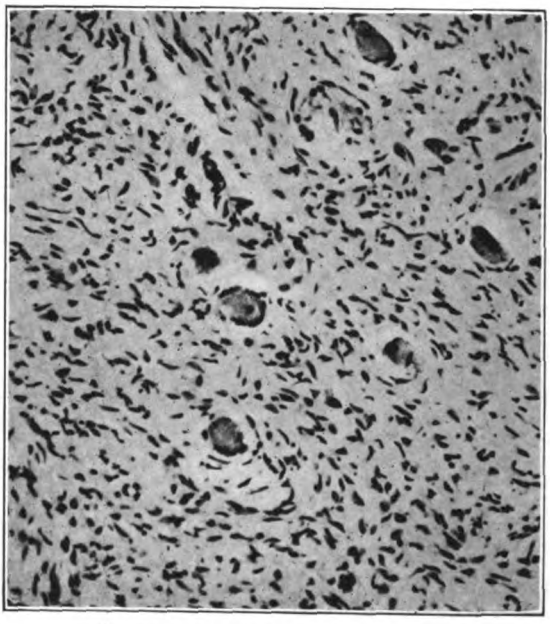


FIG. 236. GANGLIONEUROMA

Multiple tumors in neck and retroperitoneal region. Neurons resembling those found in sympathetic ganglia are surrounded by capsule of satellite cells and unmyelinated nerve fibers. Tissue between neurons is filled with fibroblasts and with unmyelinated nerve fibers. Cresyl violet stain

tumors. It contains nests of densely packed, lymphocyte-like round cells, the origin of which is disputed, and which are considered by some authors to be primitive neuroblasts. Multiple occurrence of such tumors has been reported.

2. NEUROBLASTOMA

Roussy and Oberling include this tumor in their group of *neurospongiomes essentiéllement neuroblastiques*, while Bailey and Cushing separate the

medulloblastoma with its bipotential medulloblast from tumors that are composed of more highly differentiated, unipolar neuroblasts. Such tumors are very cellular and are embedded in a connective tissue stroma formed by bridges between the numerous small blood vessels. From the unipolar cells, with their vesicular nuclei and their argyrophile cytoplasm condensed at one pole, there emanate long processes united in long bands and frequently ending with bulblike processes in the neighborhood of blood vessels. Rosettes formed by circles of tumor cells around a central cavity have been described (fig. 237).

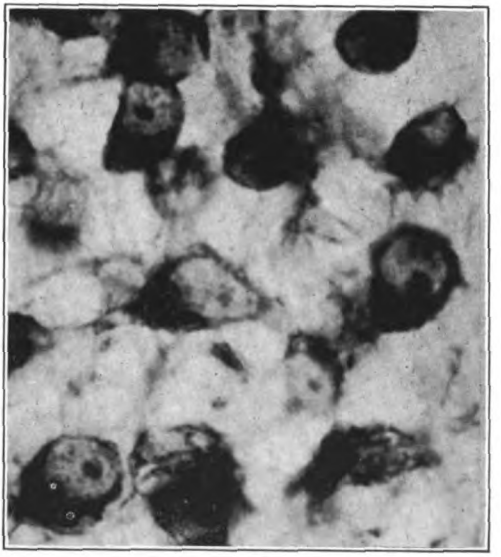


FIG. 237. NEUROBLASTOMA IN GASSERIAN GANGLION

Large neuroblasts with vesicular nucleus and deeply staining cytoplasm that occupies cell's single pole. Cresyl violet stain

Of especial interest are those tumors that arise in the adrenal medulla. In early childhood neuroblastomas prevail and are frequently bilateral; most of the tumor cells are small cells with scanty cytoplasm, arranged in rosettes. In addition, manifold stages of transition to the form of the adult neuron are seen. The ganglioneuroma is found in older persons and is a relatively rare tumor. The same is true of the chromaffinoma or pheochromocytoma. It is usually a benign, encapsulated tumor, the cells of which show affinity for chrome salts and stain an intense yellow. They resemble very malignant carcinoma cells, containing large nuclei and mitotic figures surrounded by abundant cytoplasm.

Tumors of the Ependyma

Again we may differentiate between tumors composed of a more adult type of cell, the ependymoma (*épendymocytome*), and a more embryonic type, the ependymoblastoma (*épendymoblastome*). On account of the forms that are transitional between the two types, and the presence of ependymal spongioblasts in the first-named tumor, it seems more convenient from a practical standpoint to classify both tumors under the

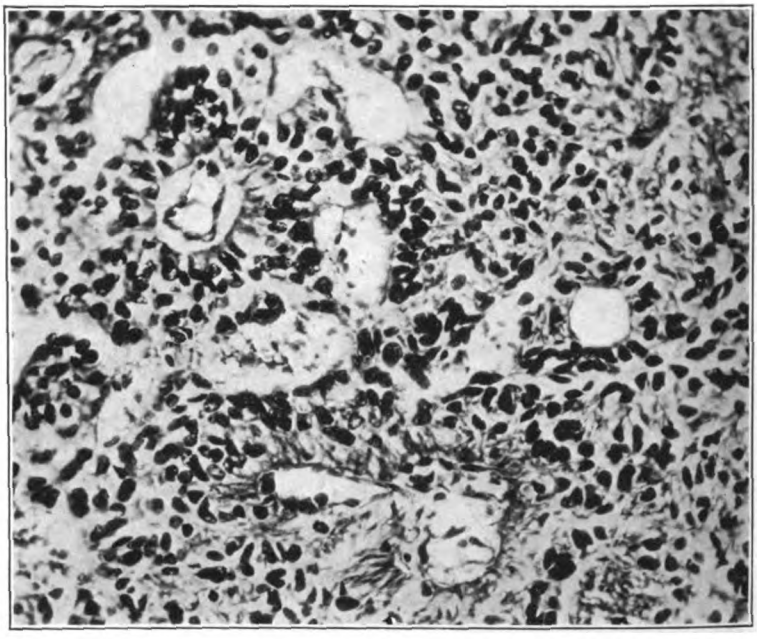


Fig. 238. Ependymoma
Pseudorosette formation around blood vessels. Davenport stain

single term ependymoma. The tumor occurs with relatively greater frequency in young persons up to the age of 20.

The type cell of the ependymoblastoma resembles the ependymal spongioblast. It is differentiated from its predecessor, the primitive spongioblast, by absence of cilia and by the presence of blepharoplasts within the cytoplasm of the cell body instead of at the bases of the cilia. The cells form circles around small vascular channels. Hematoxylin-eosin preparations produce the impression that between the nuclei of the tumor cells and the walls of the vascular channels a faintly stained clear space is left, but in phosphotungstic acid–hematoxylin or pyridine-silver preparations, or by

Hortega's oligodendroglia method, the coarse tails of these cells are seen filling out the perivascular spaces. In the ependymomas the tumor cells have lost the tail-like processes, but blepharoplasts are still found in the cytoplasm. They are of polygonal type, resembling the adult ependymal cells, and form circular linings around vascular channels. The connective tissue stroma is abundant and differentiates them from the more embryonic ependymoblastoma (fig. 238).

Both types of this tumor are usually found in the fourth ventricle, but ependymomas and ependymoblastomas have also been found in the cerebral cortex, arising from the lining of the lateral ventricles, and in the septum pellucidum. Their harder consistency, nodular form, and reddish gray color distinguish them from the soft, red medulloblastomas, which may be found in similar locations. Cyst formation at the surface and deposits of calcium salts producing roentgen ray shadows have been described as occurring in cerebral ependymomas. The fluid content of the cysts does not coagulate on exposure to the air, in contrast to the cystic fluid from astrocytomatous cysts (Fincher and Coon).

Roussy and Oberling include an *épendymogliome* in this group. They describe it as arising near the ependymal lining of the aqueduct, which is normal. The tumor consists of tubular cavities, suggesting the possibility that this *épendymogliome* could better be classified with the neuro-epitheliomas.

Tumors of the Choroidal Epithelium

The tumors of this group are either slowly growing papillomas, imitating in their histologic structure the adult choroid plexus, or more rapidly growing neoplasms of more primitive structure that may even develop implantation metastases in the piarachnoid.

The epithelium covering the villi of the choroid plexus follows a line of development different from that of the ependymal cells lining the walls of the lateral ventricles. The latter develop from the medullary epithelium through primitive and ependymal spongioblasts. In the ependymomas they are characterized by the blepharoplasts, which they inherit from the primitive spongioblasts. The choroidal epithelium, however, is supposed to develop directly from the medullary epithelium. It does not possess blepharoplasts or cilia in adult man. Here the cells are cuboidal, with large round or oval nuclei and a coarsely granulated cytoplasm.

The papillomas are more or less true copies of the choroid plexus, from which they arise. They consist of villi that contain a central core of connective tissue and blood vessels and that are covered with a layer of cuboidal or more elongated columnar epithelium. The central core may be well developed, as was seen in one example, a very slowly growing tumor that

Tumors of the Ependyma

Again we may differentiate between tumors composed of a more adult type of cell, the ependymoma (*épendymocytome*), and a more embryonic type, the ependymoblastoma (*épendymoblastome*). On account of the forms that are transitional between the two types, and the presence of ependymal spongioblasts in the first-named tumor, it seems more convenient from a practical standpoint to classify both tumors under the

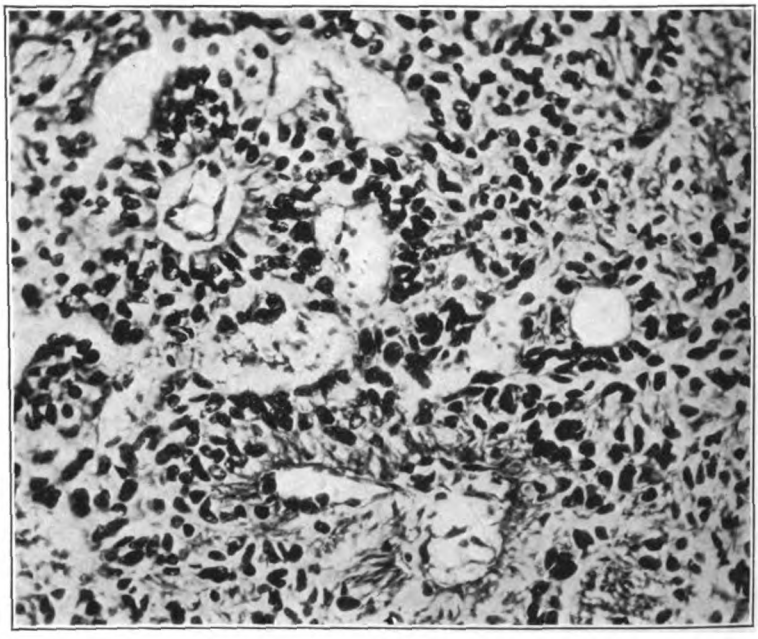


Fig. 238. Ependymoma
Pseudorosette formation around blood vessels. Davenport stain

single term ependymoma. The tumor occurs with relatively greater frequency in young persons up to the age of 20.

The type cell of the ependymoblastoma resembles the ependymal spongioblast. It is differentiated from its predecessor, the primitive spongioblast, by absence of cilia and by the presence of blepharoplasts within the cytoplasm of the cell body instead of at the bases of the cilia. The cells form circles around small vascular channels. Hematoxylin-eosin preparations produce the impression that between the nuclei of the tumor cells and the walls of the vascular channels a faintly stained clear space is left, but in phosphotungstic acid–hematoxylin or pyridine-silver preparations, or by

Hortega's oligodendroglia method, the coarse tails of these cells are seen filling out the perivascular spaces. In the ependymomas the tumor cells have lost the tail-like processes, but blepharoplasts are still found in the cytoplasm. They are of polygonal type, resembling the adult ependymal cells, and form circular linings around vascular channels. The connective tissue stroma is abundant and differentiates them from the more embryonic ependymoblastoma (fig. 238).

Both types of this tumor are usually found in the fourth ventricle, but ependymomas and ependymoblastomas have also been found in the cerebral cortex, arising from the lining of the lateral ventricles, and in the septum pellucidum. Their harder consistency, nodular form, and reddish gray color distinguish them from the soft, red medulloblastomas, which may be found in similar locations. Cyst formation at the surface and deposits of calcium salts producing roentgen ray shadows have been described as occurring in cerebral ependymomas. The fluid content of the cysts does not coagulate on exposure to the air, in contrast to the cystic fluid from astrocytomatous cysts (Fincher and Coon).

Roussy and Oberling include an *épendymogliome* in this group. They describe it as arising near the ependymal lining of the aqueduct, which is normal. The tumor consists of tubular cavities, suggesting the possibility that this *épendymogliome* could better be classified with the neuro-epitheliomas.

Tumors of the Choroidal Epithelium

The tumors of this group are either slowly growing papillomas, imitating in their histologic structure the adult choroid plexus, or more rapidly growing neoplasms of more primitive structure that may even develop implantation metastases in the piarachnoid.

The epithelium covering the villi of the choroid plexus follows a line of development different from that of the ependymal cells lining the walls of the lateral ventricles. The latter develop from the medullary epithelium through primitive and ependymal spongioblasts. In the ependymomas they are characterized by the blepharoplasts, which they inherit from the primitive spongioblasts. The choroidal epithelium, however, is supposed to develop directly from the medullary epithelium. It does not possess blepharoplasts or cilia in adult man. Here the cells are cuboidal, with large round or oval nuclei and a coarsely granulated cytoplasm.

The papillomas are more or less true copies of the choroid plexus, from which they arise. They consist of villi that contain a central core of connective tissue and blood vessels and that are covered with a layer of cuboidal or more elongated columnar epithelium. The central core may be well developed, as was seen in one example, a very slowly growing tumor that

had arisen in a lateral ventricle and merely indented the wall without producing occlusion of the foramen of Monro. In others the central connective tissue undergoes mucoid degeneration. In a third type the central core consists of only a thin layer of connective tissue upon which the columnar cells are arranged. Such a papilloma was seen invading the piarachnoid at the base of the pons and cerebellum. In this case the choroid plexus in the lateral and in the third ventricle presented many epithelial cells that had changed from the normal, cuboidal type into columnar cells, this feature indicating the neoplastic transformation (figs. 239, 260).

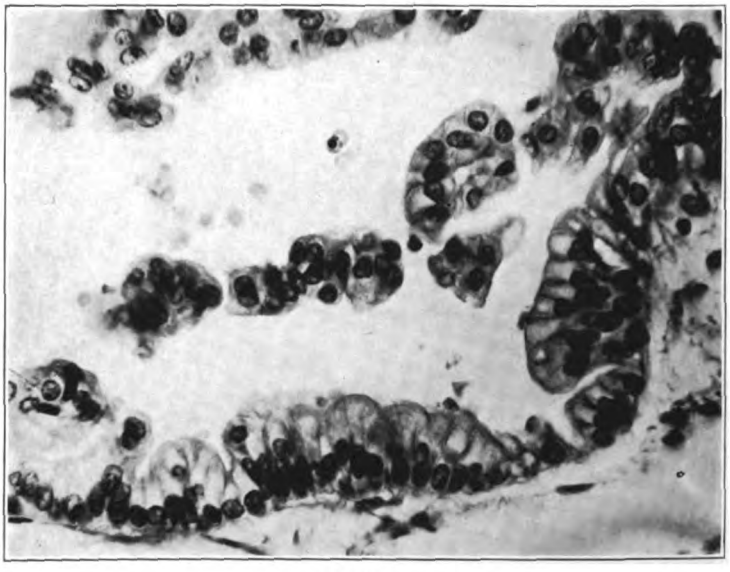


FIG. 239. PAPILLOMA
Metastasized to piarachnoid by seeding. Van Gieson stain

TUMORS OF THE BLOOD VESSELS

Traditionally, a discussion of angioblastomas includes a group of malformations of the blood vessels that clinically produce the symptoms of tumor but that have none of the histologic characteristics of neoplasms. These *angiomatous malformations* represent hyperplasias of capillaries, veins, or arteries and an increase of the various cellular elements of these, but not a qualitative change, i.e., neoplastic disease. With Cushing and Bailey one may differentiate between telangiectases on the one hand and venous and arterial angiomas on the other. The first group is characterized by an accumulation of numerous small capillaries lined with endothelium

and separated by glia, with the floor of the fourth ventricle and the pons as sites of predilection. But they have also been reported as occurring in other parts of the brain and spinal cord. The venous angiomas occur in the form of simple or serpentine varices, i.e., sacciform or convoluted extensions (fig. 240). A third group is formed by the racemose type (angioma venosum racemosum), which consists of tangles of large tortuous veins, either situated superficially, covering the surface of the brain, or occupying the interior of a lobe. Histologically, they show in sections numerous veins of different sizes with thin or hyalinized walls. These are

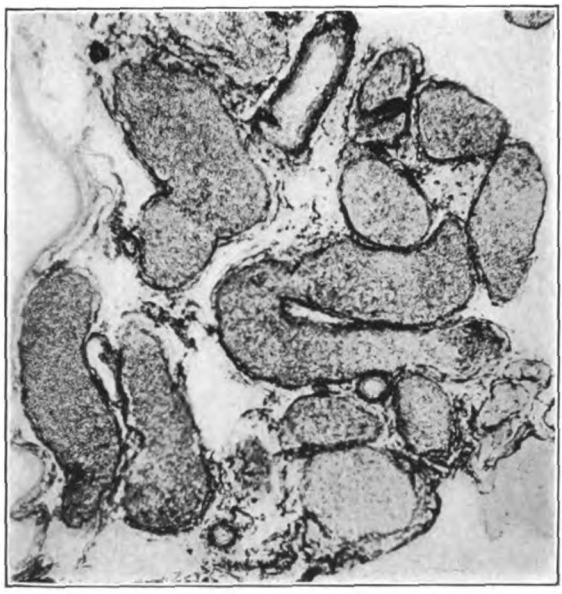


FIG. 240. ANGIOMA VENOSUM

Piarachnoid of occipital pole. Condition occurred in combination with naevus cutaneus of face. Mallory phosphotungstic acid-hematoxylin stain

recognized as veins by the absence of an elastica interna and by the fact that they present a single layer of endothelial cells, a few circularly arranged smooth muscle fibers, and a thin adventitia. They are separated by brain tissue that is partly transformed into a fibrous glia scar. Venous angiomas may be associated with congenital nevi of the face.

The arterial, or, better, arteriovenous angiomas present combinations of enlarged arteries that are in direct communication with enlarged veins. They take their origin from pial vessels and therefore are mostly situated on the surface of the brain. From there they may extend in wedge-shaped form

had arisen in a lateral ventricle and merely indented the wall without producing occlusion of the foramen of Monro. In others the central connective tissue undergoes mucoid degeneration. In a third type the central core consists of only a thin layer of connective tissue upon which the columnar cells are arranged. Such a papilloma was seen invading the piarachnoid at the base of the pons and cerebellum. In this case the choroid plexus in the lateral and in the third ventricle presented many epithelial cells that had changed from the normal, cuboidal type into columnar cells, this feature indicating the neoplastic transformation (figs. 239, 260).

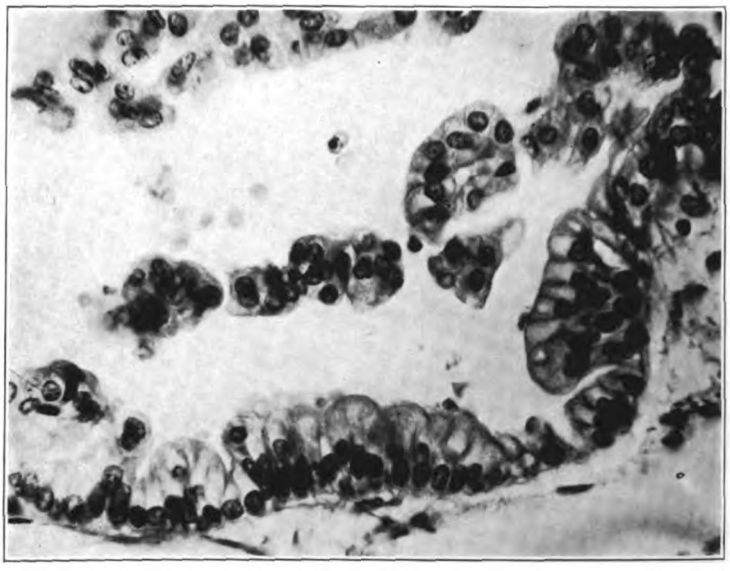


FIG. 239. PAPILLOMA
Metastasized to piarachnoid by seeding. Van Gieson stain

TUMORS OF THE BLOOD VESSELS

Traditionally, a discussion of angioblastomas includes a group of malformations of the blood vessels that clinically produce the symptoms of tumor but that have none of the histologic characteristics of neoplasms. These *angiomatous malformations* represent hyperplasias of capillaries, veins, or arteries and an increase of the various cellular elements of these, but not a qualitative change, i.e., neoplastic disease. With Cushing and Bailey one may differentiate between telangiectases on the one hand and venous and arterial angiomas on the other. The first group is characterized by an accumulation of numerous small capillaries lined with endothelium

and separated by glia, with the floor of the fourth ventricle and the pons as sites of predilection. But they have also been reported as occurring in other parts of the brain and spinal cord. The venous angiomas occur in the form of simple or serpentine varices, i.e., sacciform or convoluted extensions (fig. 240). A third group is formed by the racemose type (angioma venosum racemosum), which consists of tangles of large tortuous veins, either situated superficially, covering the surface of the brain, or occupying the interior of a lobe. Histologically, they show in sections numerous veins of different sizes with thin or hyalinized walls. These are

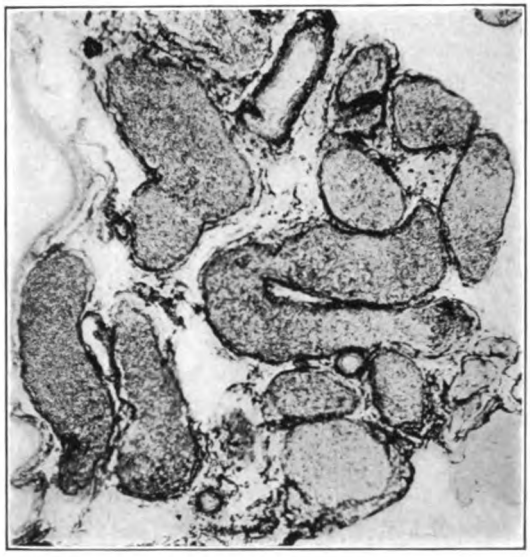


FIG. 240. ANGIOMA VENOSUM

Piarachnoid of occipital pole. Condition occurred in combination with naevus cutaneus of face. Mallory phosphotungstic acid-hematoxylin stain

recognized as veins by the absence of an elastica interna and by the fact that they present a single layer of endothelial cells, a few circularly arranged smooth muscle fibers, and a thin adventitia. They are separated by brain tissue that is partly transformed into a fibrous glia scar. Venous angiomas may be associated with congenital nevi of the face.

The arterial, or, better, arteriovenous angiomas present combinations of enlarged arteries that are in direct communication with enlarged veins. They take their origin from pial vessels and therefore are mostly situated on the surface of the brain. From there they may extend in wedge-shaped form

into the brain itself, sometimes penetrating as far as the lateral ventricles. During life these tumors are seen actively pulsating, and their bright red blood differentiates them from the venous angiomas with their darker blood. They may consist of single serpentine-like, distended arterial trunks; more commonly they form dense coils of convoluted vessels of different sizes. Histologically, the faulty anlage of the arteries is revealed by proliferation of the intima into nodules containing numerous elastic fibers, by splitting or absence of the elastica interna, and by formation in the media of nodules resembling minute leiomyomas. The vessel walls may undergo fatty degeneration or become calcified, with small aneurysm formation ensuing from the diminished elasticity. Like the venous angiomas, the vessels are separated from one another by brain tissue that has been transformed into a fibrous glia scar.

A peculiar combination of angiomas of the cerebral cortex and of the piarachnoid with nevi of the face has been described as *Sturge-Weber disease*. In the meninges the tumor is usually a venous angioma, while in the cortex, veins or precapillaries may have proliferated. The cortical vessels undergo calcification at an early stage and the changes may then easily be demonstrated in X-ray pictures. Clinically the condition frequently appears in association with epilepsy (fig. 241).

The *hemangioblastomas* can best be understood if we compare their structure with that of embryonic hematogenous tissue. In the area pellucida of the embryo, in the region of the mesenchyme, large, somewhat spindle-shaped cells grow together into long, solid cords. The interior of these cords becomes liquefied, forming the plasma, while the outer wall represents the endothelial lining. These primitive capillaries grow by formation of solid sprouts that become hollow. In other cords the interior is transformed into a hemoglobin-containing mass ("blood island") that is finally subdivided into red blood cells. The type cells of the hemangioblastomas are large epithelioid cells of various shapes, with more or less abundant granulated cytoplasm and large, eccentrically placed nuclei with fine granules of chromatin. These cells may form solid masses, or they may separate in the form of bands, forming numerous cavernous spaces.

A third type of hemangioblastoma is composed mainly of numerous capillaries lined with endothelial cells and separated by an intricate network of reticular fibers that may be well demonstrated by Perdrau's method. Between the capillaries strands of swollen cells may be found; these in sections from embedded material have a foamy appearance and in frozen sections may be seen laden with fat. These cells are usually referred to as "pseudoxanthomatous" cells. They have been identified with neuroepithelial cells or with compound granular corpuscles (hemangio-endothelioma). Cushing and Bailey, however, believe their origin to be from

the endothelial cells of the capillary network, which swell and undergo fatty degeneration.

These different types of cellular arrangement and vessel formation may be combined in various ways. Accordingly, one may distinguish between predominantly capillary, predominatly cellular, and predominantly cavernous hemangioblastomas (fig. 242).

These tumors are most frequently found in the cerebellum. They frequently become cystic through an active transudation of fluid from the

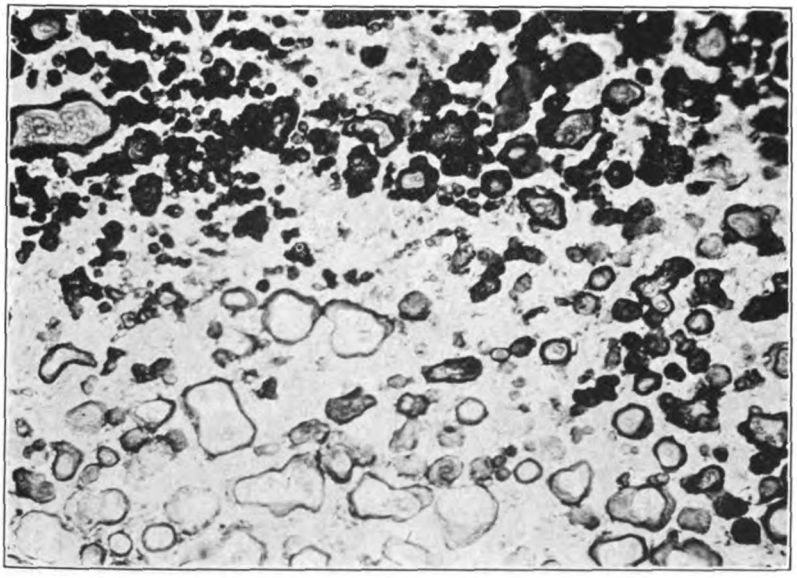


FIG. 241. STURGE-WEBER DISEASE

Angioma of occipital cortex, with calcification of wall of many of thin-walled blood vessels. Second angioma was found in meninges overlying this area of cerebral cortex

vessels of the tumor, which distends the tumor and compresses the surrounding brain tissue. This fluid is xanthochromic and resembles blood plasma in its chemical composition.

Berblinger (1922) and Lindau (1926) called attention to the fact that many of the cerebellar hemangioblastomas are coincident with angioma of the retina (Hippel's disease), and with cystic pancreas or cystic kidney. Less frequent are combinations with hypernephroma, hemangioma of the liver, angioma of the spinal cord, and syringomyelia of glioblastomatous origin. Lindau therefore thought that these combinations may indicate

into the brain itself, sometimes penetrating as far as the lateral ventricles. During life these tumors are seen actively pulsating, and their bright red blood differentiates them from the venous angiomas with their darker blood. They may consist of single serpentine-like, distended arterial trunks; more commonly they form dense coils of convoluted vessels of different sizes. Histologically, the faulty anlage of the arteries is revealed by proliferation of the intima into nodules containing numerous elastic fibers, by splitting or absence of the elastica interna, and by formation in the media of nodules resembling minute leiomyomas. The vessel walls may undergo fatty degeneration or become calcified, with small aneurysm formation ensuing from the diminished elasticity. Like the venous angiomas, the vessels are separated from one another by brain tissue that has been transformed into a fibrous glia scar.

A peculiar combination of angiomas of the cerebral cortex and of the piarachnoid with nevi of the face has been described as *Sturge-Weber disease*. In the meninges the tumor is usually a venous angioma, while in the cortex, veins or precapillaries may have proliferated. The cortical vessels undergo calcification at an early stage and the changes may then easily be demonstrated in X-ray pictures. Clinically the condition frequently appears in association with epilepsy (fig. 241).

The *hemangioblastomas* can best be understood if we compare their structure with that of embryonic hematogenous tissue. In the area pellucida of the embryo, in the region of the mesenchyme, large, somewhat spindle-shaped cells grow together into long, solid cords. The interior of these cords becomes liquefied, forming the plasma, while the outer wall represents the endothelial lining. These primitive capillaries grow by formation of solid sprouts that become hollow. In other cords the interior is transformed into a hemoglobin-containing mass ("blood island") that is finally subdivided into red blood cells. The type cells of the hemangioblastomas are large epithelioid cells of various shapes, with more or less abundant granulated cytoplasm and large, eccentrically placed nuclei with fine granules of chromatin. These cells may form solid masses, or they may separate in the form of bands, forming numerous cavernous spaces.

A third type of hemangioblastoma is composed mainly of numerous capillaries lined with endothelial cells and separated by an intricate network of reticular fibers that may be well demonstrated by Perdrau's method. Between the capillaries strands of swollen cells may be found; these in sections from embedded material have a foamy appearance and in frozen sections may be seen laden with fat. These cells are usually referred to as "pseudoxanthomatous" cells. They have been identified with neuroepithelial cells or with compound granular corpuscles (hemangio-endothelioma). Cushing and Bailey, however, believe their origin to be from

the endothelial cells of the capillary network, which swell and undergo fatty degeneration.

These different types of cellular arrangement and vessel formation may be combined in various ways. Accordingly, one may distinguish between predominantly capillary, predominatly cellular, and predominantly cavernous hemangioblastomas (fig. 242).

These tumors are most frequently found in the cerebellum. They frequently become cystic through an active transudation of fluid from the

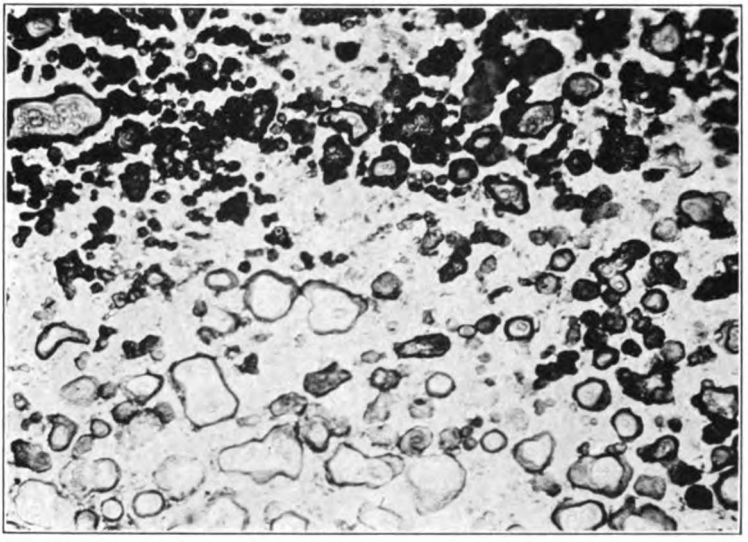


FIG. 241. STURGE-WEBER DISEASE

Angioma of occipital cortex, with calcification of wall of many of thin-walled blood vessels. Second angioma was found in meninges overlying this area of cerebral cortex

vessels of the tumor, which distends the tumor and compresses the surrounding brain tissue. This fluid is xanthochromic and resembles blood plasma in its chemical composition.

Berblinger (1922) and Lindau (1926) called attention to the fact that many of the cerebellar hemangioblastomas are coincident with angioma of the retina (Hippel's disease), and with cystic pancreas or cystic kidney. Less frequent are combinations with hypernephroma, hemangioma of the liver, angioma of the spinal cord, and syringomyelia of glioblastomatous origin. Lindau therefore thought that these combinations may indicate

congenital maldevelopment, probably of the mesoderm of the third fetal month (Lindau's disease).

Sometimes it is difficult to decide whether the excessive vascularity of a glioblastoma is a true neoplastic process, a combination of ectodermal and mesodermal neoplastic disease, or whether it is merely an abundant telangiectasis. The nature of the tissue that separates the numerous capillaries will determine the diagnosis. If the separating structure consists of tumor cells, brain tissue, or fibrous glia scar tissue, there can be no doubt that a capillary hemangioma is present (fig. 243). Cushing and Bailey state that

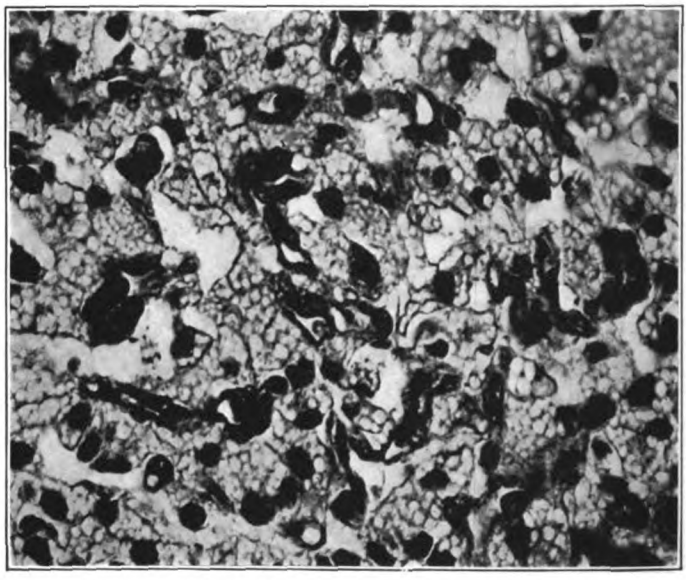


FIG. 242. HEMANGIOBLASTOMA
Cerebellum. Newly formed capillaries and "pseudoxanthomatous" cells between them. Hematoxylin-eosin stain

hemangioblastomas of the cerebrum are exceedingly rare. They are inclined to accept as such only four of the cystic tumors of this type that have been reported in the literature. Other authors, however, put more emphasis on the simultaneous neoplasia of both glial and mesenchymal tissue. They point to the extensive development of argyrophile networks, the glomerulus-like formations of capillaries, the concentrically arranged tumor cells in the walls of larger vessels (Spatz, Scherer). Glioblastoma developing close to the ventricular wall shows an intensive proliferation of angioma-like capillaries (angioglioma).

Tumors of the Hypophysis

The invasion of the suprasellar area at the base of the hypothalamus by tumors arising from the hypophysis or infundibulum, and their subsequent destruction of cranial nerves, the tuber cinereum, and other parts of the brain, justifies a more detailed description of these neoplasms.

Theoretically, one may expect neoplastic disease of the anterior lobe, the pars medialis (rudimentary in man), the posterior lobe, and the different cellular remnants of the craniopharyngeal duct lining the infundibulum. Practically, mostly tumors of the first and of the last group are encountered. The cystic formations that may be found between the two lobes—cavities

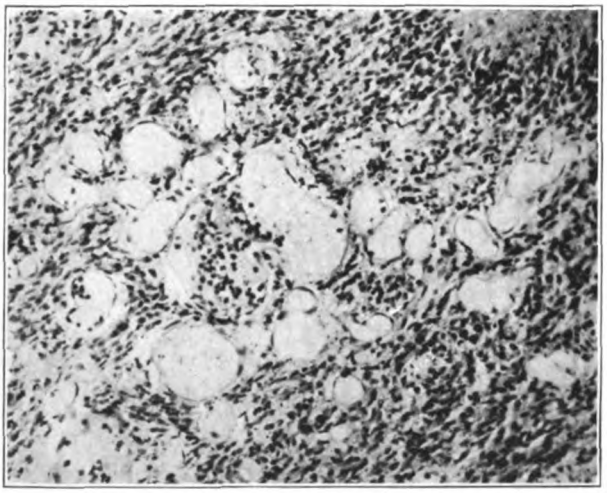


Fig. 243. Telangiectasis in Glioblastoma Multiforme
Widened capillaries are separated by tumor cells. Van Gieson stain

lined with cuboidal epithelium and representing remnants of the embryonic hypophysial cavity—do not seem to give rise to neoplasms. Gliomas, fibromas, sarcomas, or hemangioblastomas that may have arisen from the different structures of the pars nervosa (posterior lobe) have been described. Since we cannot rule out the possibility that glioma arising from the optic nerve or tumor arising from the meninges may have invaded the sella turcica, there is still doubt as to the hypophysial origin of such growths (Bailey). They have, however, been produced experimentally (Weil) (fig. 207).

The adenomas that originate from the anterior lobe are subdivided into chromophobe and chromphile (eosinophilic) adenomas and rare transitional types.

The *chromophobe adenoma*, which grows rapidly and destroys the normal structures of the hypophysis, produces the clinical picture of pituitary dystrophy, infantilism, or dystrophia adiposogenitalis (Fröhlich's disease). By pressure of the growing neoplasm, the sella turcica may be destroyed and the sphenoidal cells may be invaded. Next, the tumor grows into the extradural spaces. By compression of the optic and olfactory nerves, indentation of the floor of the third ventricle, and pressure on the midbrain and pons, severe clinical symptoms may be produced. It is rare for this tumor to invade the subarachnoidal spaces directly; implantation metastases have been found in the corpus callosum, and invasions of the

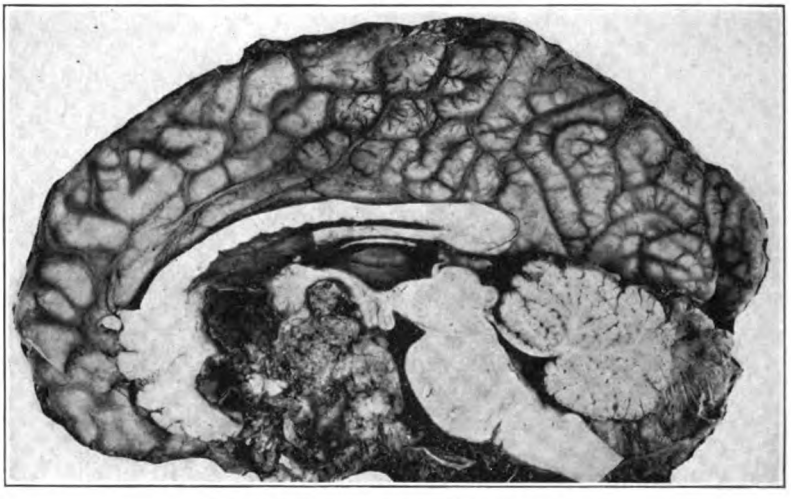


FIG. 244. ADENOMA OF HYPOPHYSIS

Chromophobe type, associated with Fröhlich's syndrome. Sagittal section through brain. Tumor compressing floor of third ventricle. Metastatic nodules were found in anterior part of corpus callosum

base of the skull and the cervical vertebrae and metastases in the liver have been reported.

Histologic examination of the chromophobe type shows elongated or polygonal cells with abundant cytoplasm; the latter stains faintly with eosin and contains numerous fine mitochondria that may be demonstrated by staining with phosphotungstic acid–hematoxylin. The nuclei are oval, pyknotic, stain intensely with hematoxylin, and are differentiated by these characteristics from the round, vesicular nuclei of the chromophile type, which show only scanty chromatin granules when stained with basic dyes. The chromophobe adenomas are frequently very vascular and contain a

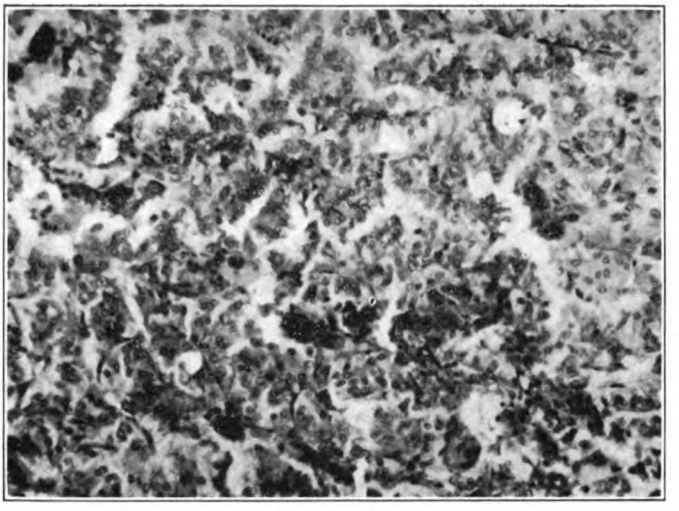


FIG. 245. ADENOMA OF HYPOPHYSIS
In case of Fröhlich's syndrome. Chromophobe type. Hematoxylin-eosin stain

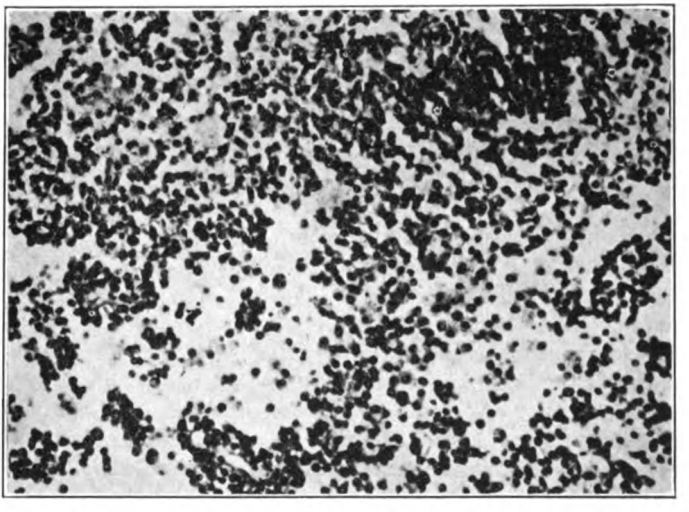


FIG. 246. ADENOMA OF HYPOPHYSIS
In case of acromegaly. Chromophile type. Hematoxylin-eosin stain

stroma of connective tissue that subdivides them into cellular islands. Sometimes the tumor cells are arranged in branching strands, imitating the structure of the normal anterior lobe (figs. 244, 245).

The eosinophilic or *chromophile adenomas* give rise to the clinical symptom of acromegaly, which indicates a hyperfunction of the normal endocrine secretion of the anterior lobe. The type cell, with polygonal or round sharply defined outlines, has a cytoplasm that stains intensely with eosin and that contains fine (alpha) granules. The nuclei are vesicular, and multinuclear forms occur. Blood vessels and connective tissue stroma are scanty, and the tumor cells do not form typical arrangements. Adenomas of mixed, transitional form contain both types of cells, with vesicular and pyknotic nuclei and with a small outer ring of alpha granules in the eosinophilic cell (fig. 246).

Basophilic adenoma has been described in connection with hirsutism, localized adiposity of the head and trunk, amenorrhea and impotence, and hypertension (Cushing's disease). However, this clinical syndrome resembling adrenal virilism may also be present without any basophilic adenoma. Besides, it should be remembered that even in normal, healthy individuals, conglomerations of basophilic cells may be seen in the pituitary, simulating small adenomas.

TUMORS OF THE CRANIOPHARYNGEAL DUCT

The remnants of the embryonic craniopharyngeal duct may give rise to various intracranial tumors. These remains are (1) cysts lined with ciliated epithelium and situated between the anterior and posterior lobes of the hypophysis (remnant of Rathke's pouch); (2) squamous epithelium, lining the upper and the lower border of the infundibulum; (3) between these, the pars tuberalis, a primitive glandular structure that is rudimentary in adult man.

There are mainly two types of tumors of the embryonic duct, arising very probably from the squamous epithelial remnants—squamous epithelial papillary cysts and adamantinomas. The two are occasionally classified together as "craniopharyngiomas."

The *squamous epithelial papillary cysts* usually are suprasellar tumors that do not invade the brain but merely compress the overlying cranial nerves and indent the floor of the third ventricle. They are well encapsulated, and their inner walls are formed by papillary structures. Microscopically, they present islands of squamous epithelium that show stellate forms in the interior. Centers of degenerated cells are replaced by fibroblasts forming collagenous tissue and blood vessels. Around such foci the tumor cells assume columnar forms and radiate toward the center (fig. 247).

The *adamantinomas* may assume a more aggressive character of growth. They may invade the sella turcica and completely destroy the hypophysis, producing the clinical picture of hypopituitarism. They may also break through the dura mater and invade the third ventricle and its walls, causing occlusion of the foramina of Monro and producing internal hydrocephalus. Histologically, they are made up of arborizing strands of squamous epithelium embedded in a loose stroma of argyrophile embryonic connective

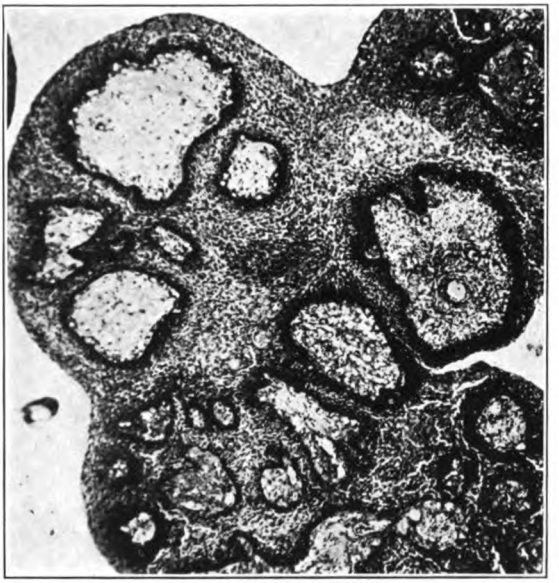


FIG. 247. SQUAMOUS EPITHELIAL PAPILLARY CYST

Islands containing loose connective tissue and blood vessels are surrounded by cylindric cells. Squamous epithelium is seen between these islands and cuboidal cells at outer surfaces. Hematoxylin-eosin stain

tissue. The outer zone in these cellular islands is formed by a single row of high columnar cells, arranged perpendicular to the surface; this closely resembles the structure of the adamantinomas of the lower jaw. In the anterior one finds stellate formation intermingled with the squamous epithelium (fig. 248).

It has often been doubted whether all of these squamous epithelial cysts that are found in the brain arise from embryonic rests, because occasionally they may be found within the third ventricle or even the brain tissue itself

without any connection with the infundibular region. The fact that similar tumors may be produced experimentally in rats by means of methylcholanthrene, by metaplasia of the mesothelial lining of the arachnoidal membrane, suggests such a possibility also in relation to human tissue (Weil).

Other tumors that may arise in this region are *lipomas* (together with osteomas or chondromas), *teratomas*, and *sarcomas*.

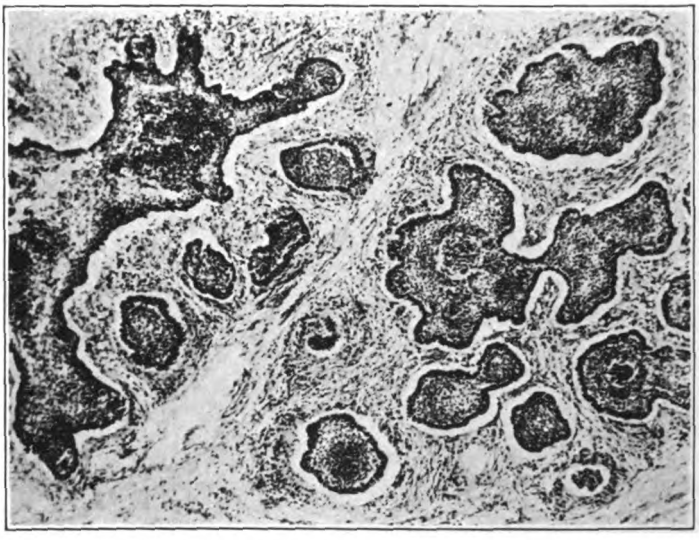


FIG. 248. ADAMANTINOMA

Tumor had broken through floor of third ventricle and formed metastases within wall of ventricle. Islands of squamous epithelium with arborization. Outer layer of ameloblast-like cells. Islands are embedded in loose stroma of argyrophile connective tissue. Van Gieson stain

TUMORS OF THE PINEAL GLAND

Older persons once in a while present markedly enlarged pineal glands, measuring up to 20 mm. in diameter, which on histologic examination show a normal configuration, with an increase of intercellular glial and mesenchymal stroma. These may be compared to the pituitary hyperplasias without neoplastic transformation. The center in such hyperplastic pineal glands frequently is cystic and filled with a colloidal mass (fig. 249).

The *pinealomas* show a mosaic-like arrangement of large cells separated by a connective tissue stroma and intermingled with small round cells. The first type is represented by large epithelioid cells with abundant granular cytoplasm. Their nuclei are round or oval and contain scanty fine chromatin granules and one or two large nucleoli. The small, round cells resemble lymphocytes with scanty cytoplasm and darkly stained nucleus (hema-

toxylin-eosin stain). These pinealomas may either be encapsulated tumors compressing the corpora quadrigemina and cerebellum, or they may in-

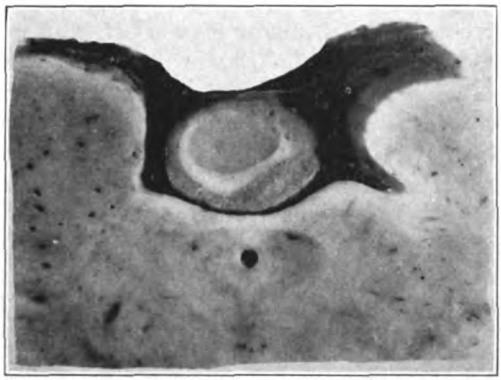


FIG. 249. HYPERTROPHY OF PINEAL GLAND WITH COLLOIDAL DEGENERATION OF CENTER
Coronal section through gland and midbrain with aqueduct of Sylvius

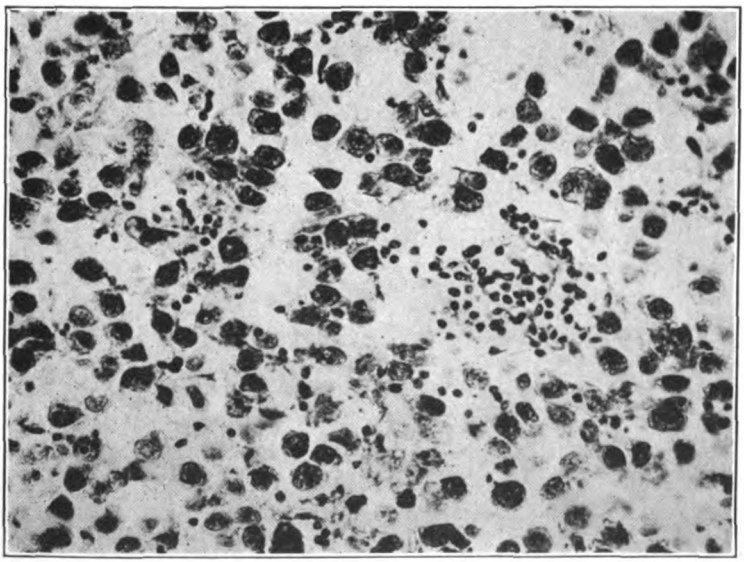


FIG. 250. PINEALOMA
Hematoxylin-eosin stain
(*P. Bailey. Courtesy Archives of Pathology*)

filtrate these structures and even invade the third ventricle anteriorly (fig. 250).

The *pinealoblastomas* do not show the large epithelioid cells, but are mainly composed of small round or pear-shaped cells with small oval nuclei and scanty cytoplasm. They may be without any definite arrangement or may form pseudorosettes around blood vessels. Silver impregnation reveals spongioblasts, a feature that induced Bailey and Horrax to call them pinealomas of spongioblastic type.

It is frequently stated in the literature that pubertas praecox (macrogenitosomia praecox) is connected with tumor of the pineal gland. This fact, however, is borne out in only about one-third of all cases in which the patients are below the age of puberty.

It is of interest to note the relatively large number of teratomas in pubertas praecox cases. The recorded instances are increased to 8 if we add to older observations 6 cases of pubertas praecox collected by Horrax and Bailey from 1911 to 1921. In other words, in 8 out of 16 cases of pineal gland tumor the neoplasms were teratomas. They were described as cystic tumors containing cartilaginous, bony, and hairy structures, with well developed stratified epithelium, hair follicles, and sebaceous glands.

Tumors of the Nerves

The tumors that are found originating in the roots of the cranial and spinal nerves or in the peripheral nerves may be subdivided into neoplasms that contain newly formed nerve fibers, neuromas, and growths that arise from the sheaths of the nerves, neurinomas.

The first-named tumor, *neuroma verum gangliocellulare* (*névrome vrai*), consists of myelinated or unmyelinated nerve fibers that show no definite arrangment and that usually are combined with islands of neurons, thus representing stages of transition to the form of the ganglioneuroma. They are frequently found arising in sympathetic nerves and as congenital tumors of the head. The "neuroma" developing at the proximal cut end of a nerve is a hyperplasia and not a true neoplasm.

The *neurinomas* may be subdivided as those arising from (1) Schwann sheath cells, (2) the peri- and endoneurium, and (3) the glial tissue that replaces the mesenchymal connective tissue shortly before the nerves enter the brain or the spinal cord. There is considerable divergence of opinion about the existence of the first-named type of tumor. Some, adhering to the opinion of Masson, believe that the type cell of the neurinoma is the neoplastic sheath cell; these authors accordingly speak of peripheral gliomas. Others, who form the majority, assume with Mallory that the elongated cells with their typical arrangement are neoplastic fibroblasts that form fibroglia and collagenous fibers. Therefore they differentiate between peri- and endoneurial fibroblastomas that may occur as solitary tumors or as multiple nodule formations. Occasionally, one may find refer-

ence in the literature to Antoni's classification of neurinoma A, designating a tumor with polar orientation, and neurinoma B, a tumor with reticular formation. Tissue cultures of such tumors produce growth of Schwann sheaths cells (Murray). The possibility that both Schwann sheath cells and fibroblasts become neoplastic has been discussed above.

The *solitary neurinomas* have been found, in the order of their frequency, in peripheral nerves (sciatic, median, ulnar, radial), in cranial nerves (acoustic, trigeminal, accessory, glossopharyngeal), and in the roots of the spinal nerves. Grossly, they are well localized tumors that assume rounded forms in the periphery and more elongated shapes in the cranial cavity. The histologic appearance is that of elongated, oval nuclei with scanty fibrillary cytoplasm at both poles, presenting no definite outlines. The typical arrangement of these nuclei is in long, streaming rows, palisading,

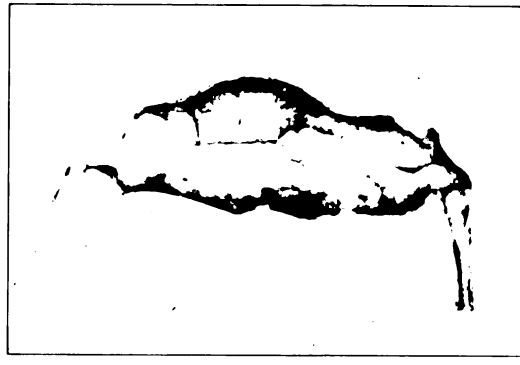


FIG. 251. NEURINOMA OF ULNAR NERVE

intercrossing, or forming wide whorls (figs. 251–54). In the peripheral tumors of sensory nerves, one may see whorl formations, produced by spiral lamellae of tumor cells, that have been compared to tactile end organs (nodules of Verocay). Under certain methods of silver impregnation (Foot's modification of Bielschowsky's method; Hortega's modification of Achucárro's method) long, dark-staining fibers are seen running along the rows of nuclei. Besides these argyrophile fibers, numerous coarser collagenous fibers can be demonstrated by the van Gieson method. Most of the fibers of the diseased nerves are destroyed. In correspondence with the time elapsed since onset of the lesion, different stages of degeneration may be found, from swollen myelin sheaths and axis-cylinders to final disappearance of both and replacement by sheath cells and connective tissue.

The vascularity of these tumors varies. Together with hyalinization of the vessel walls, one may find homogeneous staining of necrotic areas, re-

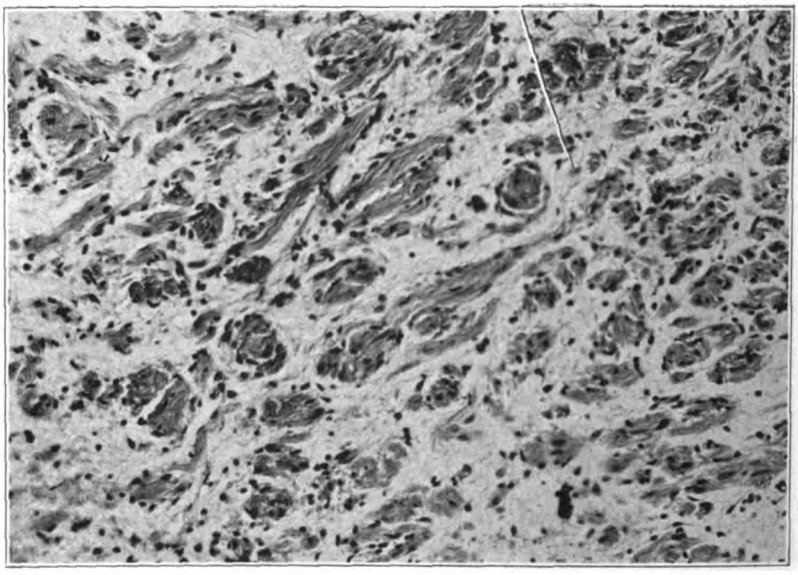


FIG. 252. NEURINOMA OF PERIPHERAL NERVE

Proliferation of both peri- and endoneurium with formation of fuchsinophile collagenous connective tissue surrounding nerve fibers and myxomatous tissue between them. Van Gieson stain. (Cf. fig. 195)

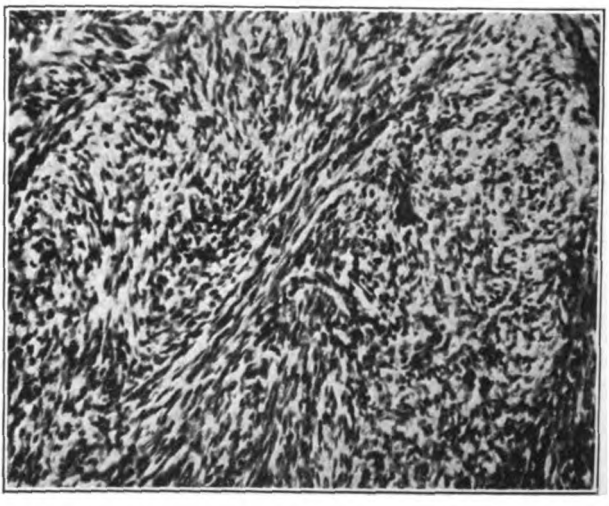


FIG. 253. NEURINOMA

Solitary tumor of cervical nerve. Growth had become malignant after several operations and invaded surrounding muscle tissue. Van Gieson stain

sembling the features of myxematous tissue. Cyst formation is another feature in these "perineurial fibroblastomas."

As a rule, these solitary neurinomas are benign tumors that merely compress the neighboring brain tissue and do not infiltrate the tissue in the periphery. Sometimes, however, without any apparent cause—frequently following operations—they show a more cellular appearance, lose the palisading arrangement of the nuclei, and invade the muscle, connective, and fat tissue of the neighboring region. The frequency of such "sarcomatous" transformation has been estimated to be as high as 10 per cent.

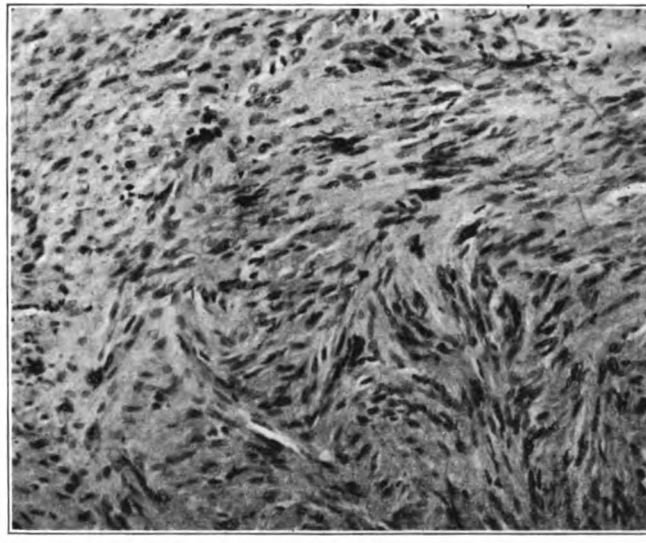


FIG. 254. NEURINOMA OF ACOUSTIC NERVE
Long chain arrangement of elongated, oval tumor nuclei. Hematoxylin-eosin stain

Among the *multiple neurinomas*, Recklinghausen's disease (molluscum fibrosum multiplex, *neurofibromatose de Recklinghausen*) is the relatively more frequent form. Distributed all over the skin, with the exception of the palmar surface of the hands and feet, are numerous nodules, varying from the size of a pinhead to that of a walnut, or even larger. Microscopically, they present a proliferation of the endoneurium of the peripheral nerves of the skin. Between the nerve fibers, and pushing these aside, are chains of elongated nuclei, similar to those described above in relation to the solitary neurinomas. Toward the periphery of the nodules this typical arrangement disappears. The endoneurial connective tissue is increased, with an increased number of nuclei of various sizes and forms

scattered through it. It may lose all structural differentiation and appear myxomatous. In general, the histologic appearance of these multiple nodules is not so uniform as in the endocranial solitary neurinomas. The two types of neoplastic tissue reaction, the palisading elongated nuclei and the irregular forms in a connective tissue reticulum, are mixed in various relations. The nerve fibers themselves may be well preserved or show demyelinization, with swelling of the axis-cylinders, but rarely are they completely destroyed (figs. 255, 256).

Besides these skin nodules, multiple neurinomas of the peripheral nerves and of the cauda equina, as well as solitary intracranial neurinomas of the

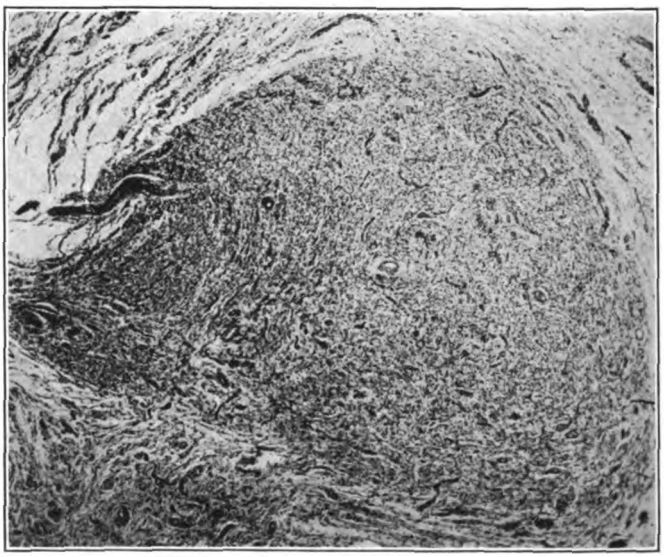


FIG. 255. RECKLINGHAUSEN'S DISEASE
Single subcutaneous nodule. Hematoxylin-eosin stain

cranial nerves, are found. Pigmented moles, osteomalacia combined with syringomyelia, and glioblastomas point to a generalized defect in development. Infantile progressive hypertrophic neuritis (Dejerine-Sottas), with its abnormal increase in endoneurial connective tissue, has been likened to Recklinghausen's disease.

Multiple neurinoma formation in the skin may be associated with thickening and proliferation of cutis and subcutis (*Rankenneurome*) and with thickening of the bones leading to a diffuse enlargement of a lower extremity—elephantiasis neuromatosa.

Gliomas may be expected in the olfactory and optic nerves, which contain

a neuroglial endoneurium, and near the exits of cranial nerves and spinal nerve roots (cf. chap. III). Indeed, the tumors that arise from within the optic nerve are typical gliomas. They are composed either of cells with round or irregular nuclei and scanty, vacuolated cytoplasm, which form cellular masses interspersed with fine fibers, or spindle-shaped glia cells and coarse fibrils arranged in strands, thus sometimes resembling polar spongioblastomas. Tumors of the optic nerve may show cyst formation together with intense vacuolization of the neoplastic cells (Verhoeff).

Diffuse gliomatosis of the olfactory nerves has been described in connection with glioblastomas of the brain, but apparently the minor clinical

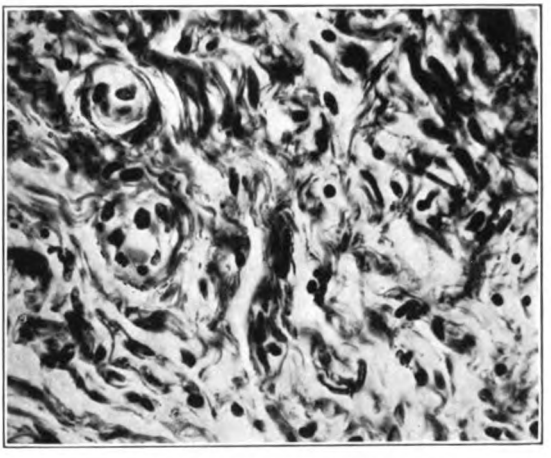


FIG. 256. RECKLINGHAUSEN'S DISEASE

Same tumor as in fig. 255. Formation of numerous fine argyrophile fibers. Hortega's silver carbonate method, modification 2

significance of disturbance of the sense of smell has never focused the attention of the pathologist on this nerve.

In the subarachnoidal space of the spinal cord, there have been found gliomas that in rare instances were seeding metastases from gliomas of the brain, but that in other instances had to be considered as primary tumors (astroblastomas, ependymomas). The authors considered them to have arisen either from heterotopic glia tissue or from the marginal zone of the spinal cord. It is possible, however, that they may have originated from the glia forming the endoneurium of the posterior roots before they enter the spinal cord.

Such a point of origin appears likely also for gliomatous tissue that forms

part of accoustic neurinomas. Theoretically, one should also expect gliomas to arise in neoplastic disease of the intracranial part of other cranial nerves (fig. 257).

A few instances of neuro-epitheliomas in the median and ulnar nerves have been reported (Lanford and Cohn, Stout). It is difficult to explain their origin if one does not assume embryonic remnants of spongioblastic tissue, or if one does not admit that Schwann sheath cells may undergo such a neoplastic transformation.

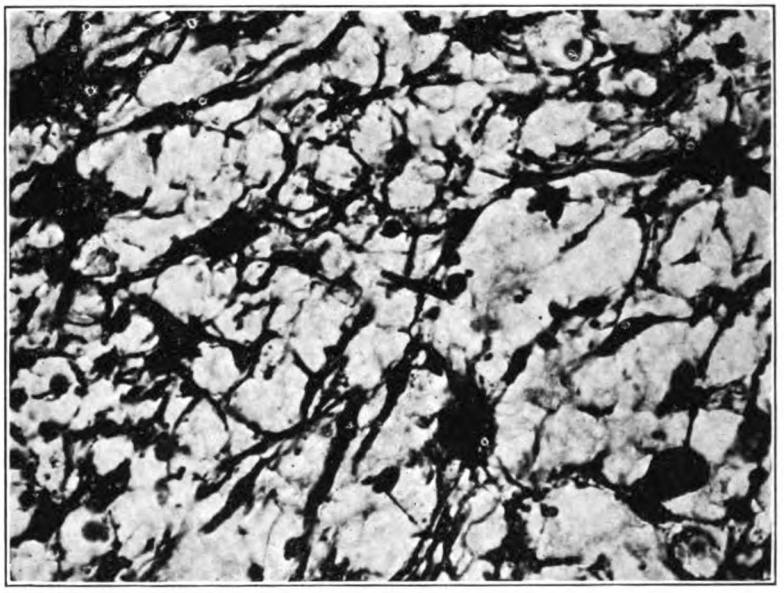


FIG. 257. GLIOMA FORMATION IN CONNECTION WITH ACOUSTIC NEURINOMA
Astrocytes and oligodendrocytes are seen together with more primitive spongioblast-like forms. Davenport stain

TUMORS OF THE SPINAL CORD

In their histologic make-up the tumors that have been described as occurring in the spinal cord and its sheaths do not differ from intracranial tumors. There is, however, a difference in their relative frequency and in their effect on the nervous tissue. In a comparison of the figures for extramedullary (Elsberg) and for extracerebral tumors (Cushing, omitting pituitary adenomas in the calculation), the difference is not striking: 11 per cent and 23 per cent are the figures for neurinomas, and 52 per cent and 36 per cent for endotheliomas. But in comparing the figures for intramedullary (Kernohan et al.) and for intracerebral tumors (Cushing), it is

interesting to note that adult astrocytomas are rare in the spinal cord, while they form 37 per cent of the cerebral gliomas. On the other hand, one-half of all the intramedullary tumors are ependymomas, as compared with

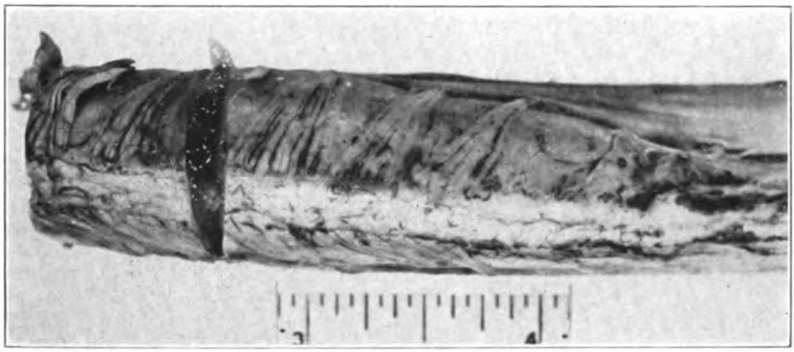


FIG. 258

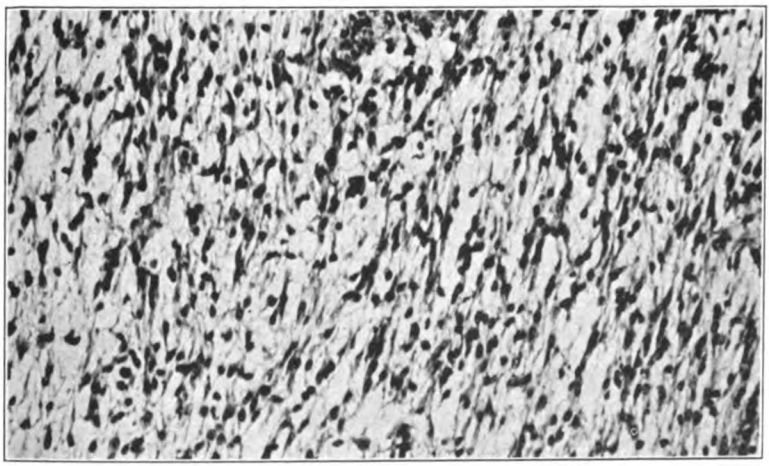


FIG. 259

FIGS. 258, 259. GLIOBLASTOMA OF SPINAL CORD

Fig. 258. Enlarged spinal cord, compressing spinal nerve roots.

Fig. 259. Longitudinal section through spinal cord. Elongated spongioblasts follow original course of fibers. Van Gieson stain

only 4 per cent of the brain tumors. The other gliomas -glioblastomas, medulloblastomas, and polar spongioblastomas- are represented in approximately the same relation (cf. tables 19, 20; figs. 258, 259).

The great number of ependymomas among the intramedullary tumors

may be explained as due the labile condition of the ependymal cells of the central canal. As a rule, in contrast to the findings in laboratory mammalia, a patent canal is not found throughout the whole axis of the spinal cord in adult humans. More frequently one meets with a canal lined by a single layer of cells in the lower dorsal segments, while in cervical and lumbar segments the ependymal cells form irregular clusters, sometimes arranged in two or three separated groups. Occasionally, tubule formations are seen, somewhat resembling true rosettes (fig. 260).

TABLE 20.—*Extramedullary Tumors of the Spinal Cord and Extracerebral Tumors*

Type of Tumor	Extramedullary Tumors of the Spinal Cord (Elsberg, 1925)			Extracerebral Tumors (Cushing, 1932)	
	In Various Sites	In Conus and Cauda	Extradural	No.	Percentage*
	Percentage Distribution				
Fibroma	15		14		
Neurinoma	11			176	16.0
Endothelioma (meningioma)	52	67	7	271	30.0
Sarcoma	10	17	64	14	1.5
Neuroblastoma		8			
Lipoma	5	8			
Dermoid	2			2	0.2
Chondroma			7		
Leiomyoma	2				
Tuberculoma			7		
Total no. of cases	42	12	14	463	

* The percentage distribution of extracerebral tumors was calculated from a total of 920 cases: pituitary adenomas, 360; meningiomas, 271; acoustic tumors, 176; congenital tumors, 113.

SYRINGOMYELIA

Relatively often, syringomyelia is found in gliomas of the spinal cord. The cavity (syrinx) is formed by a central necrosis of the tumor, with final liquefaction and absorption of the necrotic tissue. The predilection of this disease for the cervical segments and for the base of the posterior columns adjacent to the posterior commissure has been attributed to the presence of remnants of embryonic spongioblasts, which indicate here the final line of closing of the neural tube and which may become neoplastic (figs. 261, 262). The neoplastic process extends into upper and lower segments, with the cavity in the central segments gradually extending and becoming lined with intact tumor tissue. This may undergo a kind of hyalinization. The cells disappear and are replaced by a dense fibrous scar forming the wall of the cavity. Frequently the mesenchyme is in-

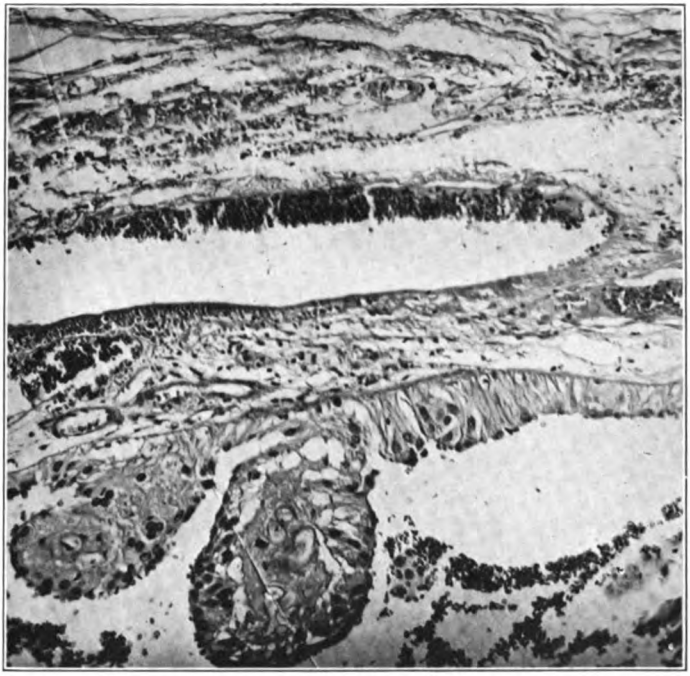


FIG. 260. PAPILLOMA OF SPINAL CORD

Encapsulated tumor in lumbar region, compressing spinal cord. Neoplastic ependymal cells are attached to base membrane and are supplied with ciliae that float in fluid of cystlike spaces. Van Gieson stain. (Cf. fig. 239)

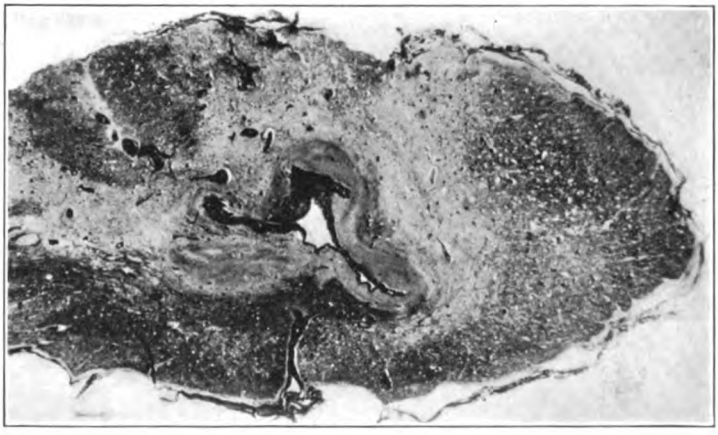


FIG. 261. SYRINGOMYELIA

Transverse section through cervical spinal cord. Glioblastoma surrounding large cyst, which is lined with one layer of endothelial cells. Van Gieson stain

volved in the neoplastic disease. One finds a proliferation of capillaries, thickening of the walls of the smaller arteries, and an increase in connective tissue fibers, which grow into the normal tissue and intermingle with the glia wall. The glioblastoma may extend into the medulla oblongata or develop independently there, with cavity formation (syringobulbia) (figs. 263, 264).

It should be emphasized that this process does not originate in the central canal, which is intact in early cases, but which finally may become part of the cavity. Widening of the central canal (hydromyelia) may occur in inflammations of the spinal cord with an increased accumulation of fluid

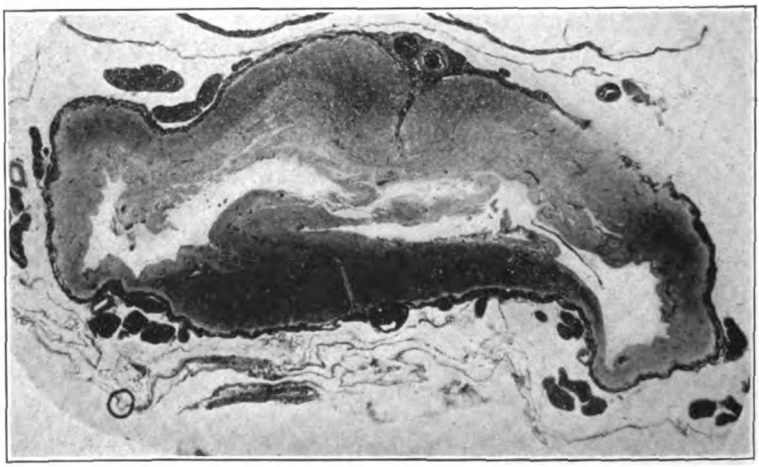


FIG. 262. SYRINGOMYELIA

Glioblastoma of cervical spinal cord. Cavities formed by necrosis of tumor tissue. Van Gieson stain.

or (as demonstrated experimentally) through a blocking of the upper, medullary end of the central canal (fig. 265).

Table 19 indicates that intramedullary tumors give a longer history of preoperative symptoms than intracerebral tumors. This appears somewhat paradoxic at first. One would suppose that a growth like a glioblastoma within the narrow spinal canal would lead to a more severe and abrupt interference with physiologic functions and be more destructive there than in the brain. The explanation given by Kernohan and his co-workers seems plausible—namely, that intramedullary and intracerebral tumors grow at the same rate, but that the symptoms are produced earlier in the spinal cord, while they may be overlooked in the brain during the early stages of a glioblastoma.

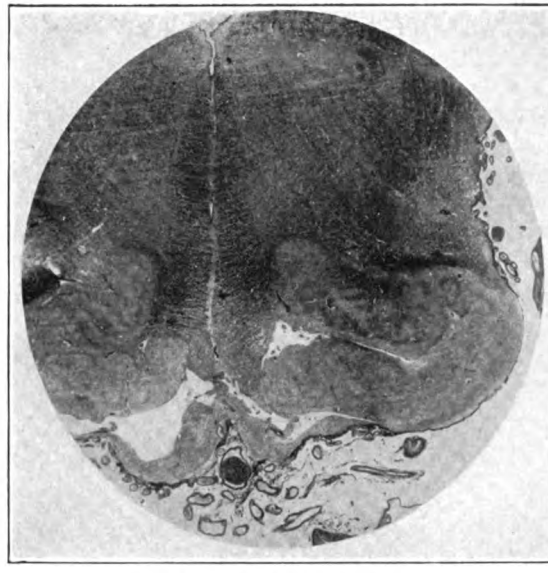


FIG. 263. SYRINGOBULBIA

Glioblastoma involving inferior olives and pyramids. Cavity formation by necrosis of tumor tissue. Van Gieson stain

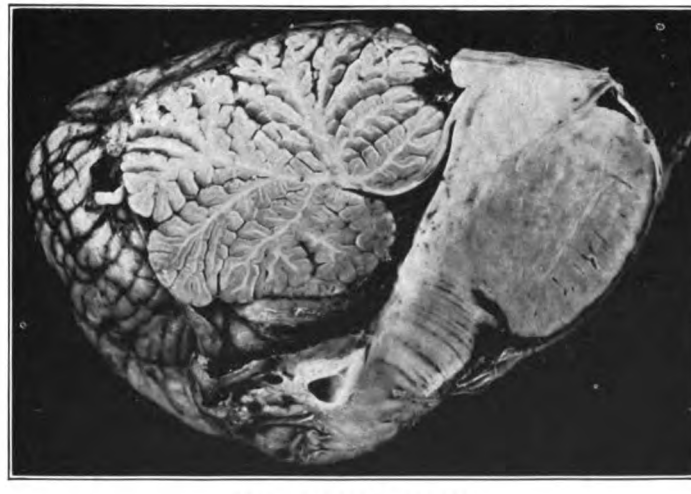


FIG. 264. SYRINGOBULBIA

Sagittal section through pons, medulla oblongata, and cerebellum. Formation of encapsulated cysts at lower end of medulla oblongata and upper cervical spinal cord. (Same case as in fig. 261)

Metastatic Tumors

Tumors that develop in other organs by metastasis from primary tumors of the brain are extremely rare. Those which have been described have been confined as regional metastases to the subarachnoidal spaces and to the spinal cord. The medulloblastomas that develop in the roof of the fourth ventricle form seeding metastases along the base of the cerebellum, the medulla oblongata, and the cervical spinal cord. Small tumor nodules or diffusely spread tumor cells may be found embedded in the meshes of the

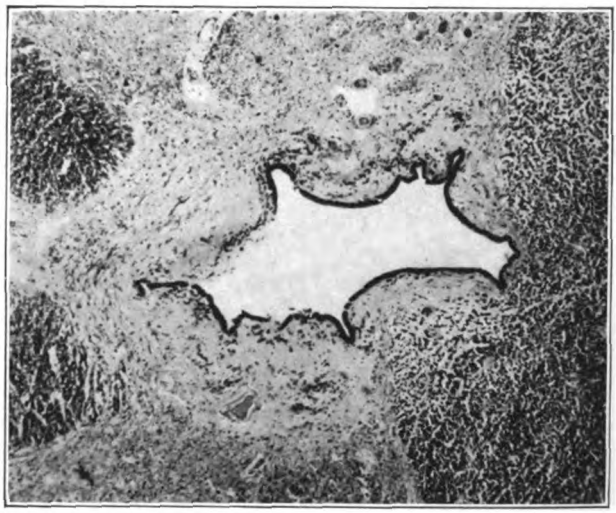


Fig. 265. Hydromyelia

Transverse section through dorsal spinal cord. Widening of central canal, with partial destruction of ependymal cells and reactive glia proliferation in environment. Van Gieson stain

arachnoidal membrane, attached to the spinal cord, or even invading the latter, with destruction of the invaded area (fig. 266).

Spinal metastases of an astrocytoma have been described by Russell and Cairns. The tumor had invaded the lateral ventricle from the pulvinar and formed nodules in the subarachnoidal space over the superior velum medullare and finally over the spinal cord. Here numerous miliary nodules consisting of fibrillary astrocytes were found.

There have been descriptions of papillomas of the choroid plexus that formed regional metastases along the subarachnoidal spaces of the spinal cord, invading the cauda equina and producing an intense proliferation of connective tissue.

Malignant tumors of other organs may form metastases in the brain and spinal cord and their sheaths. Sjoegren, who undertook a systematic study of 1000 cases of carcinoma found in 13,000 autopsies in a Swedish hospital, reported cerebral metastases in 4.7 per cent, though 50 per cent of these tumors had formed metastases in other organs of the body. These brain metastases arose from primary carcinomas of the following organs: prostate, 22 per cent; breast, 19 per cent; lung, 12 per cent; uterus, 3.5 per cent. It is interesting to note that Cushing found a ratio of 4.3 per cent for

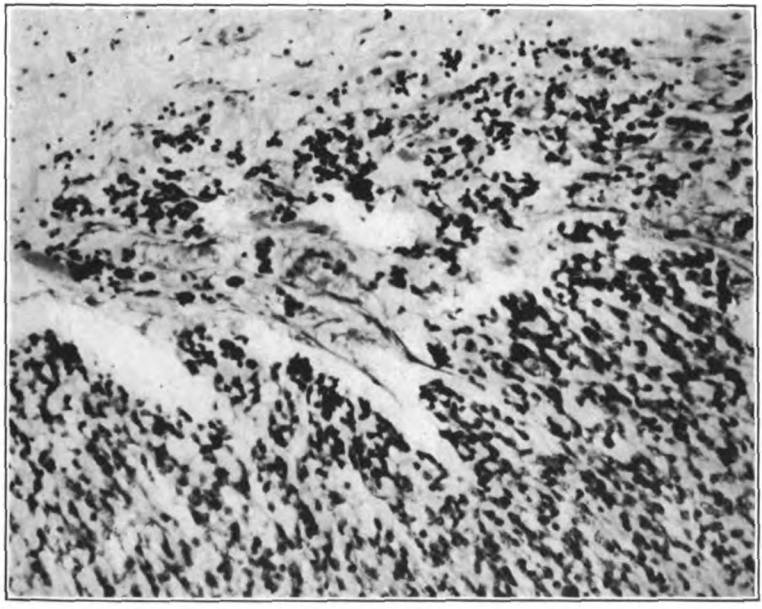


FIG. 266. MEDULLOBLASTOMA METASTASES TO PIARACHNOID AND CERVICAL SPINAL CORD
Hematoxylin-eosin stain

metastatic and invasive tumors in 2000 verified intracranial tumors. In our material of intracranial tumors, derived from surgical cases and general hospital autopsies, intracranial carcinoma metastases were found in approximately 5 per cent of cases. The distribution of cases according to origination in the different organs was: breast, 30 per cent; intestines, 30 per cent; bronchi, 18 per cent (figs. 267–70).

Sarcoma metastases are less frequently found intracerebrally. They are more frequent in the form of metastases in the vertebra and of extradural tumors in cases of myelogenic, small round cell sarcomas (fig. 271).

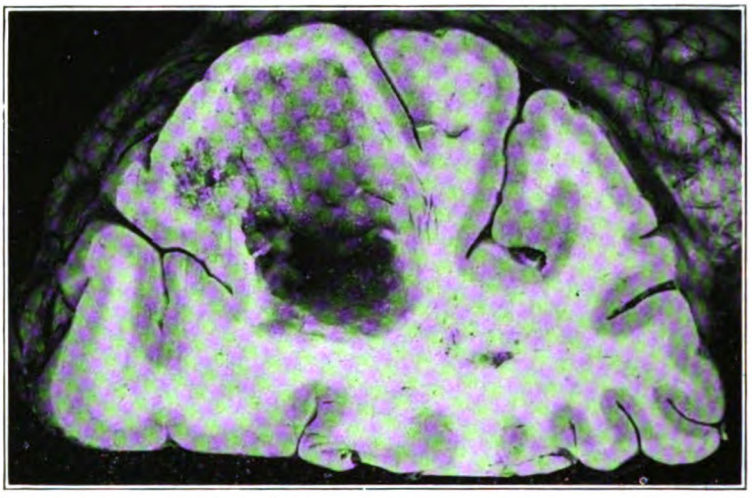


FIG. 267. METASTASES OF PRIMARY CANCER OF LUNGS TO FRONTAL LOBE
Cystic degeneration of inner part of tumor

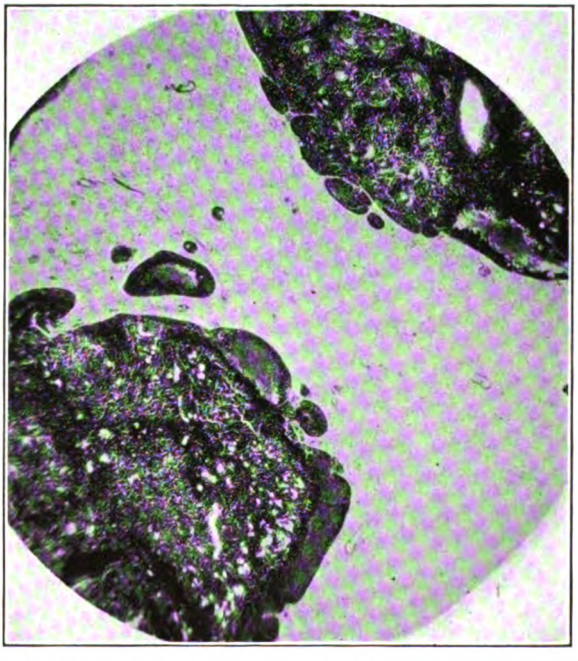


FIG. 268. METASTASES OF PRIMARY CANCER OF BREAST TO BRAIN
Progressive mesenchymal or glial reaction is completely absent. Van Gieson stain

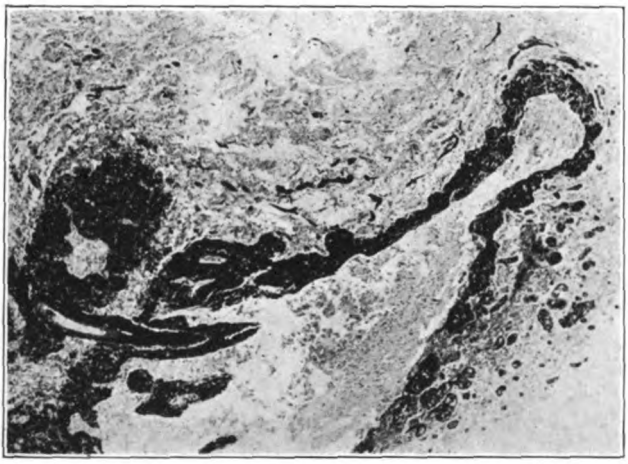


FIG. 269. METASTASES OF PRIMARY CANCER OF NASOPHARYNX TO MENINGES AND TEMPORAL LOBE

Area of softening surrounds metastases. Van Gieson stain

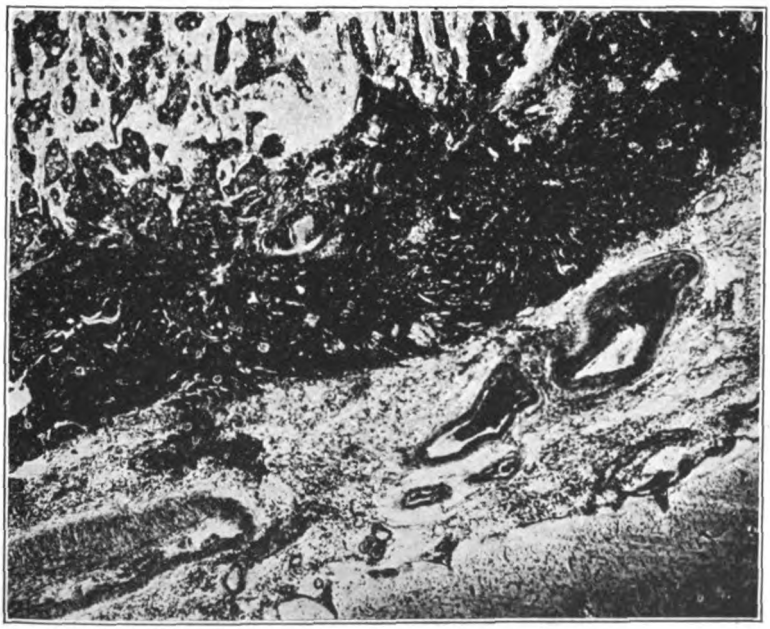


FIG. 270. CARCINOMA METASTASES TO MENINGES

Carcinoma of breast invading dura mater of brain. Mild inflammatory reaction of underlying piarachnoid. Van Gieson stain

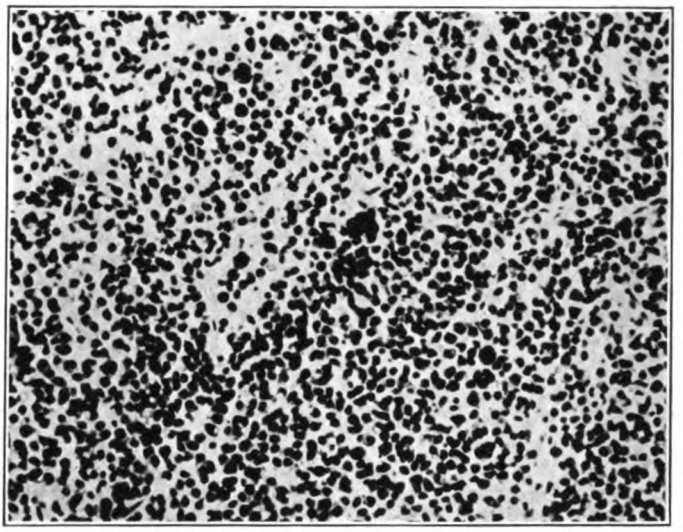


FIG. 271. SMALL ROUND CELL SARCOMA INVADING DURA MATER OF DORSAL SPINAL CORD
Van Gieson stain

FIG. 272. CHORDOMA INVADING SPINAL CANAL AND COMPRESSING CAUDA EQUINA

If one studies under the microscope the effect of carcinoma metastases upon the brain tissue, one is surprised at the mildness or even absence of defense reaction in both ectodermal glia and mesenchymal tissue. The

TABLE 21.—*Intracranial Tumors (Cushing, 1902–1931)*

Type of Tumor	No. Patients	Percentage of Total	Case Mortality Percentage	Operative Mortality Percentage
Glioma	862	43.7	25.9	17.2
Pituitary adenoma	360	18.2	7.1	6.2
Meningioma	271	13.7	20.8	11.0
Acoustic tumor	176	8.9	14.6	11.4
Craniopharyngioma	92	4.7	21.8	14.6
Cholesteatoma	13	0.7	23.1	16.6
Other, congenital form	8	0.4		
Metastatic and invasive form	85	4.3	28.6	22.5
Tuberculoma	33	1.7	50.0	42.9
Syphiloma	12	0.6	0.0	0.0
Hemangioblastoma	25	1.3	25.0	13.6
Hemangioma	16	0.8	0.0	0.0
Primary sarcoma	14	0.7	50.0	35.3
Papilloma	12	0.6	27.3	13.4

interior of the metastasis frequently consists of necrotic brain and tumor tissue forming a granular homogeneous mass without scavenger cell formation. Cystic degeneration may also be present. The zone immediately

TABLE 22.—*Relationship of Gliomas to Tumors of the Brain*

Period	Author	Total Autopsies	Brain Tumors			Gliomas
			Percentage of All Autopsies	Percentage of All Brain Tumors		Percentage of Primary Brain Tumors
				Primary	Metastatic	
1855–1878	Gurlt, Vienna	14,630	1.49	77	23	
1892–1923	Rapp, Tübingen	7,642	2.07			
1854–1931	Rudershausen, Heidelberg	31,698	1.72	81	19	52
1920–1937	Flock, Freiburg	8,172	2.48	84	16	37
	Total	62,142	1.81	80	20	49

surrounding the tumor may show a mild edema, but very rarely proliferation of fibrous glia. Only in a case of chorionepithelioma has an excessive glial fibrosis together with connective tissue overgrowth surrounding the invading tumor been seen (fig. 28). Occasionally a mild progressive reac-

tion may take place in other carcinomas (hypernephroma). Areas of softening in the region remote from the tumor are not the rule.

Neurons and glia cells in the zone adjacent to the invading carcinoma show various phases of degenerative change; swelling and shrinkage appear, but no scavenger activity in the form of neuronophagia is seen. Somewhat more remote from this zone a mild perivascular cellular infiltration of lymphocytes and a few plasma cells may occur. Excessive perivascular cuff formation of both cell types, and formation of dense walls opposing the invading tumor, were observed in a cancer that had invaded the skull and formed metastases in the temporal lobe and the pons.

Carcinoma metastases are usually multiple. They invade the cerebral hemispheres and the cerebellum simultaneously, spread into the subarachnoidal spaces, and invade the sheaths of the cranial nerves and spinal nerve roots. In contrast to the mild reaction of the glia, invasion of the meninges or nerve sheaths produces an intense inflammatory reaction with excessive formation of collagenous fibers. These encapsulate the tumor cells and inhibit their growth.

If a large carcinoma metastasis is formed in one hemisphere, the other hemisphere will frequently be found to be enlarged and edematous, while there is also an edema of the overlying piarachnoid. One may try to explain this phenomenon appearing in combination with the clinical symptom of encephalitis by assuming a diffusion of toxic metabolic products of the cancer cells into the cerebral fluids, with production of an inflammatory reaction.

XIII

CONGENITAL MALFORMATIONS

THE DEVELOPMENT of the nervous system may be arrested or deviated at any stage, from the first anlage of the medullary plate up to its final evolution after birth. Resulting malformations may present themselves as complete absence of the brain, *anencephalia*, or of the spinal cord, *amyelia*. In anencephalia the primitive eye vesicles may be developed and contain layers of rods and cones but no neurons and nerve fibers nor optic nerves and tracts. In amyelia the spinal ganglia and their central processes may be present, even forming posterior roots; the muscles of the extremities are also developed and supplied with nerves, though the anterior roots are absent.

In absence of part of the brain, *hemicephalia*, the cerebral hemispheres and the diencephalon may be missing, with rudiments of corpora quadrigemina, pons, and cerebellum present. Instead of the missing cerebrum, there may be found a racemose conglomeration of blood vessels (area cerebrovasculosa). It is of interest to know that in congenital hemicephalia the adrenal glands are extremely small. This is due to atrophy of the hypophysis. Adrenalectomy in animals leads to an increase in the brain weight, with a corresponding increase of its different chemical constituents.

Different structures of the central nervous system may be undeveloped. Oculomotor nuclei may be absent, but well developed eye muscles present. The nuclei of Goll and of Burdach may be absent, or the pyramidal tracts not formed. Absence of the corpus callosum may be disclosed as an accidental finding at autopsy in mentally normal persons or may be combined with idiocy. Marchiafava's disease represents a primary degeneration of the anterior two-thirds of the corpus callosum (fig. 273). Excessively small brains (*micrencephalia*) with weights from 300 to 400 Gm. in adults, and excessively large brains (*megalencephalia*) with weights up to 2850 Gm., are other extremes of cerebral development. The latter condition may be combined with a generalized neoplastic tendency and diffuse glioblastoma formation in the brain stem (figs. 230, 279).

CORTICAL MALFORMATION

Anencephalia, amyelia, or other gross defects with which the organism does not survive are not of any practical importance to the neuropathol-

ogist, but malformations in the cyto-architecture of the brain are of considerable interest in connection with defects of mental development. In the course of their migration from the central matrix toward the periphery, neuroblasts may be arrested in the intermediary zones that later develop into the white matter. Such an inhibition of migration may be diffuse, leading to pachygyria, at the same time, however, excepting gyri that are close to the center of growth near the ventricles—the gyrus cinguli, hippocampus, and area striata. In the clinical aspect, such disturbances of growth are combined with mental deficiency or epilepsy. The inhibition of migration may be circumscribed and may produce wormlike pro-

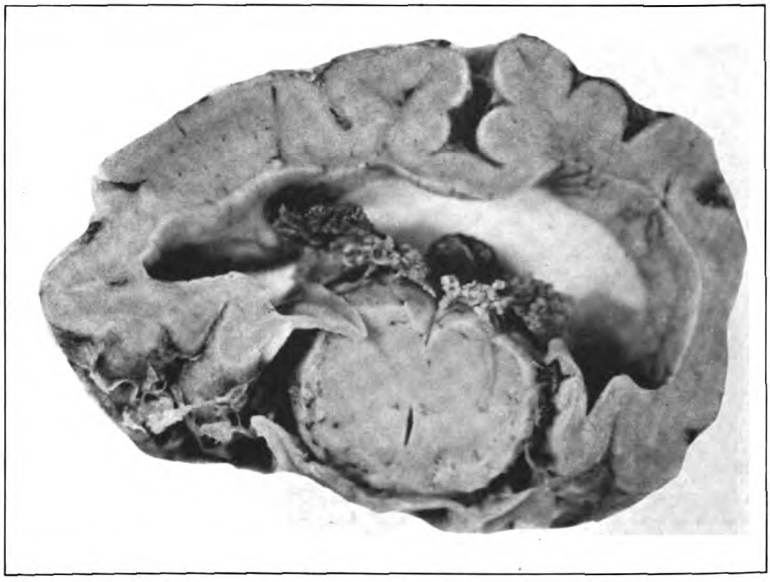


FIG. 273. CONGENITAL ABSENCE OF CORPUS CALLOSUM

jections of deep gyri into the white matter. Finally, such an inhibition may involve large areas of the cerebral cortex or the cerebellum as a whole.

Islands of neuroblasts grow independently and are found as *heterotopias of neurons* in the brain after birth. In sections stained for myelin sheaths, they can easily be recognized by the spotty appearance of the white matter (figs. 274, 275). They may comprise different stages of neuronal development, from that of primitive neuroblasts to that of well developed pyramidal cells with Nissl structure. Frequently such heterotopias are combined with malformation of the cortex. Some of these malformations are: (1) agyria, the brain having the appearance of that of an embryo, with smooth surface; (2) pachygyria, in which a few broad, plump, large gyri

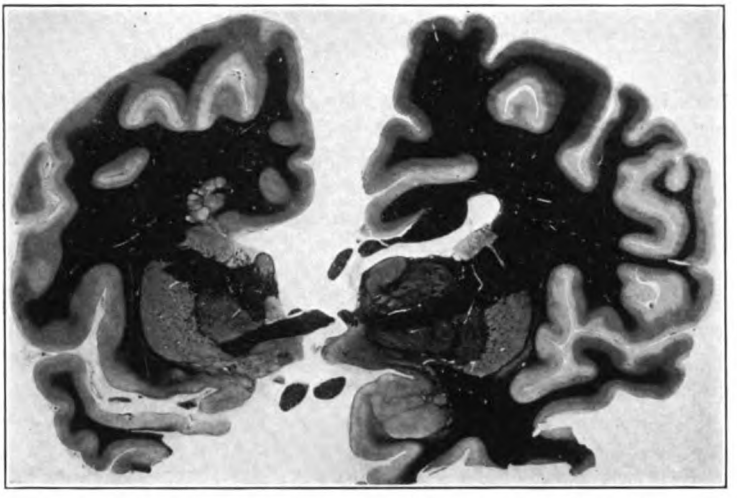


FIG. 274. HEMIATROPHY OF BRAIN WITH HETEROTOPIA OF GRAY MATTER
Frontal section through brain. Pachygyria of convolutions of left hemisphere (with exception of temporal lobe, which is normal). Weil stain

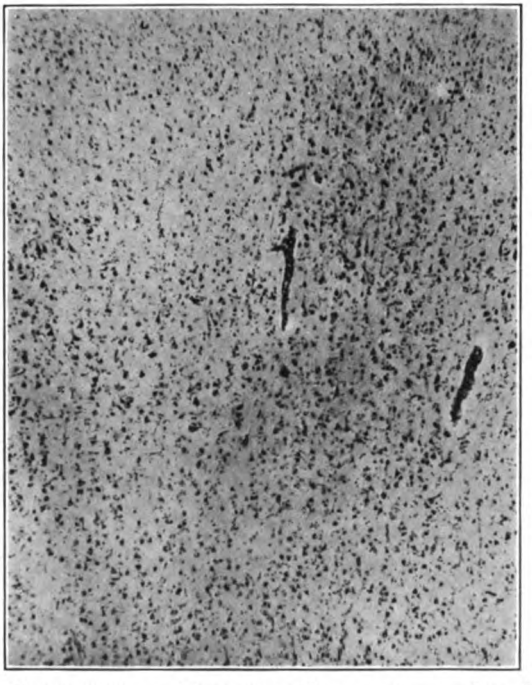


FIG. 275. HEMIATROPHY OF BRAIN WITH HETEROTOPIA OF GRAY MATTER
Cyto-architecture of pachygyric convolution: first frontal gyrus. Cresyl violet stain

appear; (3) microgyria, characterized by numerous small gyri that in extreme cases give to the cortex a verrucous appearance (status verrucosus). The cyto-architecture of these malformed gyri is markedly changed as compared with that of the normal cortex. In agyria the cortex is very thin and contains three or four layers of neurons in different stages of development. In pachygyria, six layers may be present, but the transition to white matter is indistinct, with stripes of neurons continuing into the subcortex. In microgyria, many pictures of malformation have been described—absence of striation or primitive subdivision into four layers, dense accumulation of neurons or sparse distribution. Different stages of development are present—primitive cells with large vesicular nuclei, multinuclear cells, well formed pyramidal cells arranged with the long axis parallel to the surface, and very large but well formed cells.

Such cortical malformations may be combined with defects in myelinization. With micro- and pachygyria there may also be poor development of the myelin sheaths in the subcortex. In parts there may be excessive development, producing the picture of intense myelinization of the outer tangential fibers, or darkly staining islands of myelinated fibers (*plaques fibromyéliniques*) may be present. A similar picture has been described above as status marmoratus of the striate body. The argument regarding the origin of the latter condition applies also to these hypermyelinated plaques. They may represent condensation of myelinated fibers or excessive regeneration of myelin sheaths in scar tissue—occurrences of prenatal life or during the first year of postfetal life (infection). The origins of all these malformations may go back to any period of embryonic life. They may be due to intra-uterine disturbances, such as infection, trauma, or disturbance of hormone or vitamin supply. Such malformation has been produced experimentally—e.g., by feeding to pregnant rats a diet deficient in riboflavin, which led to manifold anatomic abnormalities (Warkany and Schraffenberger).

Tuberous Sclerosis

Synonyms: German, *tuberöse Sklerose;* French, *maladie de Bourneville.*

Malformation of gyri and of cyto-architecture may be combined with neoplastic transformation of nervous tissue, as in tuberous sclerosis ("diffuse neurospongioblastosis"—Globus, Selinsky, and Strauss).

Macroscopically, the brain may present a normal convolutional development and only single gyri may show marked widening, characterized by a lighter, grayish or white color; or mushroom-like, isolated larger islands of cortex of the same light grayish color may interrupt a gyrus that is otherwise normal in a gross view (fig. 276). The cerebellar cortex may undergo similar transformation. Tumors may be found simultaneously in other

organs—in the retina (glioma), kidneys (multiple rhabdomyoma), heart (angioleiolipofibroma), or in the liver, ovaries, thyroid, or suprarenal glands (adenoma). Copper-colored nevi of the skin, pendulous fibromas, or adenoma sebaceum together with these tumor formations, indicates a generally defective anlage.

Microscopically both neuron and glia show pathologic changes. Most impressive are the abnormalities of the glia. In sections of cortical tumors stained for glia fibers, one may see dense zones formed by a tangled network of coarse glia fibers and arranged in different layers. A similar picture of

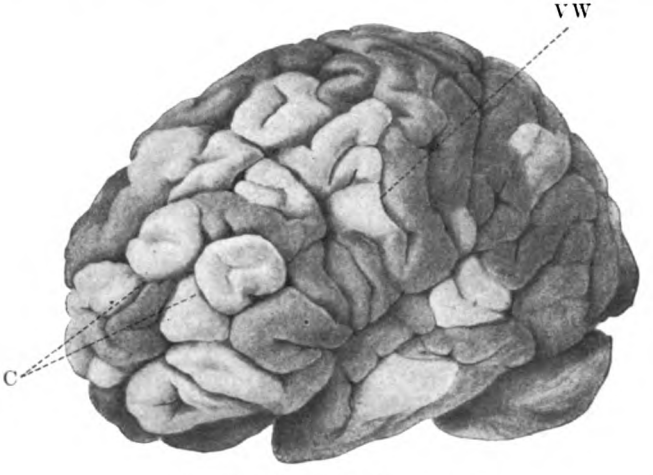


FIG. 276. TUBEROUS SCLEROSIS

C = localized umbilicus-like neoplastic gyri. V W = part of normal gyrus with beginning neoplastic transformation

(Schob, F.: in Handb. d. Geisteskr., 1930. Courtesy Julius Springer)

dense glia proliferation of tumor-like character (like "ruffled hair") has been described above (chap. XII) in relation to degenerative diseases of the spinal cord (Friedreich's disease and Dejerine-Sottas interstitial hypertrophic progressive neuritis).

In sections stained with cresyl violet, a marked increase in glia nuclei may be seen. They have various shapes and may be confined to the outer zone or may invade the whole cortex. In silver-impregnated material numerous bizarre, atypical glia cells are recognized. They may be multinuclear, elongated, oval, large, and rich in fibrous processes, or small, oval, with only a few fibers. Giant glia cells may be accumulated around blood vessels or arranged as diffuse glia foci.

A similar polymorphous appearance is found among the neurons of the blastomatous cortex. The cyto-architecture has undergone marked destruction. Some neurons show states resembling different forms of degeneration—shrinkage, balloon-like swelling, vacuolization. Besides these, extremely large forms are seen—elongated, spindle-shaped cells and cells resembling a Medusa. Despite the presence of well stained neurofibrils, it is sometimes difficult to differentiate these cells from atypical large glia cells, which also may show fibrillation of their processes in silver-impregnated preparations. Such atypical forms are not confined to the tumor-like trans-

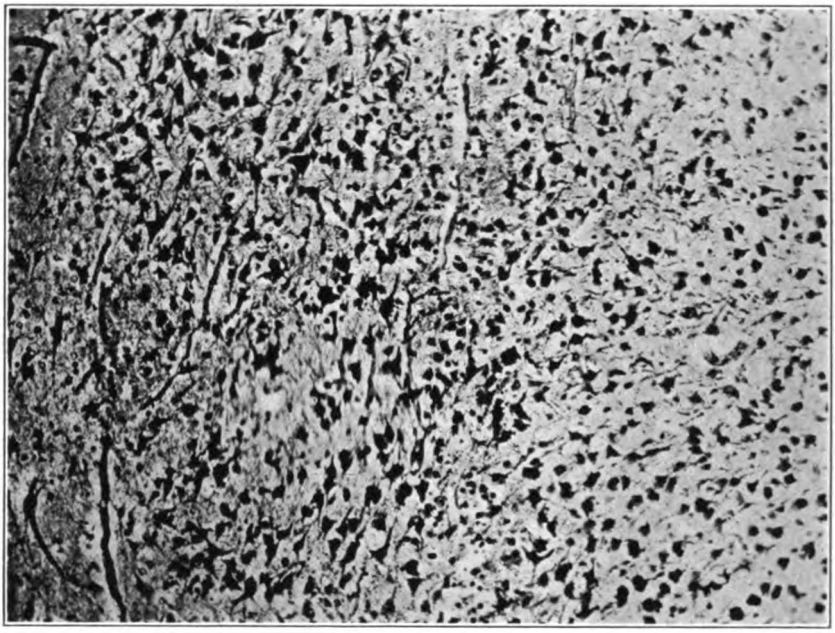


FIG. 277. TUBEROUS SCLEROSIS

Neoplastic gyrus. Davenport stain. Tumor cells in periphery of cortex without any definite cyto-architecture

formations of the cortex but may also be found in more nearly normal gyri and in heterotopic subcortical foci, in which they are intermingled with blastomatous glia cells (figs. 277, 278).

Tumor-like nodules may be seen protruding into the lateral ventricles and attached to the inner wall. Their histologic structure resembles that of isolated subependymal glioblastomas. The nodule consists of a peripheral zone of elongated, spindle-shaped cells (spongioblastoma polare) intermingled with a dense meshwork of neuroglia fibers, and a more cellular, less compact central part. Here various forms of large glia cells may be seen,

some with one or more large nuclei and abundant cytoplasm, and some giant spider forms. Precipitates in irregular forms, or forms resembling corpora amylacea, are intermingled with the tumor cells or are found around blood vessels. They may stain intensively with cresyl violet or hematoxylin.

Malformations of the Sheaths of the Central Nervous System

Malformation of the sheaths of the central nervous system may be found either in the bony cavities or in the meninges. The vertebral canal may be open (spina bifida or rachischisis), owing either to a defect of the processi spinosi and the posterior half of the vertebral arch (holorachischisis com-

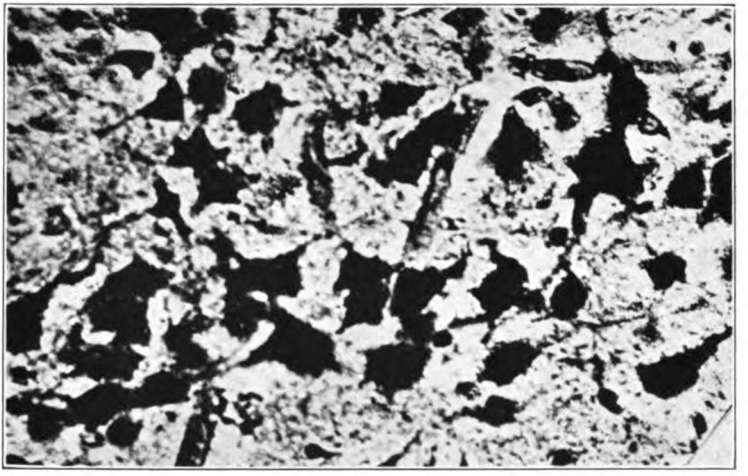


Fig. 278. Tuberous Sclerosis

Same section as in fig. 277. Higher magnification, demonstrating bizarre forms of large glia cells

bined with amyelia), or, in milder forms, to a fissure in the posterior part of the vertebrae. This condition seems to occur in as many as 1 per 1000 of all newborn children, predominantly in the lumbosacral region. Through the fissure the meninges and spinal cord tissue may protrude, forming a tumor-like mass (spina bifida cystica). This protrusion may distend the overlying skin or may be unnoticeable externally (spina bifida occulta). In the latter case, however, there is frequently a localized hypertrichosis or a scarlike retraction indicating the underlying bony defect, which may easily be detected in roentgen ray pictures. The cystic protrusion may be formed by the meninges alone (dura or piarachnoid separately or combined—meningocele), by the spinal cord with the meninges (myelomeningocele), or

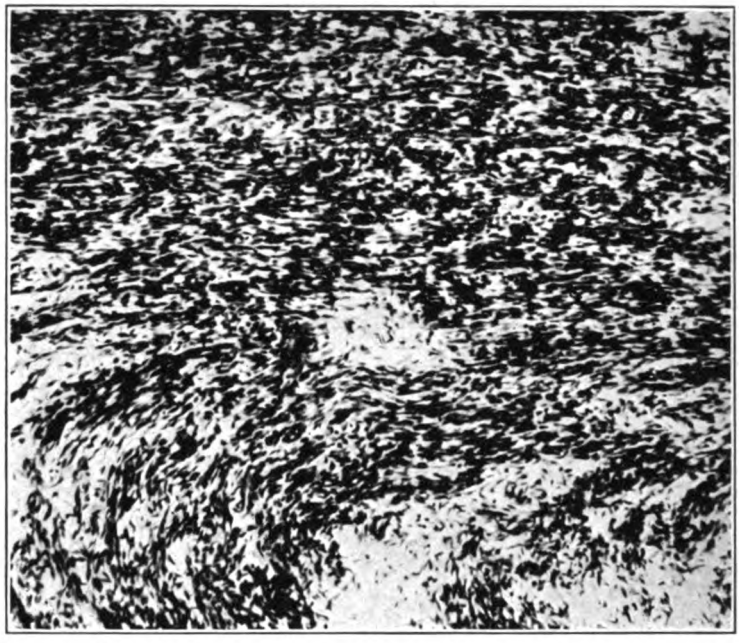


FIG. 279. DIFFUSE GLIOBLASTOMATOSIS IN CASE OF MEGALENCEPHALIA

In parts of brain stem, neoplastic cells were arranged in form of polar spongioblastoma ("central neurinoma"), with elongated nuclei, in long chains, streaming in same direction. Cresyl violet stain. (Cf. fig. 230)

FIG. 280. SPINA BIFIDA WITH MENINGOCELE

by a spinal cord that has been widened by a hydromyelia and has penetrated through the meninges (myelocystocele), or that causes the meninges also to protrude (myelocystomeningocele). Such a malformation may be combined with a defect of the spinal cord itself, such as persistence of an embryonic fissure (dysraphia) resulting from excessive proliferation of connective tissue or dermoid cysts that prevented a closing of the open tube. Such a picture may simulate a double spinal cord, a condition that seems to occur only in very rare cases (figs. 280, 281).

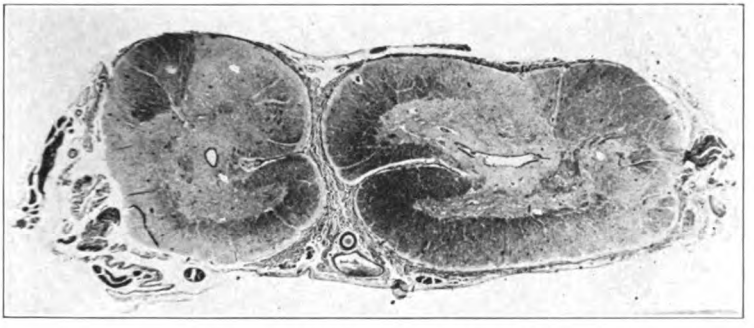


FIG. 281. DUPLICATION OF SPINAL CORD

In child, 5 months old, with spina bifida. Malformation began in lower dorsal segments and continued downward throughout spinal cord. Above, there was marked hydromyelia of middorsal segments, glioblastoma in upper dorsal and lower cervical segments. Transverse section of lumbar region. Van Gieson stain

HYDROCEPHALUS INTERNUS

Usually hydrocephalus internus leads to a uniform distention of the cranial cavity. The condition is characterized by an enormous dilatation of the ventricular system, which is filled with an excessive amount of fluid, and by a reduction in the size of the cortex. One may differentiate, as does Schob, between a hydrocephalus ex vacuo and a destructive hydrocephalus. The first form may be considered a congenital malformation only if it follows an agenesis of the cortex. In the second form the well developed cortex is destroyed by the increased internal pressure, which first affects the white matter. The hydrocephalus may be produced by an interference with absorption of the fluid eliminated by the choroid plexus, by occlusion of the foramina of Monro, of the aqueduct, or of the foramina of Magendie and of Luschka. Such an occlusion will result either in a dilatation of the lateral ventricles or in a dilatation of the latter combined with widening of either the third or the fourth ventricle. Such a mechanical block may be produced by tumor or by inflammatory processes. The high proportion

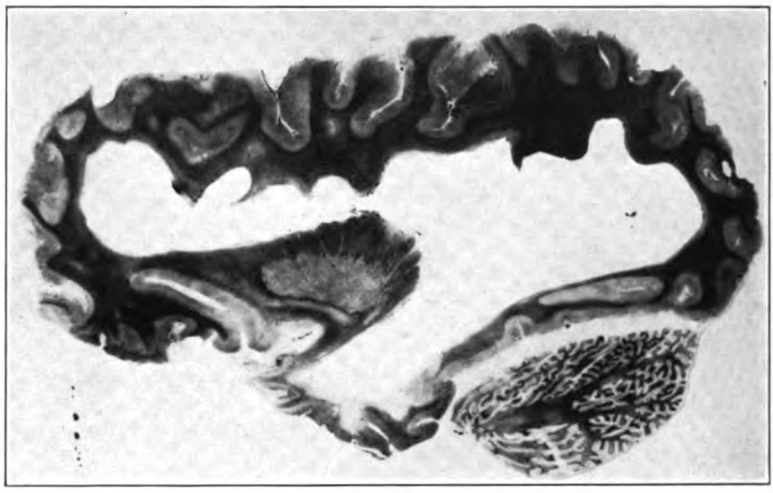


FIG. 282

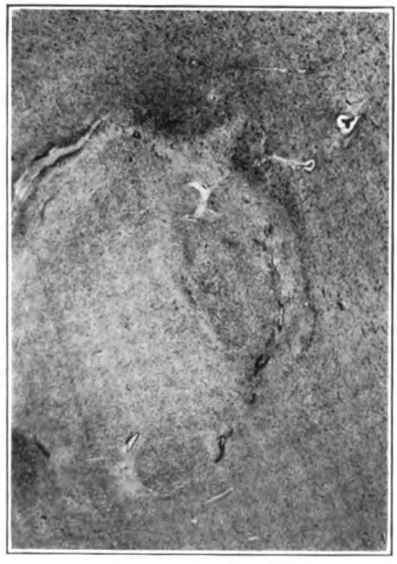


FIG. 283

FIGS. 282, 283. CONGENITAL HYDROCEPHALUS INTERNUS

Fig. 282. Sagittal section through brain. Widening of both lateral ventricle and inferior horn. Weil stain.

Fig. 283. Same case. Section through midbrain. Occlusion of aqueduct of Sylvius, following encephalitis (possibly syphilitic). Van Gieson stain

(10 per cent) of syphilitics among children with internal hydrocephalus (7 per cent of all autopsies—Hodenfeld) is correlated with the finding of encephalitis, which in the midbrain may lead to an occlusion of the sylvian aqueduct. In rare cases, an inferior horn of a lateral ventricle may be widened following occlusion due to cohesion of opposite ventricular walls. In the presence of patent foramina, interference with reabsorption of the cerebrospinal fluid may lead to an internal hydrocephalus (in meningitis affecting the pacchionian bodies or the perineural lymphatics of the cranial nerves) (figs. 100, 282, 283). Blocking of the foramina of Monro may be produced by the so-called colloidal cyst of the third ventricle. This is supposed to be a remnant of the paraphysis (Bailey). Its wall consists of hya-

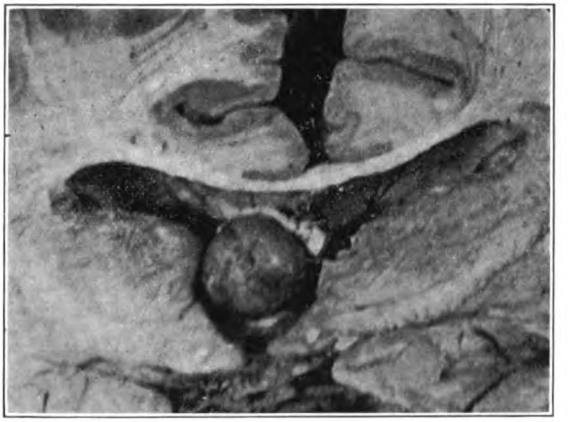


FIG. 284. COLLOIDAL CYST OF THIRD VENTRICLE
Attached to fornix and surrounded by tela chorioidea

line transformation of connective tissue, containing lymphatic channels lined with endothelial elements. The presence of acicular slits within the colloidal center testifies that at some time in the development of the cyst, fatty acids must have been formed (figs. 214, 284).

Frequently internal hydrocephalus is subdivided into a congenital and an acquired form. It is evident from what has been said above that in most cases it is impossible to decide whether a mechanical block of the ventricular system originated in pre- or postnatal life. Furthermore, we are not able at present, in the absence of such a block, to give histologic evidence that an internal hydrocephalus represents a true congenital malformation, i.e., a defect in the development of the mechanism of production and absorption of cerebrospinal fluid (fig. 285).

The neuropathologist is frequently confronted with the problem of deciding whether a pathologic condition is a defect of the embryonic anlage, with subsequent inhibited or aberrant development, or whether it is the end result of destructive processes active during intra-uterine life. Examples of this latter etiology have been cited in previous chapters—i.e., cortical atrophies, cyst formations, porencephalia, localized sclerosis. In other cases a decision is more difficult, especially in the frequent examples of congenital defect of movement. Three possibilities may be considered: (1) an aplasia of muscles or motor nuclei, i.e., a defective anlage; (2) intra-uterine muscular atrophy following disease of a lower motor neuron (infection, vascular lesion); (3) localized disease of peripheral nerves or of a muscle or muscle group, with retrograde nuclear atrophy. Pathologic reports in the

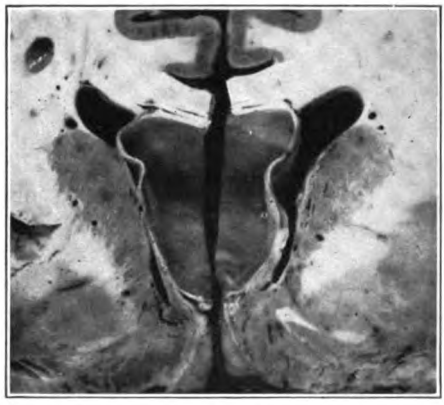


FIG. 285. CYST OF FIFTH VENTRICLE (SEPTUM PELLUCIDUM)

literature furnish examples of each of the three groups, especially of defects in the course of the cranial nerves. The lack of a progressive glia reaction and the absence of the neurons of the motor nucleus in question have been cited in favor of the theory of an aplasia, a defective anlage. One should, however, always be conscious of the fact that in the embryonic central nervous system, glia reaction and fibrous scar formation may be completely absent, and that a lesion may heal without leaving any histologic traces. In order to prove the existence of an isolated nuclear aplasia, normal development of the corresponding muscle group and other concomitant developmental defects in the central nervous system may be cited.

LITTLE'S DISEASE

It need not be emphasized that all the cases of congenital diplegia that have played such an important role in the literature under the name of

FIG. 286

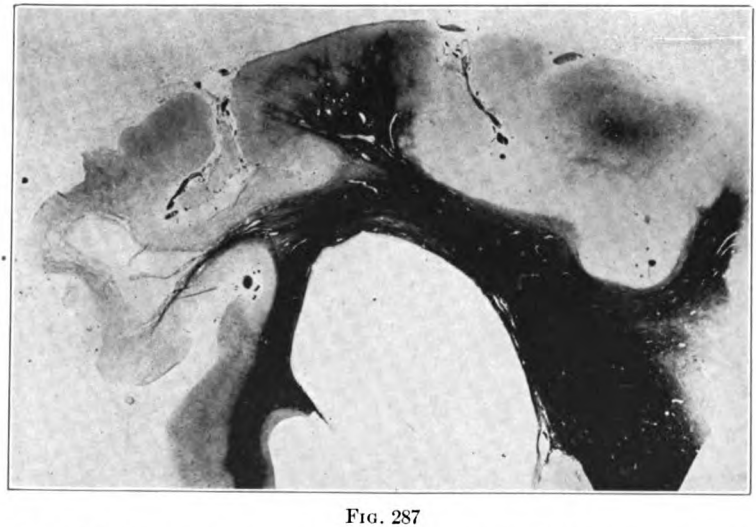


FIG. 287

FIGS. 286, 287. TWO CASES OF CONGENITAL CEREBRAL DEFECT WITH MENTAL DEFICIENCY

Fig. 286. Necrosis and demyelinization of white matter. Weil stain.
Fig. 287. Porencephalia. Weil stain

(Courtesy Dr. R. P. Mackay)

"Little's disease" pathologically represent many etiologies. True aplasias of the prerolandic area or of the pyramidal tracts are as difficult to prove as aplasia of the motor nuclei of cranial nerves, and mental defects find their pathologic counterpart in the remains of traumatic or inflammatory lesions of the brain, the spinal cord, or their meninges (figs. 286, 287). In other cases the defect in movement is combined with malformation of the cortex (micrencephalia, microgyria, pachygyria), with heterotopias and internal hydrocephalus. Furthermore, it is possible that birth trauma may be combined with congenital defects of development. Evidence of birth trauma due to anoxia has been produced experimentally in laboratory animals by ligation of the uterine vessels or the umbilical cords. In guinea pigs the clinical sequelae of more than eight minutes of anoxia were convulsions, ataxia, conditions simulating a decerebrate state, etc., with behavioral changes developing some time after survival. The histopathologic sequelae were cortical atrophies, disturbance of cellular architecture, gliosis, and hemorrhages (Windle and Becker).

APPENDIX

TABLE 23.—*Weight of Brain in Relation to Age, Sex, and Stature**

Age in Years	Weight in Grams		
	Males		Females
	Cerebrum	Total Brain	Total Brain
1–2		1105	995
3–6		1170	1100
7–13		1400	1165
14–19		1360	1240
20–29	1200	1365	1250
30–39	1180	1350	1230
40–49	1170	1310	1220
50–59	1120	1320	1270
60–69	1140	1320	1200
70–79	1150	1305	1140

* Figures calculated as mean values from data on English brains published by Pearl for the cerebrum and by Gladstone for the total brain (Biometrika *4:* 104, 118, 1905)

TABLE 24.—*Weight of Male and Female Brains in Relation to Stature**

In adults from 20 to 80 years of age

Stature (Cm.)	Weight of Brain in Grams			Percentage Distribution of Different Brain Weights		
	Male		Female	Male		Female
	Cerebrum	Total Brain	Total Brain	Cerebrum	Total Brain	Total Brain
147			1150			2
150			1110			3
152			1205			11
155	1140	1290	1195	1	3	11
157	1130	1285	1200	2	3	14
160	1150	1280	1250	3	5	16
162	1150	1270	1230	7	3	18
165	1160	1265	1280	10	9	7
168	1170	1300	1230	15	3	11
170	1200	1320	1280	15	16	7
173	1190	1350		14	19	
175	1190	1390		9	22	
178	1160	1375		11	5	
180	1210	1380		4	5	
183	1190	1410		6	3	

* Tables 24 to 27 from Roessle, R., and Roulet, F.: Mass und Zahl in der Pathologie, Berlin, 1932.

TABLE 25.—*Relation of Circumference of Skull, Capacity of Skull, and Volume of Brain*

Age (Yr.)	Circumference of Skull (Cm.)		Capacity of Skull (Cc.)		Volume of Brain (Cc.)	
	Male	Female	Male	Female	Male	Female
0–½	35.5	35.6	534	507	499	478
½–1	41.0	39.8	850	767	772	700
2	44.1	44.5	1079	1028	929	976
3	47.2	45.7	1232	1128	1123	1038
4	48.7	46.7	1279	1163	1190	1049
5–6	50.2	47.8	1372	1207	1300	1147
7–10	50.4	49.5	1424	1315	1333	1204
11–15	51.5	50.8	1426	1331	1285	1213
16–19	52.7	50.7	1444	1243	1289	1099
20–29	52.7	50.9	1411	1260	1223	1148
30–39	53.3	51.3	1441	1306	1279	1193
40–49	53.2	51.2	1439	1286	1264	1164
50–59	53.8	51.4	1471	1286	1275	1146
60–69	53.4	51.3	1447	1289	1237	1143
70–79	53.8	51.3	1466	1284	1212	1088
80–89	53.6	51.6	1451	1299	1164	1072

TABLE 26.—*Weight of Brain, Weight of Body, and Length of Body in Correlation with Age and Sex*

Age (Yr.)	Male			Female		
	Weight of Brain (Gm.)	Weight of Body (Kg.)	Length of Body (Cm.)	Weight of Brain (Gm.)	Weight of Body (Kg.)	Length of Body (Cm.)
At birth	386.8	3.12	51.6	363.8	2.97	50.0
Birth–½	498.9	3.21	54.8	490.9	3.12	54.4
½–1	673.4	4.47	67.0	706.2	5.18	65.8
1	965.0	10.58	77.1	944.3	9.55	81.1
2	972.5	9.48	82.4	947.0	9.62	85.4
3	1164.0	15.30	89.8	1156.3	14.52	100.4
4	1175.0	18.43	102.2	1119.0	12.50	105.5
5	1406.7	17.32	110.2	1262.5	17.10	111.2
6	1410.0			1168.0	14.60	112.0
7	1373.7	18.27	117.5	1293.3	19.20	120.3
8	1166.6	21.00	128.0	1230.0	26.90	122.5
9				1360.0	26.00	128.0
10	1243.3	23.86	132.3	1130.0	19.80	128.0
11	1455.0	27.00	136.0	1268.3	28.70	127.2
12	1480.0	35.05	150.1	1200.0	20.00	129.0
13	1426.6	32.23	139.9	1240.0	29.70	146.8
14	1310.0	38.96	149.0	1283.7	34.10	153.7
15	1340.0	44.48	154.8	1262.5	41.50	150.3

TABLE 26.—*Continued*

Age (Yr.)	Male			Female		
	Weight of Brain (Gm.)	Weight of body (Kg.)	Length of Body (Cm.)	Weight of Brain (Gm.)	Weight of Body (Kg.)	Length of Body (Gm.)
16	1348.0	47.18	161.9	1307.5	44.40	154.7
17	1356.8	46.75	162.4	1220.0	43.60	152.3
18	1392.0	43.43	164.4	1284.5	46.50	156.5
19	1370.0	52.86	169.1	1254.3	46.05	154.7
20	1399.8	49.06	167.6	1260.3	53.07	159.5
21–25	1404.0	55.00	169.2	1242.2	47.48	157.0
26–30	1389.3	53.94	167.7	1223.3	48.98	157.1
31–40	1387.2	56.62	167.0	1271.2	50.31	156.1
41–50	1360.8	57.23	166.7	1240.2	54.14	153.8
51–60	1337.6	57.19	165.8	1253.6	51.91	154.1
61–70	1306.4	54.07	164.2	1209.7	49.14	153.8
71–80	1265.9	54.27	164.3	1150.2	46.06	158.1
Over 80	1170.9	48.62	160.8	1061.2	38.80	150.5

TABLE 27.—*Amount of Cerebrospinal Fluid in Relation to Time Elapsed after Death (W. H. Schultze)*

Time Elapsed after Death (Hr.)	No. of Cases	Amount of Fluid (Cc.)	Specific Gravity of Fluid
1–5	52	102	1005.5
6–10	34	75	1006.5
11–15	31	65	1006.5
16–20	19	60	1006.6
21 and over	23	49	1008.0

TABLE 28.—*Specific Weight of Various Parts of Brain (W. H. Schultze)*

	Cerebrum	Cerebellum	Pons
Male	1.0417	1.0425	1.0431
Female	1.0411	1.0450	1.0430

TABLE 29.—*Changes in Weight and Volume of Brain during Different Stages of Embedding*

Stage of Preparation	Weight (Gm.)		Volume (Cc.)	
	Embryo (4 Mo.)	Adult (36 Yr.)	Embryo (4 Mo.)	Adult (36 Yr.)
Untreated	50	1480	50	1435
Formalin, 3 wk.	50	1560	50	1550
Alcohol, 80%	26	1482	24	1510
Alcohol, absolute	15	1140	16	1300
Alcohol-ether	15	1050	16	1250

TABLE 30.—*Chemical Composition of Gray and White Matter of Human Brain at Different Ages**

Values of components calculated in percentage relation to total solids

Components	Total Brain	Gray Matter		Corpus Callosum		
	6 Wk.	2 Yr.	19 Yr.	Newborn	2 Yr.	19 Yr.
Water: percentage relation to fresh tissue	88.8	84.5	83.2	89.9	76.4	69.7
Solids: percentage relation to fresh tissue	11.2	15.5	16.8	10.1	23.6	30.3
Water-soluble elements	20.3	15.8	15.4	18.2	9.1	6.3
Proteins	46.6	48.4	47.1	48.4	31.9	27.1
Lipoids	33.1	35.8	37.5	33.4	59.0	66.5
Phosphatides	24.2	24.7	23.7	23.1	26.3	31.0
Cerebrosides	6.9	8.6	8.8		17.2	16.6
Sulfatides	1.6		1.2	3.3		8.7

* Schmitz, E.: Chemie des zentralen und peripheren Nervensystems. Handb. d. norm. u. path. Physiol. *9:* 47, 1929.

AUTOPSY AND FIXATION OF THE CENTRAL NERVOUS SYSTEM

It is possible to perform an autopsy immediately after death only under very favorable circumstances. In most cases one must be satisfied with a six hour delay that may be extended to twenty-four hours or more. The longer the interval between death and fixation of the nervous tissue, the greater will be the impairment of its staining qualities. Therefore various methods have been devised to obtain a fixation in situ.

Injection of a 30 per cent solution of formol (40 per cent solution of formaldehyde in water = 100 per cent formalin) into both carotid arteries, after the blood has been washed out by perfusion with 0.9 per cent sodium chloride solution at body temperature, has been recommended. Others (Ostertag) are not in favor of such a method, claiming that the region surrounding the blood vessels of the brain is fixed differently from the rest of the nervous tissue, and that such a method always presents an anemic brain. Ostertag advises perforating the lamina cribrosa with a needle, 15 cm. long, introduced through the nose and connected by a rubber tube to a syringe. With this, from 15 to 20 cc. of a 20 per cent formalin solution is slowly injected. It is claimed that this small amount is sufficient to fix the whole central nervous system in situ.

For removal of the brain, a joint committee under the auspices of the New York Academy of Medicine has suggested a standard necropsy that is described in detail:

"The scalp is to be divided by an incision behind the ear, extending from one mastoid process to the other. The incision is to pass over the vertex when the hair is abundant, or somewhat posterior to this line when it is sparse. In women, the hair is to be parted along the projected line of incision to avoid cutting it. For the same reason, after the initial incision has been made, the knife should be carried in such manner that its sharp edge faces the dissector. Care should be taken not to tear or otherwise injure the scalp. The scalp is reflected backward and forward, so that the calvarium is exposed anteriorly slightly above the frontal eminences and posteriorly somewhat behind the occipital protuberance.

"Before the skull is sawed, the line through which the saw is to be carried should be mapped out with the aid of a sharp instrument. The temporal muscles are to be cut on a plane parallel with the projected line, to preserve stumps on either side long enough to provide for suturing and immobilization of the replaced calvarium.

"The removal of the skull cap is to be planned and carried out in such a manner as to insure its secure approximation. This is best accomplished by sawing in two intersecting lines which meet at an obtuse angle behind the ear, the anterior incision commencing at the level of the hair line."

After the skull cap has been removed, the dura mater is cut from its connections with the skull, and the head is tilted backward. While an assistant supports the brain with his hands, it is gently pushed backward and, beginning with the olfactory bulbs, the optic nerves, and the infundibulum, all the cranial nerves are cut. Finally, the cervical spinal cord is cut transversely, and the brain is removed.

"Before closing the cranial cavity, every effort should be made to provide against leakage. This is best carried out by the following procedures: (*a*) by ligating the carotid and vertebral arteries, (*b*) by plugging the foramen magnum tightly with cotton, and (*c*) by filling the cranial cavity with oakum.

"In suturing the skin, a moderately small needle should be used so as to avoid leakage and disfigurement."*

---

* Arch. Path. *14:* 701, 1932.

For removal of the spinal cord, a longitudinal section through the skin is made along the midline of the back. The skin is reflected to both sides, and the muscles of the back are removed. Next, on each side, the laminae of the vertebrae are cut with the help of a sharp chisel and a hammer. Beginning with the cervical vertebrae, the entire posterior part of the spine is then pulled off. After the spinal nerve roots have been cut, the spinal cord with the dura mater is gently lifted from the spinal canal, pull or pressure being avoided.

Before fixation one should make it a routine to describe briefly the appearance of the dura mater and its sinuses (which should be opened), the piarachnoid, the vessels at the base, and the configuration of the gyri. Weight and volume (in 10 per cent formalin) should also be noted.

For fixation of the removed brain and spinal cord, formaldehyde (solution of formaldehyde U.S.P. 40 per cent = formol = formalin) is usually used in routine laboratory work at present. It is recommended that the formalin be preserved in brown bottles, the bottom of which should be covered with powdered calcium carbonate (chalk), in order to neutralize any formic acid that may be formed. The 10 per cent solution of formalin is made by mixing 1 part of formalin with 9 parts of a 0.9 per cent solution of sodium chloride in tap water. Use of an isotonic solution of calcium chloride (1.2 per cent) has been recommended, but the fact that calcium salts easily produce artefacts of the nuclear chromatin and the cellular cytoplasm should be taken into consideration.

Choice of the fixative depends upon the method of staining that is to be used later. The following staining methods, described for formalin-fixed tissue, will be adequate for routine laboratory diagnostic work. For demonstration of certain ferments (oxydases), only a few hours' fixation with formalin is permitted. Alcohol fixation (95 per cent) must be applied if one wants to demonstrate inorganic substances such as iron, calcium, or pigments, or for detailed studies of neurons and the chromatin bodies. Müller's fluid, formerly the favorite fixative, is now used only for the Marchi method. For the different methods of staining oligodendroglia and microglia, a fixation in formalin-ammonium bromide has been recommended (2 Gm. ammonium bromide in 100 cc. of 14 per cent solution of formalin).

The most difficult problem in fixing the brain and spinal cord is that of whether one should fix the organ in toto or immediately cut out small pieces for fixation. In the study of tracts of nerve fibers, or in the demonstration of systemic degenerations, of the distribution of plaques of demyelinization, or of the extension of neoplastic growth, and in similar cases one may wish to preserve the anatomic structure. After the ventricles have been opened through a cut in the corpus callosum, the brain is suspended by a string attached to the basilar artery in a large 2-gallon jar filled with 10 per cent formalin. The formalin should be renewed after one or two days, and the brain may be cut after one week, though many prefer a three weeks' fixation for the preparation of large slides. For the cutting of the brain, Edinger's microtome or a device similar to that constructed by G. T. Rasmussen may be used. For fixation, the spinal cord is cut into pieces from 2 to 3 cm. in length, after the dura mater has been opened.

If one wishes to study a neoplasm or a given part of the brain, blocks are prepared from the fresh brain and fixed in from ten to fifteen times their volume of 10 per cent formalin. For routine laboratory work, the selection may include, as recommended by Spielmeyer, blocks from the following structures:

1. Posterior part of first frontal convolution
2. Both central convolutions, approximately at borderline of middle and upper third

3. First temporal convolution
4. Region of cornu Ammonis
5. Region of calcarine fissure
6. Middle of basal ganglia together with island of Reil
7. Posterior portion of basal ganglia with island of Reil
8. Region of oculomotor nuclei
9. Inferior olives
10. Vermis and cerebellar hemispheres
11. Spinal cord segments: cervical and lumbar enlargement; upper cervical, upper and lower dorsal and sacral segments

STAINING METHODS

The ideal for the staining of nervous tissue would be a technic that would allow one to stain all the different structures, in serial sections of the same block, by specific methods—axis-cylinders, myelin sheaths, the different structures of the neurons, the different forms of glia, and the various components of the mesenchymal derivatives.

The following methods for formalin-fixed material, as applied in the routine work of the writer's laboratory, represent an attempt to come as close as possible to this goal.

In sections from material embedded in celloidin (parlodion), the following structures are stained: axis-cylinders (Davenport), myelin sheaths (Weil), Nissl bodies and nuclei (cresyl violet), connective tissue (van Gieson, Foot), microglia and oligodendroglia (Weil-Davenport modification of Stern method).

In frozen sections from formalin-fixed material, the different glial elements may be stained as follows: astrocytes with Cajal's gold sublimate; microglia with Kanzler's modification of Hortega's method. If paraffin sections are available, glia fibers can be well stained with Holzer's method.

Tumor material is embedded in paraffin, and sections are stained as a routine by the Davenport (tumor modification), van Gieson, and hematoxylin-eosin methods. In our experience these three methods are sufficient to allow detailed study of most of the tumors that occur.

For the staining of fatty products of degeneration, the sudan III method for frozen sections will be sufficient for routine examination.

If specific methods for more detailed study are wanted, Spielmeyer's book (*Technik der mikroskopischen Untersuchung des Nervensystems*) will give further guidance.

Embedding

1. celloidin or parlodion

The celloidin or parlodion is washed several times with distilled water and dried in the air. A quantity of 60 gm. is dissolved in 1 liter of equal parts of absolute alcohol and ether (pro narcosis), and the bottle is turned every morning until the mass is dissolved.

The blocks of brain tissue are washed in running water overnight and dehydrated in different strengths of alcohol. The length of time required for dehydration depends upon the size of the block. Whole brain sections (from 1 to 2 cm. thick) should remain at least 2 days in each change of alcohol, the amount of which should be at least four times the volume of the block. Smaller blocks require from 12 to 24 hours, small pieces of tumor a few hours. The concentrations of alcohol used are 80 per cent, 95 per cent, and 100 per cent. Next, the tissue is placed in a mixture of equal parts of absolute alcohol and ether for from 12 to 24 hours and then into a 3 per cent solution of celloidin (parlodion) for 1 day. The container should be carefully closed to avoid evaporation. Finally, the blocks are placed in a 6 per cent solution of celloidin (parlodion), which is allowed to evaporate gradually until the consistency is that of a stiff jelly. The hardened celloidin encasing the tissue blocks is cut up and shaped, and the resultant celloidin blocks are preserved in 50 per cent alcohol, which will harden them sufficiently. Sections should also be kept in 50 per cent alcohol, not in higher concentrations.

2. PARAFFIN

Small blocks of tissue, not more than 5 mm. thick, should be used. After they have been washed and dehydrated as above, the absolute alcohol is replaced by a mixture of equal parts of absolute alcohol and xylol (½ hour), next by xylol (until clear—approximately 1 hour), and then by equal parts of xylol and paraffin (½ hour in paraffin oven). Following this they are placed for from 1 to 1½ hours each in two changes of paraffin, and finally they are embedded in paper containers. For brain, spinal cord, and tumor tissue, paraffin of from 55 to 58 C. melting point is used; for peripheral nerves, the paraffin used should be of from 61 to 63 C. melting point. Only in very hot summer weather is the latter used for the other nervous tissues.

1. AXIS-CYLINDERS

DAVENPORT METHOD

Fix material in 10 per cent formalin and embed in either paraffin or celloidin. Cut paraffin sections 8 to 10 microns, celloidin sections 20 microns thick.

1. Coat sections with celloidin.
   Paraffin sections: Remove paraffin with xylol and run through absolute alcohol and ether–absolute alcohol mixture. Place slides in 1.5 per cent solution of celloidin for 1 minute. Wipe off excess celloidin from back of slide and allow celloidin to set in air for about ½ minute. Try to get equal amount of celloidin over all parts of section. Place slide in 80 per cent alcohol for from 3 to 5 minutes.
   Celloidin sections: Mount sections from 80 per cent alcohol, while still wet, on albuminized slide. Blot section dry with bibulous paper. Place immediately in 1.5 per cent solution of celloidin. Remove celloidin from back of slide, allow it to set, then place in 80 per cent alcohol for from 3 to 5 minutes.
2. For silver impregnation, dissolve 10 Gm. of silver nitrate (reagent quality) in 10 cc. of distilled water. Add 90 cc. of 95 per cent alcohol.
   For axis-cylinders: Add from 5 to 7 drops of normal nitric acid to each 50 cc. of silver solution. Impregnate for from 2 to 4 hours at 37 C., or until sections are pale yellow in color.
   For tumors (gliomas): Add 3 drops of normal nitric acid to each 50 cc. of silver. Stain overnight at 37 C.
3. For developing, dissolve 3 Gm. of pyrogallic acid (resublimed) in 95 cc. of 95 per cent alcohol; add 5 cc. of pure (37 per cent) formalin (reagent quality). Just before using developer, add 5 drops of 50 per cent Karo corn syrup to pyrogallic acid solution. Watch color of sections, checking with microscope, in order not to overstain sections. Development usually takes about 2 minutes. Gliomas must be stained darkly in order to bring out cell processes.
4. Wash out pyrogallic acid in two changes of 80 per cent and 95 per cent alcohol. Remove celloidin in two changes of ether–absolute alcohol. If desired, celloidin may be removed after toning.
5. Transfer sections through 70 per cent alcohol into water.
6. Tone in dilute solution of gold chloride (0.1 per cent) to which 4 drops of glacial acetic acid per 50 cc. of solution has been added.
7. Wash quickly in distilled water. Fix in 5 per cent sodium thiosulfate for 2 minutes.
8. Wash thoroughly in distilled water, dehydrate with graded alcohols, clear in xylol, and mount with neutral Canada balsam.

BODIAN'S PROTARGOL METHOD

For fixation the following solution is recommended: formalin, 5 cc.; glacial acetic acid, 5 cc.; 80 per cent ethyl alcohol, 90 cc. Paraffin-embedded sections are to be used. Celloidin should be removed.

A. *Staining solution:* 1 per cent aqueous solution of protargol (silver albumose), prepared by allowing powder to float on surface of water. Add piece of metallic copper (penny) to staining dish.

B. *Reducing solution:* 1 per cent solution of hydroquinone in water, with addition of 5 Gm. of sodium thiosulfate (hyposulfite).

1. Remove paraffin and run section down to water.
2. Stain for from 12 to 48 hours in solution A at 37 C. Discard solution.
3. Wash in distilled water.
4. Reduce in solution B for from 5 to 10 minutes.
5. Wash in at least three changes of distilled water.
6. If sections are not sufficiently stained, steps 2 to 5 should be repeated.
7. Tone with gold (not necessary):
   a) Place in 1 per cent aqueous gold chloride solution with 3 drops of glacial acetic acid per 100 cc. Leave section for from 2 to 5 minutes in this solution.
   b) Wash in distilled water.
   c) Transfer to 1 per cent solution of oxalic acid and leave in this until sections have faint blue or purple color.
   d) Leave sections for from 5 to 10 minutes in 5 per cent solution of sodium thiosulfate (hyposulfite).
   e) Wash in several changes of distilled water. Counterstains like cresyl violet, neutral red, etc., may be used.
   f) Dehydrate, clear, and mount.

Sections of old formalin-fixed material may be treated overnight with 5 per cent acetic acid solution after paraffin has been removed.

2. Myelin Sheaths

WEIL METHOD

This stain may be used for sections embedded either in paraffin or celloidin, but the best results are obtained with celloidin sections, cut from 25 to 30 microns thick. If paraffin material is used, the sections should be cut 15 microns thick and the paraffin removed before staining. If frozen sections are used, they should be carried through 95 per cent alcohol and absolute alcohol into xylol and back through alcohol into water.

1. Wash sections in distilled water.
2. Stain for from 10 to 30 minutes at 50 to 55 C. in mixture of equal parts of solutions *a* and *b* following. Mix fluids just before using.

   a) 4 per cent solution of iron alum (iron ammonium sulfate, ferric).
   b) 1 per cent solution of hematoxylin, made up by adding 90 cc. distilled water to 10 cc. of 10 per cent alcoholic (absolute) solution of hematoxylin that has been ripened for at least 6 months.

   Note. *Do not filter this stain. Do not use it twice.*

Paraffin sections should be stained for from 10 to 15 minutes. Celloidin sections should be stained for from 20 to 30 minutes. For 10 celloidin sections of brain stem cut 30 microns thick, use at least 50 cc. of stain.

3. Wash twice in tap water.
4. Differentiate in 4 per cent solution of iron alum. For celloidin sections, differentiate until gray matter or degenerated areas can just be distinguished. For paraffin sections, differentiate just long enough to remove stain from back of slide. Care should be taken not to overdifferentiate in iron alum, for in so doing fine fibers are lost.
5. Wash three times in tap water.
6. Complete differentiation (controlled under microscope) in following solution:

borax	10.0 Gm.
potassium ferricyanide	12.5 Gm.
distilled water	1000.0 cc.

7. Wash twice in tap water.
8. Wash sections for 30 seconds in dilute ammonia water (about 6 drops of 28 per cent ammonia added to 100 cc. of water).
9. Wash in distilled water.
10. Dehydrate in alcohol, clear in xylol, and mount in *neutral* Canada balsam.

3. Nissl Bodies and Nuclei

a) cresyl violet stain

1. Wash either celloidin or paraffin sections in distilled water.
2. Stain in 1 per cent solution of cresyl violet (Grübler's *Cresylechtviolett*) for 1 minute.
3. Wash twice in distilled water.
4. Begin differentiating in 95 per cent alcohol, removing most of excess stain in this alcohol.
5. Continue differentiating in absolute alcohol.
6. Complete differentiation in absolute alcohol to which 1 drop of Canada balsam has been added. Check differentiation under microscope.
7. Wash in four changes of xylol in order to remove all traces of alcohol.
8. Mount in *neutral* Canada balsam.

Note. Cresyl violet is very sensitive to sunlight and heat, and sections will fade out if left in either.

b) end point staining with thionin method of windle, rhines, and rankin

Carnoy's fluid, other alcoholic fixing fluids, or 10 per cent formalin is recommended. Paraffin-, celloidin-, or nitrocellulose-embedded sections may be used.

A. *Buffer solution:* Use acetate buffer (Michaelis, 1931); avoid phosphate buffers.

B. *Stock dye solution:* Thionin (C.P.), 1 Gm.; distilled water (redistilled and boiled to make it free of carbon dioxide), 100 cc.

To each 10 cc. of buffer solution (A) add 0.25 cc. of stock solution (B). The *p*H of the buffer should be between 3.0 and 5.0 and should be determined by a potentiometer. Different cellular elements will be stained with different intensity according to the change in *p*H.

1. Remove paraffin and transfer slides through graded alcohols to water free of carbon dioxide.
2. Stain for 20 minutes at room temperature in buffered staining fluid.
3. Rinse in distilled water.
4. Transfer to two changes of 70 per cent alcohol and leave for about 5 minutes until no more dye washes out. If decolorization of sections stained at *p*H of from 4.5 to 5.0 is desired, place them in 0.2 per cent solution of acetic acid for from 2 to 5 minutes.
5. Put through three changes of distilled water free of carbon dioxide. Dehydrate, clear, and mount.

The results of staining are as follows: at *p*H 3.0 to 4.0, Nissl's granules stain purplish blue, nuclei and neuroglia cytoplasm blue, and the background is very pale blue or clear; at *p*H 4.0 to 5.0, neuroglia stains darker, and the background is likewise darker, but unstained following decolorization.

4. Connective Tissue

a) van Gieson method (for collagenous fibers)

1. Stain either celloidin or paraffin material for 10 minutes in mixture of equal parts of solutions *a* and *b* following (Weigert hematoxylin).

   a) 1 per cent alcoholic hematoxylin. (Ripen 10 Gm. of hematoxylin in 100 cc. of absolute alcohol for 6 months. Dilute this solution 1:9 with 95 per cent alcohol before using.)

   b) 29 per cent ferric chloride, 4 cc.; distilled water, 95 cc.; 25 per cent hydrochloric acid, 1 cc. (1 part of 37 per cent hydrochloric acid + 3 parts of water).

2. Wash in distilled water.
3. Differentiate for from ½ to 3 minutes in following solution:

1 per cent acid fuchsin (water solution)	10 cc.
picric acid, saturated aqueous solution	100 cc.

   For paraffin sections, especially tumors, a few drops of saturated acid fuchsin may be added to this mixture in order to stain the connective tissue more intensively. Celloidin sections usually require longer differentiation in the picric acid–fuchsin mixture than do paraffin sections (from 1½ to 3 minutes).

4. Dip into distilled water.
5. Wash in 70 per cent, 95 per cent, and absolute alcohol.
6. Clear in xylol to which 3 drops (per 50 cc.) of saturated *alcoholic (absolute)* picric acid solution has been added. Mount from this acidified xylol. This intensifies color of background and keeps sections from fading.

b) Foot's modification of Bielschowsky method

Paraffin sections fixed in formalin and Zenker's solution may be used. If formalin sections only are available, the paraffin should be removed by ordinary methods and the sections should be kept in Zenker's solution overnight. Wash in two changes of distilled water and proceed as under 2.

1. Remove paraffin in xylol; transfer through alcohol into distilled water.
2. Place in 0.5 per cent solution of iodine in 95 per cent alcohol for 5 minutes.
3. Wash in distilled water; place in 0.5 per cent aqueous solution of sodium thiosulfate for 5 minutes.
4. Wash in tap water.
5. Place in 0.25 per cent aqueous solution of potassium permanganate for 5 minutes.
6. Wash in two sets of tap water.
7. Place in 5 per cent solution of oxalic acid for 20 minutes.
8. Wash in two changes of tap water, then in distilled water.
9. Place in 2 per cent aqueous solution of silver nitrate for 48 hours. Avoid direct exposure to light.
10. Wash rapidly in distilled water.
11. Place in freshly prepared ammoniacal silver solution, made as follows: Add 20 drops of 40 per cent solution of sodium hydroxide drop by drop to 20 cc. of 10 per cent aqueous solution of silver nitrate (reagent quality); dissolve precipitate in 26 per cent ammonia water, adding drop by drop under constant shaking (excess of ammonia should be avoided); allow small part of precipitate to remain undissolved, and filter; make up the filtrate to 80 cc. with distilled water. Keep section for 30 minutes in this solution, protected from direct light.
12. Wash quickly in distilled water.
13. Reduce in 5 per cent neutral formalin (Merck's blue label) for 30 minutes; change formalin solution after first 15 minutes.
14. Wash in distilled water.
15. Tone in 1 per cent aqueous solution of gold chloride for 1 hour.
16. Wash in distilled water.
17. Place in 5 per cent aqueous solution of sodium thiosulfate for 2 minutes.
18. Carry through several changes of tap water, dehydrate in alcohol, clear in xylol, and mount with balsam.

Counterstaining of the section by van Gieson's method will stain the larger collagenous fibers red. Without counterstaining, however, the reticulum will stand out more sharply defined and the sections will be more suitable for photographic reproduction.

5. Micro- and Oligodendroglia

Stern method: Weil-Davenport modification

1. *Microglia:* Oligodendroglia is also stained. The best results have been obtained in cases presenting pathologic glia proliferation, general paresis, arteriosclerosis, etc.
   a) Wash celloidin sections in distilled water.
   b) For silver impregnation, add 10 per cent silver nitrate by drops to 2 cc. of concentrated ammonia, shaking solution in order to prevent forming of precipitate. When very fine precipitate is formed, clear solution by adding 1 drop of ammonia. Slowly add 10 per cent silver nitrate until solution is slightly opalescent. If too much silver nitrate is added, solution may again be cleared with ammonia and silver nitrate, added until correct point (slight opalescence) is reached. Sometimes staining of microglia cannot be obtained with solutions at this first stage of opal-

escence. On addition of another drop of silver nitrate and prolongation of time of staining to 15 seconds, better results may be obtained. It is essential to avoid formation of precipitates. Stain section for from 10 to 20 seconds in this solution.

c) Transfer section to solution of formaldehyde (reagent quality) prepared by diluting 1 part of solution of formaldehyde U.S.P. with distilled water to make 6 parts; move rapidly until section is coffee brown in color.

d) Wash in at least two changes of distilled water.

e) Dehydrate, clear, and mount. Transfer sections immediately from xylol into balsam, because they fade if left in xylol.

2. *Oligodendroglia:*

a) Wash in distilled water and then place in distilled water to which 1 drop of ammonia for each 10 cc. of water has been added.

b) Prepare silver solution as for microglia, using 15 per cent silver nitrate instead of 10 per cent. Stain sections for from 15 to 20 seconds. It is usually necessary to vary staining time, since different tissues require different lengths of time in silver.

c) Transfer to solution of formaldehyde (prepared by diluting 1 part of solution of formaldehyde U.S.P. with water to make 10 parts).

d) Wash in two changes of distilled water.

e) Dehydrate with alcohol, clear in xylol, and mount with balsam.

6. Astrocytes

Cajal Gold Sublimate Method

Tissue that has been fixed in formalin or in ammonium bromide-formalin mixture for 2 days may be used. Cut frozen sections 20 to 30 microns thick. Tissue will cut better if washed in tap water for ½ hour before cutting, to remove formaldehyde.

1. Wash sections in distilled water.
2. Stain for 4 hours, *keeping in dark place*, in following solution:

1 per cent gold chloride	5 cc.
1 per cent mercuric chloride	25 cc.
distilled water	5 cc.

3. Wash in distilled water.
4. Fix for 2 minutes in 5 per cent solution of sodium thiosulfate.
5. Wash thoroughly in distilled water.
6. Mount on slide, blot with bibulous paper, and dehydrate in 95 per cent and absolute alcohol. This prevents section from curling and shrinking in alcohol.
7. Clear in xylol and mount with balsam.

Note. The ammonium bromide-formalin mixture used for fixation is prepared as follows:

ammonium bromide	15 Gm.
formalin, reagent quality	100 cc.
distilled water	400 cc.

Tissue should be fixed in this solution for not longer than 2 days and then should be cut immediately.

7. Microglia

KANZLER METHOD

This is a modification of the Hortega method for microglia.

Cut frozen sections from 25 to 30 microns thick. Material fixed in formalin or formalin–ammonium bromide may be utilized.

1. Heat sections until vapors arise (60 C.) in ammonium bromide–formalin mixture (cf. note under method for astrocytes).
2. Without washing, bring sections into following solution for from 5 to 8 seconds, keeping in motion constantly:

antiformin	3 cc.
alcohol, 70 per cent	10 cc.

3. Wash twice in distilled water.
4. Impregnate for from 8 to 10 seconds in following solution, keeping in constant motion by means of glass rod:

10 per cent silver nitrate	5 cc.
10 per cent sodium carbonate (reagent quality)	15 cc.

Dissolve precipitate in concentrated ammonia solution; add drop by drop and avoid excess of ammonia.

5. Develop quickly (in from 5 to 10 seconds) in 2 per cent solution of formalin, keeping section in constant motion. Renew solution frequently and use at least 100 cc. for not more than 5 frozen sections about 1 inch square.
6. Wash in two changes of distilled water.
7. Tone in 0.1 per cent solution of gold chloride for from 10 to 20 minutes.
8. Rinse in distilled water.
9. Fix for 1 minute in 5 per cent solution of sodium thiosulfate.
10. Wash in two changes of distilled water.
11. Mount on slide and blot with bibulous paper.
12. Dehydrate in 95 per cent and absolute alcohol and clear in xylol (using Coplin jars). Mount in balsam.

8. Glia Fibers

HOLZER METHOD

This method gives best results with paraffin-embedded material.

1. Cut sections from 8 to 10 microns thick, remove paraffin in xylol, carry section through alcohol into distilled water. Then place for 3 minutes in following mixture:

0.5 per cent solution (freshly prepared) of phosphomolybdic acid	10 cc.
95 per cent alcohol	20 cc.

2. Drain off fluid and cover section with:

absolute alcohol	2 cc.
chloroform	8 cc.

3. Cover section, while still wet, with following stain, allowing it to remain for 30 seconds:

crystal violet	0.5 Gm.
absolute alcohol	2.0 cc.
chloroform	8.0 cc.

4. Wash quickly in alcohol-chloroform mixture (2), then in absolute alcohol, 95 per cent alcohol, and water.
5. Place section for 1 minute in 10 per cent solution of potassium bromide or cover with this solution.
6. Wash in distilled water and blot dry with bibulous paper.
7. Differentiate in following mixture:

aniline oil	6 cc.
chloroform	9 cc.
ammonia, 25 per cent solution	1 drop

8. Wash in xylol.

If section has been overstained, repeat process of differentiation until glia proliferation is sharply defined. Wash thoroughly in xylol and mount in balsam.

9. Fat Stain

Cut frozen sections of formalin-fixed material 20 microns thick.

1. Wash in distilled water.
2. Place in 70 per cent alcohol for 1 minute.
3. Stain in saturated solution of sudan III in 70 per cent alcohol for 20 minutes.
4. Wash in 70 per cent alcohol for a few seconds and transfer to distilled water.
5. Counterstain in Weigert's hematoxylin (cf. van Gieson's method) for 5 seconds.
6. Wash in two changes of water.
7. Mount in warm gelatin heated in water bath:

finest gelatin	4 Gm.
distilled water with 1 crystal of thymol added	21 cc.
glycerin	25 cc.

Instead of sudan III other fat stains may be used, such as oil red O or sudan black.

10. Hematoxylin-Eosin Stain

1. Stain for 10 seconds in Weigert's hematoxylin (cf. van Gieson method) or in any other of the hematoxylin preparations used in the histology laboratory.
2. Wash in distilled water, then in tap water.
3. Transfer to 70 per cent alcohol.
4. Counterstain in 0.5 per cent alcoholic solution of eosin Y for from 10 to 30 seconds.
5. Wash in 95 per cent alcohol; dehydrate in absolute alcohol and transfer to xylol.
6. Mount in balsam.

BIBLIOGRAPHY

NEUROPATHOLOGY: TEXTBOOKS

AMERICAN NEUROLOGICAL ASSOCIATION: A Classification of neurological, psychiatric and endocrine disorders. New York, 1928.

COURVILLE, C. B.: Pathology of the central nervous system. Mountain View, Cal., 1937.

HASSIN, G. B.: Histopathology of the peripheral and central nervous system. Ed. 2. New York, 1940.

PENFIELD, W. (ed.): Cytology and cellular pathology of the nervous system. New York, 1932.

SPIELMEYER, W.: Histopathologie des Nervensystems. Berlin, 1922.

———: Die Anatomie der Psychosen. Handb. d. Geisteskr., vol. 11, pt. 7, 1930.

1. AUTOLYSIS AND FIXATION

Autolysis

BURN, C. G.: Experimental study of post mortem bacterial invasion in animals. J. Infect. Dis. **54:** 388, 1934.

JUNGMANN, H., AND KIMMELSTIEL, P.: Über den Ursprung der Milchsäure im Zentralnervensystem. Biochem. Ztschr. **212:** 347, 1929.

MECO, O.: Auto-neuroendotossina. Riv. di pat. nerv. **41:** 439, 1933.

STONE, W. E.: Acid soluble phosphorus compounds of cerebral tissue. J. Biol. Chem. **149:** 29, 1941.

Action of Ferments

GIRI, K. V.: Brain phosphatase. Biochem. J. **30:** 1089, 1936.

HUBBARD, R. S., AND NETER, E.: Glycolysin in the spinal fluid of patients with meningitis. Arch. Path. **30:** 631, 1940.

KERR, S. E., AND MCCHANTUS, M.: Carbohydrate metabolism of brain. J. Biol. Chem. **117:** 217, 1937.

OPPENHEIMER, C.: Die Fermente und ihre Wirkungen. Ed. 5. Leipzig, 1925-29.

Effect of Formalin Fixation

DAVENPORT, H. A.: Acid versus neutral formalin solution as a neurological fixative. Stain Technol., vol. 9, no. 2, 1934.

FERRARO, A.: Acute swelling of the oligodendroglia and grapelike areas of disintegration. Arch. Neurol. & Psychiat. **20:** 1064, 1928.

MLADENOVIC, M., AND LIEB, H.: Über den Einfluss der Formalinfixierung von Organen auf die Extrahierbarkeit der Lipoide. Ztschr. f. Physiol. Chem. **181:** 221, 1929.

WEIL, A.: The influence of formalin fixation on the lipoids of the central nervous system. J. Biol. Chem. **83:** 601, 1929.

2. DISEASES OF THE NEURON

Equivalent Picture

NISSL, F.: Über eine neue Untersuchungsmethode des Centralorgans. Neurol. Centralbl. **15:** 947, 1896.

Normal Variations and Postmortem Changes

ALEXANDER, L.: Neurofibrils in systemic disease and in supravital experiments. Arch. Neurol. & Psychiat. **32:** 933, 1934.

——— AND MYERSON, A.: The mineral content of various cerebral lesions as demonstrated by the microincineration method. Am. J. Path. **13:** 405, 1937.

BIELSCHOWSKY, M.: Morphologie der Ganglienzelle. Handb. d. mikroskop. Anat. d. Menschen, vol. 4, pt 1, 1928.

BODECHTEL, G., AND GAGEL, O.: Die Histopathologie der vegetativen Kerne des menschlichen Zwischenhirns. Ztschr. f. d. ges. Neurol. u. Psychiat. **132:** 755, 1931.

BORDAL, A.: Experimentelle Untersuchungen über retrograde Zellveränderungen. Ztschr. f. d. ges. Neurol. u. Psychiat. **166:** 646, 1939.

COX, A.: Ganglienzellschrumpfungen im tierischen Gehirn. Beitr. z. path. Anat. u. z. allg. Path. **98:** 399, 1937.

GAGEL, O., AND BODECHTEL, G.: Die Topik und feinere Histologie der Ganglienzellgruppen in der Medulla oblongata. Ztschr. f. Anat. u. Entwicklungsgesch. **91:** 130, 1930.

PENFIELD, W. (ed.): Cytology and cellular pathology of the nervous system. New York, 1932. Vol. 1, p. 145.

SCHERER, H. J.: Beiträge zur pathologischen Anatomie des Kleinhirns. Ztschr. f. d. ges. Neurol. u. Psychiat. **136:** 559, 1931; **139:** 337, 1932.

WILLIAMS, E. Y.: Structural changes in the granular layer of the cerebellum. Arch. Path. **17:** 206, 1934.

3. THE GLIA AND ITS PATHOLOGY

BELETZKY, W. K.: Morphologische Analyse der Mesenchym Reaktion in Progressiver Paralyse. Acta Med. Sc. **83:** 53, 1934.

DEL RIO-HORTEGA, P.: Microglia. In Penfield, W. (ed.): Cytology and cellular pathology of the nervous system, New York, 1932, vol. 2, p. 481.

KING, L. S.: Vital staining of neuroglia. Arch. Path. **19:** 656, 1935.

PENFIELD, W.: Neuroglia, normal and pathological. In Penfield, W. (ed.): Cytology and cellular pathology of the nervous system, New York, 1932, vol. 2, p. 421.

4. PATHOLOGY OF THE MYELIN SHEATH AND THE AXIS-CYLINDER

Experimental Demyelinization

DENNY-BROWN, D., AND BRENNER, C.: Lesion of peripheral nerve resulting from compression by spring clip. Arch. Neurol. **52:** 1, 1944.

FERRARO, A. R., AND JERVIS, G. A.: Experimental disseminated encephalopathy in the monkey. Arch. Neurol. & Psychiat. **43:** 195, 1940.

HURST, E. W., AND COOKE, B. T.: Capillary fat embolism in brains of sheep, pigs and monkeys. Australian J. Exper. Biol. & M. Sc. **21:** 141, 1943.

POLLAK, E.: Formen des Markscheidenzerfalles im zentralen Nervensystem. Jahrb. f. Psychiat. u. Neurol. **51:** 180, 1934.

RIVERS, T. M., AND SCHWENTKER, F. F.: Encephalitis accompanied by myelin destruction. J. Exper. Med. **61:** 689, 1935.

WEIL, A.: The effect of hemolytic toxins on nervous tissue. Arch. Path. **9:** 828, 1930.

Degeneration and Regeneration of Nerve Fibers

HOOKER, D., AND NICHOLAS, J. S.: Spinal cord sections in rat fetuses. J. Comp. Neurol. **50:** 413, 1930.

HUBER, G. C.: Nerve degeneration and regeneration. In Stookey, B. (ed.): Surgical and mechanical treatment of peripheral nerves. Philadelphia and London, 1922.

RANSON, S. W.: Degeneration and regeneration of nerve fibers. J. Comp. Neurol. **22:** 487, 1912.

SCHMITZ, E.: Chemie des zentralen and peripheren Nervensystems. Handb. d. norm. u. Path. Physiol. **9:** 47, 1929.

STOEHR, P., JR.: Die peripherische Nervenfaser. Handb. d. mikroskop. Anat. d. Menschen **4[1]:** 143, 1928.

YOUNG, J. Z., AND MEDAWAR, P. B.: Fibrin suture of peripheral nerves. Lancet **1:** 126, 1940.

5. ANEMIC SOFTENING

ALAJOUINE, T., AND THUREL, R.: La pathologie de la circulation cérébrale. Rev. neurol. **65:** 1276, 1936.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE: The circulation of the brain and spinal cord. Vol. 18, 1938.

DIXON, T. F., AND MEYER, A.: Respiration of brain. Biochem. J. **30:** 1577, 1936.

GILDEA, E. F., AND COBB, S.: The effect of anemia on the central cortex of the cat. Arch. Neurol. & Psychiat. **23:** 876, 1930.

KABAT, H., AND DENNIS, C.: Resistance of young dogs to acute arrest of the cephalic circulation. Proc. Soc. Exper. Biol. & Med. **42:** 534, 1939.

MÜLLER, G.: Zur Frage der Altersbestimmungen histologischer Veränderungen im menschlichen Gehirn. Ztschr. f. d. ges. Neurol. u. Psychiat. **124:** 1, 1930.

SCHERER, H. J.: Bemerkungen zur Empfindlichkeit der Ganglienzelle. Virchows Arch. f. path. Anat. **293:** 429, 1934.

SPATZ, H.: Pathologische Anatomie der Kreislaufstörungen des Gehirns. Ztschr. f. d. ges. Neurol. u. Psychiat. **167:** 301, 1939.

WINDLE, W. F., BECKER, R. F., AND WEIL, A.: Alterations in brain structure after asphyxiation at birth. J. Neuropath. & Exper. Neurol. **3:** 224, 1944.

WOLFF, H. G.: Cerebral circulation. Physiol. Rev. **16:** 545, 1936.

WORTIS, S. B.: Respiratory metabolism of excised brain tissue. Arch. Neurol. & Psychiat. **33:** 1022, 1935.

6. ARTERIOSCLEROSIS

EATON, L. M., ET AL.: Symmetric cerebral calcification. Arch. Neurol. & Psychiat. **41:** 921, 1939.

HILLER, F.: Zirkulationsstörungen im Gehirn. Arch. f. Psychiat. **103:** 1, 1935.

LEARY, T.: The genesis of atherosclerosis. Arch. Path. **21:** 419, 1936; **32:** 507, 1941.

MORITZ, A. R., AND OLDT, M. R.: Arteriosclerosis in hypertensive and non-hypertensive individuals. Am. J. Path. **13:** 679, 1937.

NEUBÜRGER, K.: Beiträge zur Histologie, Pathogenese und Einteilung der arteriosklerotischen Hirnerkrankung. Jena, 1930.

TAYLOR, A. B., AND WHITFIELD, A. G. W.: Subarachnoid hemorrhage based on observations of eighty-one cases. Quart. J. Med. **5:** 461, 1936.

Arteriosclerosis of the Spinal Cord

DAVISON, C., AND KESCHNER, M.: Myelitic and myelopathic lesions. Arch. Neurol. & Psychiat. **29:** 332, 600, 702, 1933.

7. INFLAMMATION

ASCHOFF, L.: Das Allergieproblem vom Standpunkt des pathologischen Anatomen. Med. Welt **11:** 1023, 1937.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE: The human cerebrospinal fluid. Vol. 4, 1924.

FREMONT-SMITH ET AL.: Distribution of bromides in blood serum and cerebro-spinal fluid. Arch. Neurol. & Psychiat. **33:** 764, 1935.

FRIEDEMANN, U.: Blood-brain barrier. Physiol. Rev. **22:** 125, 1942.

FRÖHLICH, A., AND MIRSKY, I. A.: Susceptibility to convulsion in relation to age. Arch. Neurol. & Psychiat. **47:** 30, 1942.

GELLHORN, E.: The effect of hormones on cellular permeability. Ann. Int. Med. **7:** 33, 1933.

GREENFIELD, J. G., AND CARMICHAEL, E. A.: The cerebrospinal fluid in clinical diagnosis. London, 1925.

KATZENELBOGEN, S.: The cerebrospinal fluid. Baltimore, 1935.

SPIELMEYER, W.: Infektion und Nervensystem. Ztschr. f. d. ges. Neurol. u. Psychiat. **123:** 161, 1930.

WALTER, F. K.: Die Blut-Liquor Schranke. Leipzig, 1929.

8. INFECTIONS

ALPERS, B. J., AND GASKELL, H. S.: The clinical and pathologic characteristics of embolic or metastatic encephalitis. J. Neuropath. & Exper. Neurol. **3:** 210, 1944.

AMOLSCH, A. L.: Encephalitis neonatorum. Am. J. Clin. Path. **5:** 371, 1935.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE: Infections of the central nervous system. Vol. 12, 1932.

COURVILLE, C. B., AND NIELSEN, J. M.: Pathogenesis and pathological aspects of otogenous intracranial lesions. Arch. Path. **20:** 952, 1935.

DEW, H. D.: Hydatid disease of the brain. Surg., Gynec. & Obst. **159:** 321, 1934.

DOLGOPOLE, V. B., AND NEUSTADTER, M.: Meningo-encephalitis caused by Cysticercus cellulosae. Arch. Neurol. & Psychiat. **33:** 132, 1935.

FREUND, J.: Accumulation of antibodies in the central nervous system. J. Exper. Med. **51:** 889, 1930.

GALKIN, W. S.: Zur Methodik der Injektion des Lymphsystems vom Subarachnoidalraum aus. Ztschr. f. exper. Med. **72:** 65, 1930; **74:** 482, 1930.

KENNEDY, F.: Focal infections implicating the nervous system. Am. J. M. Sc. **185:** 305, 1933.

KRAMER, R.: Intracranial pathways for the extension of infections from the sphenoethmoid sinus. Arch. Path. **30:** 837, 1940.

MAXIMOW, A. A.: Inflammation: Text-book of histology. Philadelphia, 1930. P. 143.

OPALSKI, A.: Studien zur allgemeinen Histopathologie der Ventrikelwände. Ztschr. f. d. ges. Neurol. u. Psychiat. **150:** 42, 1937.

SCHWARZ, H., GOOLKER, P., AND GLOBUS, J. H.: The normal histology of infant's brains. Am. J. Dis. Child. **43:** 889, 1932.

SPATZ, H.: Über Enzephalitis und Enzephalitiden. Nervenarzt **4:** 466, 531, 1931.

Meningitis

ARMSTRONG, C., AND WOOLEY, J.: A new virus causing lymphocytic meningitis. Pub. Health Rep. **50:** 537, 1935.

PETTE, H.: Verschiedene Formen der Meningitis serosa. Zentralbl. f. Neurochir. **1:** 86, 1936.

WEED, L. H., ET AL.: A study of experimental meningitis. New York, 1920.
WERTHAM, F.: The cerebral lesions in purulent meningitis. Arch. Neurol. & Psychiat. **26:** 549, 1931.

Brain Abscess

CARMICHAEL, F. A., KERNOHAN, J. W., AND ADSON, A. W.: Genesis of cerebral abscess. Arch. Neurol. & Psychiat. **42:** 1028, 1939.
DIAMOND, I. B., AND BASSOE, P.: Abscess of the brain. Arch. Neurol. & Psychiat. **19:** 265, 1928.
EAGLETON, W. P.: Brain abscess. New York, 1922.
KNAPP, E.: Zur Pathogenese der bindegewebigen und gliösen Abkapselung von Hirnabscessen. Ztschr. f. d. ges. Neurol. u. Psychiat. **139:** 44, 1932.

Epedemic Encephalitis

ECONOMO, C. VON: Encephalitis lethargica. Berlin and Vienna, 1929.
FINDLAY, G. M., AND STERN, R. O.: Encephalomyelitis produced by neurotropic yellow fever virus. J. Path. & Bact. **40:** 311, 1935.
MCKAIG, C. B., AND WOLTMAN, H. W.: Neurological complications of epidemic parotitis. Arch. Neurol. & Psychiat. **31:** 794, 1934.
MARGULIS, M. S., SOLOVIEV, V. D., AND SHUBLADZE, A. K.: Acute primary hemorrhagic meningo-encephalitis. J. Neuropath. & Exper. Neurol. **3:** 101, 1944.
MATHESON COMMISSION: Epidemic encephalitis. New York, 1929; report 2, 1932.
SABIN, A. B.: Pathology of B virus infection. Arch. Path. **20:** 657, 1935.
WEIL, A.: Histopathology of the central nervous system in epidemic encephalitis (St. Louis epidemic). Arch. Neurol. & Psychiat. **31:** 1139, 1934.
——— AND BRESLICH, P. J.: Histopathology of the central nervous system in the North Dakota epidemic encephalitis. J. Neuropath. & Exper. Neurol. **1:** 49, 1942.

Acute Poliomyelitis

HURST, E. W.: The histology of experimental poliomyelitis. J. Path. & Bact. **32:** 567, 1929.
PETERS, G.: Über den Ausbreitungsbereich des Krankheitserregers im Zentralnervensystem bei der Heine-Medin'schen Krankheit. München. med. Wchnschr. **85:** 1073, 1938.
WARBURG, B.: Experimental poliomyelitis. J. Path. & Bact. **25:** 1191, 1931.

Tuberculosis

BERTRAND, I., AND MÉDAKOVITCH, G.: Etudes anatomiques sur la tuberculose des centres nerveux. Ann. de méd. **15:** 419, 1924.
BLACKLOCK, J. W. S., AND GRIFFIN, M. A.: Tuberculous meningitis in children. J. Path. & Bact. **40:** 489, 1935.
FURUI, T.: Studien zur Tuberkulose des Gehirns. Arb. a. d. Neurol. Inst. a. d. Wien. Univ. **29:** 248, 1927.
JAFFÉ, R. H., AND SCHULTZ, A.: Relations between tuberculomata of central nervous system and tubercular changes in other organs. Am. Rev. Tubere. **33:** 302, 1936.
KIRSCHBAUM, W.: Über die Tuberkulose des Zentralnervensystems. Ztschr. f. d. ges. Neurol. & Psychiat. **66:** 283, 1921.
TAPLAN, K.: Pathogenesis of tuberculous meningitis. Arch. Path. **28:** 122, 1939.
WAGENEN, W. P. VAN: Tuberculoma of brain. Arch. Neurol. & Psychiat. **17:** 57, 1927.

Syphilis

HASSIN, G. B.: Tabes dorsalis. Arch. Neurol. & Psychiat. **21:** 311, 1929.

JAHNEL, F.: Allgemeine Pathologie und pathologische Anatomie der Syphilis. Handb. d. Haut- u. Geschlechtskr., vol. 17, pt. 1, 1929.

NONNE, M.: Syphilis and the nervous system. Philadelphia and London, 1916.

RICHTER, H.: Zur Histogenese der Tabes dorsalis. Ztschr. f. d. ges. Neurol. u. Psychiat. **67:** 1, 1921.

STÄMMLER, M.: Über syphilitische Myelose. Beitr. z. path. Anat. u. z. allg. Path. **99:** 34, 1937.

WINKELMAN, N. W.: Syphilis of the spinal cord. Am. J. Syph. & Neurol. **19:** 378, 1935; **20:** 62, 146, 1936.

Blastomyces Infection

FREEMAN, W.: Torula infection of the central nervous system. J. f. Psychol. u. Neurol. **43:** 236, 1931.

MACBRYDE, C. M., AND THOMPSON, E. S.: Meningitis and dermatitis caused by a new variety of blastomycete. Arch. Dermat. & Syph. **27:** 49, 1933.

STODDARD, J. L., AND CUTLER, E. C.: Torula infection in man. Monog. 6, Rockefeller Inst. Med. Res., 1916.

WOLFE, A., COWAN, D., AND PAIGE, B. H.: Toxoplasmic encephalomyelitis. Am. J. Path. **15:** 657, 1939.

Acute Disseminated Encephalomyelitis

DENNY-BROWN, D., ET AL.: Pathologic features of herpes zoster. Arch. Neurol. & Psychiat. **51:** 216, 1944.

FERRARO, A., AND SCHEFFER, I.: Toxic encephalopathy in measles. Arch. Neurol. & Psychiat. **25:** 748, 1931.

GREENFIELD, J. G.: Acute disseminated encephalomyelitis (Westphal). In A system of bacteriology in relation to medicine, London, 1930, vol. 7, p. 133.

GRINKER, R. R., AND BASSOE, P.: Disseminated encephalomyelitis. Arch. Neurol. & Psychiat. **25:** 722, 1931.

HASSIN, G. B.: Neuroptic myelitis versus multiple sclerosis. Arch. Neurol. & Psychiat. **37:** 1083, 1937.

——— AND GEIGER, J. C.: Postvaccinal (cowpox) encephalitis. Ibid. **23:** 481, 1930.

——— AND RABENS, I. A.: Herpetic-meningoencephalitis. J. Neuropath. & Exper. Neurol. **3:** 355, 1944.

LEVADITI, C.: Les ultravirus provocateurs des ectodermoses neurotropes. Ann. Inst. Pasteur **45:** 673, 1930.

UNDERWOOD, E. A.: Neurological complications in varicella. Brit. J. Child. Dis. **32:** 83, 117, 241, 1935.

WOHLWILL, F.: Über Encephalomyelitis bei Masern. Ztschr. f. d. ges. Neurol. u Psychiat. **112:** 20, 1928.

Disseminated Sclerosis

ALAJOUINE, T., ET AL.: Acute multiple sclerosis with symptoms of neuromyelitis optica. Arch. Neurol. & Psychiat. **35:** 1166, 1936.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE: Multiple sclerosis. Vol. 2, 1902.

GREENFIELD, J. G., AND KING, L. S.: Observations on the histopathology of the cerebral lesions in disseminated sclerosis. Brain **59:** 445, 1936.

INNES, J. R. M.: The pathology of "swayback." Proc. Roy. Soc. Med. **29:** 406, 1936.
PUTNAM, T. J.: Studies in multiple sclerosis. Arch. Neurol. & Psychiat. **35:** 1289, 1936.
RISER, GÉRAND, AND PLANQUES: De l'encéphalomyélite nécrotique subaiguë. Rev. neurol. **67:** 455, 1937.
STEINER, G.: Krankheitserreger und Gewebsbefund bei multipler Sklerose. Berlin, 1931.
WEIL, A.: A study of the etiology of multiple sclerosis. J. A. M. A. **97:** 1587, 1931.
——— AND HEILBRUNN, G.: Demonstration of myelolytic substances in disseminated sclerosis. Proc. Soc. Exper. Biol. & Med. **48:** 233, 1941.

Diffuse Sclerosis

BOUMAN, L.: Encephalitis periaxialis diffusa. Brain **47:** 453, 1924.
GASUL, B.: Schilder's disease. Am. J. Dis. Child. **39:** 595, 1930.
GLOBUS, J. H., AND STRAUSS, I.: Progressive degenerative subcortical encephalopathy. Arch. Neurol. & Psychiat. **20:** 1190, 1928.

9. INTOXICATIONS

Volatile Solvents

DONLEY, D. E.: Toxic encephalopathy and volatile solvents in industry. J. Indust. Hyg. & Toxicol. **18:** 571, 1936.
HAMMES, E. M., AND FRARY, L. G.: Polyneuritis associated with ether anesthesia. Arch. Neurol. & Psychiat. **35:** 617, 1936.

Alcohol

BENDER, L.: Myelopathia alcoholica. Arch. Neurol. & Psychiat. **31:** 310, 1934.
LEARY, T.: Subdural or intradural hemorrhage. Arch. Path. **28:** 808, 1939.
NEUBÜRGER, K.: Über Hirnveränderungen nach Alkoholmissbrauch. Ztschr. f. d. ges. Neurol. u. Psychiat. **135:** 159, 1931.
OHKUMA, T.: Zur pathologischen Anatomie des chronischen Alkoholismus. Ztschr. f. d. ges. Neurol. u. Psychiat. **126:** 94, 1930.
PICK, L., AND BIELSCHOWSKY, M.: Das histologische Bild im Auge und im Centralnervensystem bei akuter, tödlicher Vergiftung mit Methylalkohol. Berl. klin. Wchnschr. **49:** 888, 1912.

Metrazol

WEIL, A., AND LIEBERT, E.: Neuropathologic study of six cases of psychoses in which metrazol was used. Arch. Neurol. & Psychiat. **44:** 1031, 1940.

Insulin

WEIL, A., LIEBERT, E., AND HEILBRUNN, G.: Histopathologic changes in the brain in experimental hyperinsulinism. Arch. Neurol. & Psychiat. **39:** 467, 1938.

Lead

AUB, J. C., ET AL.: Lead poisoning. Baltimore, 1926.
FERRARO, A., AND HERNANDEZ, R.: Lead poisoning. Psychiatric Quart. **6:** 121, 319, 1932.
MCKHANN, C. F.: Lead poisoning in children: the cerebral manifestations. Arch. Neurol. & Psychiat. **32:** 294, 1932.

Arsenic

COLE, H. N., ET AL.: Toxic effects following use of arsphenamines. J. A. M. A. **97:** 897, 1931.

FRITZ, E.: Seltener Hirnbefund bei Salvarsantod. Ztschr. f. d. ges. Neurol. u. Psychiat. **126:** 163, 1930.

POLLAK, E., AND RIEHL, G.: Zur Pathologie der Salvarsanschäden des Nervensystems. Jahrb. f. Psychiat. u. Neurol. **47:** 99, 1930.

RUSSELL, D. S.: Changes in the central nervous system following arsphenamine medication. J. Path. & Bact. **45:** 357, 1937.

Carbon Monoxide

SEMERAK, C. B., AND BACON, L. H.: Experimental lesions of the brain from carbon monoxide. Arch. Path. **10:** 823, 1930.

Liver Disease

BARNES, S., AND HURST, E. W.: Hepato-lenticular degeneration. Brain **48:** 279, 1925; **49:** 36, 1926; J. Path. & Bact. **31:** 303, 1928.

NEUSTADT, R.: Leber und Gehirn. Nervenarzt **4:** 653, 1931.

NICOLAJEV, V.: Zur Frage der Beziehungen zwischen Leber und Gehirn. Virchows Arch. f. path. Anat. **299:** 309, 1937.

POLLAK, E.: Lebererkrankungen und Gehirn. Jahrb. f. Psychiat. u. Neurol. **47:** 195, 1930.

STADLER, H.: Histopathologische Untersuchungen zur Frage der Beziehungen zwischen Leber und Gehirnerkrankung. Ztschr. f. d. ges. Neurol. u. Psychiat. **154:** 626, 1935.

WEIL, A., AND CRANDALL, L. A.: Pathology of central nervous system in diseases of the liver. Ztschr. f. d. ges. Neurol. u. Psychiat. **140:** 577, 1932; Arch. Neurol. & Psychiat. **29:** 1066, 1933.

Uremia

UCHIDA, K.: Pathologisch-anatomische Untersuchungen an Gehirnen nach Uraemie. Arb. a. d. Neurol. Inst. a. d. Wien. Univ. **31:** 37, 1929.

Avitaminosis

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE: The role of nutrition deficiency in nervous and mental disease. Vol. 22, 1943.

DUERCK, H.: Untersuchungen über die pathologische Anatomie der Beri-beri. Beitr. z. path. Anat. u. z. allg. Path., vol. 8 (supp.), 1908.

LANGWORTHY, O. R.: Lesions of the central nervous system characteristic of pellagra. Brain **54:** 291, 1931.

WOOLLARD, H. H.: The nature of the structural changes in nerve endings in starvation and in beri-beri. J. Anat. **61:** 283, 1926–27.

ZIMMERMAN, H. M., AND BURACK, E.: Studies on the nervous system in deficiency disease. J. Exper. Med. **59:** 21, 1934.

Subacute Combined Degeneration

CRITCHLEY, M., AND GREENFIELD, J. G.: Spinal symptoms in chloroma and leukemia. Brain **53:** 11, 1930.

GREENFIELD, J. G., AND CARMICHAEL, E. A.: The peripheral nerves in cases of subacute combined degeneration of the cord. Brain **58:** 483, 1933.

LURJE, Z. L.: Veränderungen des Nervensystems bei Leukosen. Zentralbl. f. d. ges. Neurol. u. Psychiat. **86:** 437, 1937.

WEIL, A.: Spinal cord changes in lymphogranulomatosis. Arch. Neurol. & Psychiat. **26:** 1009, 1931.

——— AND DAVISON, C.: Changes in the spinal cord in anemia. Ibid. **22:** 966, 1929.

WOHLWILL, F.: Zum Kapitel der pathologisch-anatomischen Veränderungen des Gehirns und Rückenmarks bei perniciöser Anämie. Deutsche Ztschr. f. Nervenh. **68-69:** 438, 1921.

Hormones

WEIL, A.: The phospholipids of the brain, kidneys and heart of white rats in experimental hyperthyroidism. Endocrinology **21:** 101, 1937.

———: Experimental hypothyroidism. Ibid. **29:** 919, 1941.

———: The influence of sex hormones upon the chemical growth of the brain of white rats. Growth **8:** 107, 1944.

——— AND GROAT, R. A.: The effect of adrenalectomy upon the brain of white rats. J. Neuropath. & Exper. Neurol. **3:** 374, 1944.

——— AND LIEBERT, E.: The correlation between sex and chemical constitution of the human brain. Quart. Bull. Northwestern Univ. M. School **17:** 117, 1943.

10. INJURIES

BAILEY, P.: Disease of the nervous system resulting from accident and injury. New York and London, 1909.

MARBURG, O.: Zur Pathologie der Kriegsbeschädigungen des Rückenmarks. Arb. a. d. Neurol. Inst. a. d. Wien Univ. **22:** 498, 1919.

——— AND HELFAND, M.: Injuries of the nervous system. New York, 1939.

RAND, C. W., AND COURVILLE, C. B.: Histological studies of the brain in fatal injuries to the head. Arch. Neurol. & Psychiat. **36:** 1277, 1936.

SPIELMEYER, W.: Zur Klinik und Anatomie der Nervenschussverletzungen. Ztschr. f. d. ges. Neurol. u. Psychiat. **29:** 416, 1915.

STRAUSS, I., AND SAVITSKY, N.: Head injury. Arch. Neurol. & Psychiat. **31:** 893, 1934.

WINKELMAN, N. W., AND ECKEL, J. L.: Brain trauma. Arch. Neurol. & Psychiat. **31:** 956, 1934.

Effect of Electric Shock

ALPERS, B. J., AND HUGHES, J.: Changes in the brain after electrically induced convulsions in cats. Arch. Neurol. & Psychiat. **47:** 385, 1942.

EBAUGH, F., AND NEUBÜRGER, K.: Fatalities following electric convulsive therapy. Psychiatric Quart. **17:** 20, 1943.

HEILBRUNN, G., AND WEIL, A.: Pathologic changes in the central nervous system in experimental electric shock. Arch. Neurol. & Psychiat. **47:** 918, 1942.

Effect of Roentgen Rays, Radium, and Heat

COLWELL, H. A., AND GLADSTONE, R. J.: On some histological changes produced in the mammalian brain by exposure to radium. Brit. J. Radiol. **10:** 549, 1937.

HORANYI-HECHST, B.: Experimentelle Hyperthermie. Arch. f. Psychiat. **104:** 256, 1935.

MARBURG, O., AND SGALITZER, M.: Die Röntgenbehandlung der Nervenkrankheiten. Strahlentherapie, Sonderbände, vol. 15, 1930.

SCHOLZ: Über den Einfluss von Röntgen- und Radiumstrahlen auf das Hirngewebe. Zentralbl. f. d. ges. Neurol. u. Psychiat. **74:** 430, 1934.

Anaphylaxis

DAVIDOFF, L. M., ET AL.: Anaphylaxis in decerebrated monkeys. J. Lab. & Clin. Med. **23:** 30, 1937.

FERRARO, A.: Allergic brain changes in post-scarlatinal encephalitis. J. Neuropath. & Exper. Neurol. **3:** 239, 1944.

STIEF, A., AND TOKAY, L.: Anaphylaxie und Nervensystem. Psychiat.-neurol. Wchnschr. **39:** 191, 1937.

11. DEGENERATIVE DISEASES

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE: Heredity in nervous and mental disease. Vol. 3, 1923.

———: The diseases of the basal ganglia. Vol. 21, 1942.

BAUER, J.: Constitution and disease. New York, 1942.

BING, R.: Kongenitale, heredofamiliäre und neuromuskuläre Erkrankungen. Handb. d. inn. Med., vol. 5, pt. 2, 1926.

Muscular Dystrophies

BOMPIANI, G., AND MELDOLESI, G.: Alterazioni anatomo-istologiche del pancreas in casi di distrofia muscolare progressiva. Boll. Acad. med. di Roma **62:** 250, 1936.

BRAND, E., HARRIS, M., SANDBERG, M., AND RINGER, A. L.: Studies on the origin of creatine. Am. J. Physiol. **90:** 296, 1929.

FRIESZ, J.: Beiträge zur anatomischen Kenntnis der Muskeldystrophien. Deutsche Ztschr. f. Nervenh. **112:** 318, 1930.

GLOBUS, J. H.: The pathologic findings in the heart muscle in progressive muscular dystrophy. Arch. Neurol. & Psychiat. **9:** 59, 1923.

WOHLFART, G.: Über mikroskopische Untersuchungen an 15 Fällen von progressiver Muskelatrophie ungleicher Genese. Zentralbl. f. d. ges. Neurol. u. Psychiat. **84:** 563, 1936; Svenska läk.-tidning. **33:** 538, 1936.

Dystrophia Myotonica

KESCHNER, M., AND DAVISON, C.: Dystrophia myotonica. Arch. Neurol. & Psychiat. **30:** 1259, 1933.

SLAUCK, A.: Untersuchungen auf dem Gebiete der Myopathie und Myasthenie. Ztschr. f. d. ges. Neurol. u. Psychiat. **80:** 362, 1923.

WEIL, A., AND KESCHNER, M.: Dystrophia myotonica. Tr. Am. Neurol. A., 1926; Ztschr. f. d. ges. Neurol. u. Psychiat. **108:** 687, 1927.

Myotonia Congenita (Thomsen's Disease)

BIELSCHOWSKY, M.: Myotonia congenita. J. f. Psychol. u. Neurol. **38:** 199, 1929.

Amyotonia Congenita (Oppenheim's Disease)

GURDJIAN, E. S.: Myatonia congenita. Arch. Neurol. & Psychiat. **24:** 52, 1930.

REUBEN, M. S., AND SERVER, J. J.: Amyotonia congenita. Arch. Pediat. **48:** 130, 1931.

SCHILDKNECHT, O.: Über die frühinfantile progressive spinale Muskelatrophie und ihre Beziehungen zur Myatonia congenita. Deutsche Ztschr. f. Nervenh. **134:** 163, 1934.

Amyotrophies

CH'ENG, Y. L., AND HU, C. H.: Infantile spinal muscular atrophy (Werdnig-Hoffmann). Chinese M. J. **1** (supp.): 106, 1936.

GALLINEK, A.: Zum Wesen der neuralen Muskelatrophie. Deutsche Ztschr. f. Nervenh. **114:** 74, 1930.

GREENFIELD, J. G., AND STERN, R. O.: The anatomical identity of the Werdnig-Hoffmann and Oppenheim form of infantile muscular atrophy. Brain **50:** 652, 1927.

WEINBERG, S. J.: A case of progressive neural muscular atrophy. Johns Hopkins Hosp. Bull. **49:** 61, 1931.

Amyotrophic Lateral Sclerosis

REUTER, A.: Zur Pathogenese der amyotrophischen Lateralsklerose. Deutsche Ztschr. f. Nervenh. **122:** 237, 1931.

WECHSLER, I. S., AND DAVISON, C.: Amyotrophic lateral sclerosis with mental symptoms. Arch. Neurol. & Psychiat. **27:** 859, 1932.

Heredofamilial Ataxias

ALPERS, B. J., AND WAGGONER, R. W.: Extraneural and neural anomalies in Friedreich's disease. Arch. Neurol. & Psychiat. **21:** 47, 1929.

ARANOVICH, J.: Die bibasale Atrophie des Kleinhirnrandes nach Chr. Jakob. Rev. neurol. de Buenos Aires **1:** 471, 1937.

BIELSCHOWSKY, M.: Zur Kenntnis des Friedreich Komplexes. Ztschr. f. d. ges. Neurol. u. Psychiat. **150:** 373, 1934.

HASSIN, G. B.: Marie's ataxia (olivopontocerebellar atrophy). Arch. Neurol. & Psychiat. **37:** 1371, 1937.

SCHERER, H. J.: Beiträge zur pathologischen Anatomie des Kleinhirns. Ztschr. f. d ges. Neurol. u. Psychiat. **145:** 335, 1933.

Chronic Progressive Chorea

DAVISON, C., GOODHARDT, S. P., AND SHLIONSKY, H.: Chronic progressive chorea. Arch. Neurol. & Psychiat. **27:** 906, 1932.

DUNLAP, C. B.: Pathologic changes in Huntington's chorea. Arch. Neurol. & Psychiat. **18:** 867, 1927.

JAKOB, A.: Die extrapyramidalen Erkrankungen. Monog. a. d. Gesamtgeb. d. Neurol. u. Psychiat., vol. 37, 1923.

LOTMAR, F.: Die Stammganglien und die extrapyramidal-motorischen Syndrome. Monog. a. d. Gesamtgeb. d. Neurol. u. Psychiat., vol. 48, 1926.

VOGT, C., AND VOGT, O.: Zur Lehre der Erkrankungen des striären Systems. J. f. Psychol. u. Neurol., vol. 25, 1920, supp. 3.

WAGGONER, R. W.: Sydenham's chorea. Am. J. M. Sci. **182:** 467, 1931.

WEIL, A.: A contribution to the pathology of hemichorea. Brain **51:** 36, 1928.

Parkinsonism

KOHNSTAMM, P.: Über die Beteiligung der substantia nigra am Prozess der Encephalitis epidemica. J. f. Psychol. u. Neurol. **46:** 22, 1934.

NEUSTÄDTER, M., AND LIBER, A. F.: Pathologic changes in parkinsonism. Arch. Neurol. & Psychiat. **37:** 1212, 1937.

Anaphylaxis

DAVIDOFF, L. M., ET AL.: Anaphylaxis in decerebrated monkeys. J. Lab. & Clin. Med. **23:** 30, 1937.

FERRARO, A.: Allergic brain changes in post-scarlatinal encephalitis. J. Neuropath. & Exper. Neurol. **3:** 239, 1944.

STIEF, A., AND TOKAY, L.: Anaphylaxie und Nervensystem. Psychiat.-neurol. Wchnschr. **39:** 191, 1937.

11. DEGENERATIVE DISEASES

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE: Heredity in nervous and mental disease. Vol. 3, 1923.

———: The diseases of the basal ganglia. Vol. 21, 1942.

BAUER, J.: Constitution and disease. New York, 1942.

BING, R.: Kongenitale, heredofamiliäre und neuromuskuläre Erkrankungen. Handb. d. inn. Med., vol. 5, pt. 2, 1926.

Muscular Dystrophies

BOMPIANI, G., AND MELDOLESI, G.: Alterazioni anatomo-istologiche del pancreas in casi di distrofia muscolare progressiva. Boll. Acad. med. di Roma **62:** 250, 1936.

BRAND, E., HARRIS, M., SANDBERG, M., AND RINGER, A. L.: Studies on the origin of creatine. Am. J. Physiol. **90:** 296, 1929.

FRIESZ, J.: Beiträge zur anatomischen Kenntnis der Muskeldystrophien. Deutsche Ztschr. f. Nervenh. **112:** 318, 1930.

GLOBUS, J. H.: The pathologic findings in the heart muscle in progressive muscular dystrophy. Arch. Neurol. & Psychiat. **9:** 59, 1923.

WOHLFART, G.: Über mikroskopische Untersuchungen an 15 Fällen von progressiver Muskelatrophie ungleicher Genese. Zentralbl. f. d. ges. Neurol. u. Psychiat. **84:** 563, 1936; Svenska läk.-tidning. **33:** 538, 1936.

Dystrophia Myotonica

KESCHNER, M., AND DAVISON, C.: Dystrophia myotonica. Arch. Neurol. & Psychiat. **30:** 1259, 1933.

SLAUCK, A.: Untersuchungen auf dem Gebiete der Myopathie und Myasthenie. Ztschr. f. d. ges. Neurol. u. Psychiat. **80:** 362, 1923.

WEIL, A., AND KESCHNER, M.: Dystrophia myotonica. Tr. Am. Neurol. A., 1926; Ztschr. f. d. ges. Neurol. u. Psychiat. **108:** 687, 1927.

Myotonia Congenita (Thomsen's Disease)

BIELSCHOWSKY, M.: Myotonia congenita. J. f. Psychol. u. Neurol. **38:** 199, 1929.

Amyotonia Congenita (Oppenheim's Disease)

GURDJIAN, E. S.: Myatonia congenita. Arch. Neurol. & Psychiat. **24:** 52, 1930.

REUBEN, M. S., AND SERVER, J. J.: Amyotonia congenita. Arch. Pediat. **48:** 130, 1931.

SCHILDKNECHT, O.: Über die frühinfantile progressive spinale Muskelatrophie und ihre Beziehungen zur Myatonia congenita. Deutsche Ztschr. f. Nervenh. **134:** 163, 1934.

Amyotrophies

CH'ENG, Y. L., AND HU, C. H.: Infantile spinal muscular atrophy (Werdnig-Hoffmann). Chinese M. J. **1** (supp.): 106, 1936.

GALLINEK, A.: Zum Wesen der neuralen Muskelatrophie. Deutsche Ztschr. f. Nervenh. **114:** 74, 1930.

GREENFIELD, J. G., AND STERN, R. O.: The anatomical identity of the Werdnig-Hoffmann and Oppenheim form of infantile muscular atrophy. Brain **50:** 652, 1927.

WEINBERG, S. J.: A case of progressive neural muscular atrophy. Johns Hopkins Hosp. Bull. **49:** 61, 1931.

Amyotrophic Lateral Sclerosis

REUTER, A.: Zur Pathogenese der amyotrophischen Lateralsklerose. Deutsche Ztschr. f. Nervenh. **122:** 237, 1931.

WECHSLER, I. S., AND DAVISON, C.: Amyotrophic lateral sclerosis with mental symptoms. Arch. Neurol. & Psychiat. **27:** 859, 1932.

Heredofamilial Ataxias

ALPERS, B. J., AND WAGGONER, R. W.: Extraneural and neural anomalies in Friedreich's disease. Arch. Neurol. & Psychiat. **21:** 47, 1929.

ARANOVICH, J.: Die bibasale Atrophie des Kleinhirnrandes nach Chr. Jakob. Rev. neurol. de Buenos Aires **1:** 471, 1937.

BIELSCHOWSKY, M.: Zur Kenntnis des Friedreich Komplexes. Ztschr. f. d. ges. Neurol. u. Psychiat. **150:** 373, 1934.

HASSIN, G. B.: Marie's ataxia (olivopontocerebellar atrophy). Arch. Neurol. & Psychiat. **37:** 1371, 1937.

SCHERER, H. J.: Beiträge zur pathologischen Anatomie des Kleinhirns. Ztschr. f. d ges. Neurol. u. Psychiat. **145:** 335, 1933.

Chronic Progressive Chorea

DAVISON, C., GOODHARDT, S. P., AND SHILONSKY, H.: Chronic progressive chorea. Arch. Neurol. & Psychiat. **27:** 906, 1932.

DUNLAP, C. B.: Pathologic changes in Huntington's chorea. Arch. Neurol. & Psychiat. **18:** 867, 1927.

JAKOB, A.: Die extrapyramidalen Erkrankungen. Monog. a. d. Gesamtgeb. d. Neurol. u. Psychiat., vol. 37, 1923.

LOTMAR, F.: Die Stammganglien und die extrapyramidal-motorischen Syndrome. Monog. a. d. Gesamtgeb. d. Neurol. u. Psychiat., vol. 48, 1926.

VOGT, C., AND VOGT, O.: Zur Lehre der Erkrankungen des striären Systems. J. f. Psychol. u. Neurol., vol. 25, 1920, supp. 3.

WAGGONER, R. W.: Sydenham's chorea. Am. J. M. Sci. **182:** 467, 1931.

WEIL, A.: A contribution to the pathology of hemichorea. Brain **51:** 36, 1928.

Parkinsonism

KOHNSTAMM, P.: Über die Beteiligung der substantia nigra am Prozess der Encephalitis epidemica. J. f. Psychol. u. Neurol. **46:** 22, 1934.

NEUSTÄDTER, M., AND LIBER, A. F.: Pathologic changes in parkinsonism. Arch. Neurol. & Psychiat. **37:** 1212, 1937.

Familial Amaurotic Idiocy

BATY, J. M.: Lipoid histiocytosis (Niemann's disease). Am. J. Dis. Child. **39:** 573, 1930.

EPSTEIN, E.: Beiträge zur Pathologie und Systematik der allgemeinen Lipoidosen nach chemischen und physikalisch-chemischen Gesichtspunkten. Virchows Arch. f. path. Anat. **281:** 152, 1931; **293:** 135, 1934.

HASSIN, G. B.: A study of the histopathology of amaurotic family idiocy. Arch. Neurol. & Psychiat. **12:** 640, 1924.

———: Niemann-Pick's disease. Ibid. **24:** 61, 1930.

HUEPER, W. C.: Organic lesions produced by poly-vinyl alcohol in rats and rabbits. Arch. Path. **28:** 510, 1938; **33:** 1, 1942; J. Pharmacol. & Exper. Therap. **70:** 201, 1940.

HURST, E. W.: A study of the lipoids in neuronic degeneration and in amaurotic family idiocy. Brain **48:** 1, 1925.

Cerebral Cortical Degeneration

BRAUMUHL, A. VON: Pick'sche Krankheit. Handb. d. Geisteskr. **11[7]:** 673, 1930.

FERRAO, A., AND JERVIS, G. A.: Pick's disease. Arch. Neurol. & Psychiat. **36:** 739, 1936.

GRÜNTHAL, E.: Die pathologische Anatomie der senilen Demenz und der Alzheimer'schen Krankheit. Handb. d. Geisteskr. **11[7]:** 638, 1930.

MALAMUD, W., AND LOWENBERG, K.: Alzheimer's disease. Arch. Neurol. & Psychiat. **21:** 805, 1929.

———, ———: Genealogic and clinicopathologic study of Pick's disease. Ibid. **50:** 288, 1943.

12. TUMORS

Experimental Tumors

SELIGMAN, A. M., AND SHEAR, M. J.: Production of brain tumors in mice with methylcholanthrene. Am. J. Cancer **37:** 364, 1939.

WEIL, A.: Experimental production of tumors in the brains of white rats. Arch. Path. **26:** 777, 1938.

——— AND BLUMKLOTZ, B.: Experimental intracranial epithelial cysts. J. Neuropath. & Exper. Neurol. **2:** 34, 1943.

——— AND HETHERINGTON, A. W.: Experimental tumor of the hypophysis of the white rat. J. Mt. Sinai Hosp. **9:** 842, 1942.

ZIMMERMAN, H. M.: Chemical carcinogen and animal species as factors in experimental brain tumors. J. Neuropath. & Exper. Neurol. **2:** 416, 1943.

Antigenic Properties of Tumors

REICHER, H.: Serologische Differenzierung zwischen gliösem und normalem Gehirnparenchym. Ztschr. f. Immunitätsforsch. u. exper. Therap. **80:** 85, 1933.

WEIL, A., AND LIEBERT, E.: Antigenic properties of brain tumors. J. Immunol. **30:** 291, 1936.

Tumors of the Meninges

BAILEY, P., AND BUCY, P. C.: The origin and nature of meningeal tumors. Am. J. Cancer **15:** 15, 1931.

BLAND, J. O. W., AND RUSSELL, D. S.: Histological types of meningioma. J. Path. & Bact. **47**: 291, 1938.

BROWN, H., AND KERNOHAN, J. W.: Diffuse meningiomatosis. Arch. Path. **32**: 651, 1941.

CUSHING, H., AND EISENHARDT, L.: The meningiomas. Springfield, Ill., 1938.

GLOBUS, J. H.: Meningiomas. Arch. Neurol. & Psychiat. **38**: 667, 1937.

KRAINER, L.: Die Hirn- und Rückenmarkslipome. Virchows Arch. f. path. Anat. **295**: 105, 1935.

Tumors of the Glia

BAILEY, P.: Atlas of gliomas. Arch. Path. **4**: 871, 1927.

——— AND CUSHING, H.: A classification of the tumors of the glioma group. Philadelphia, London, and Montreal, 1926.

CUSHING, H.: Intracranial tumors. Springfield, Ill., 1932.

ROUSSY, G., AND OBERLING, C.: Atlas du cancer, pts. 9, 10: Les tumeurs des centres nerveux et des nerfs périphériques. Paris, 1931.

SCHALTENBRAND, G.: Hirngeschwulst und Lebensalter. Zentralbl. f. d. ges. Neurol. u. Psychiat. **87**: 263, 1937.

SCHERER, H. J.: Das mesenchymale Gewebe der Gliome. Virchows Arch. f. path. Anat. **291**: 321, 1933.

———: Frequency of gliomas with variable histologic structures. Am. J. Cancer **34**: 333, 1938.

ZUELCH, K. J.: Über die geschichtliche Entwicklung und den heutigen Stand der Klassifikation der Hirngeschwülste. Zentralbl. f. Neurochir. **4**: 325, 1939.

Tumors of the Neuron

ALPERS, B. J., AND GRANT, F. C.: The ganglioneuromas of the central nervous system. Arch. Neurol. & Psychiat. **26**: 501, 1931.

CHRISTENSEN, E.: Ganglienzell Tumoren des Gehirns. Virchows Arch. f. path. Anat. **300**: 567, 1937.

GLOBUS, J. H.: Glioneuroma and spongioneuroblastoma. Am. J. Cancer **32**: 163, 1938.

HAVEN, H., AND WEIL, A.: Multiple ganglioneuroma. Arch. Path. **13**: 713, 1932.

WAHL, H. R.: Neuroblastoma. J. Med. Research **30**: 205, 1914.

Tumors of the Ependyma

FINCHER, E. F., AND COON, G. P.: Ependymonas. Arch. Neurol. & Psychiat. **22**: 19, 1929.

TOENNIS, W., AND ZUELCH, K. J.: Das Ependymom der Grosshirnhemisphären im Jugendalter. Zentralbl. f. Neurochir. **2**: 141, 1937.

Tumors of the Choroidal Epithelium

BIELSCHOWSKY, M., AND UNGER, E.: Zur Kenntnis der primären Epithelgeschwülste der Adergeflechte des Gehirns. Arch. f. klin. Chir. **81**: 61, 1906.

TURNER, O. A., AND SIMON, M. A.: Malignant papillomas of the choroid plexus. Am. J. Cancer **30**: 280, 1937.

Tumors of the Blood Vessels

BERGSTRAND, H., OLIVECRONA, H., AND TOENNIS, W.: Gefässmissbildungen und Gefässgeschwülste des Gehirns. Leipzig, 1936.

CUSHING, H., AND BAILEY, P.: Tumors arising from the bloodvessels of the brain. Springfield and Baltimore, 1929.

SPATZ, H.: Über multizentrisch wachsende Gliome. Zentralbl. f. d. ges. Neurol. u. Psychiat. **87:** 683, 1938.

Tumors of the Hypophysis

BAILEY, P.: Tumors of the hypophysis. In Penfield, W. (ed.): Cytology and cellular pathology of the nervous system **3:** 1131, 1932.

CUSHING, H.: The pituitary body and its disorders. Philadelphia and London, 1912.

Tumors of the Craniopharyngeal Duct

FRAZIER, C. H., AND ALPERS, B. J.: Adamantinoma of the cranio-pharyngeal duct. Arch. Neurol. & Psychiat. **26:** 905, 1931.

Tumors of the Pineal Gland

GLOBUS, J. H., AND SILBERT, S.: Pinealomas. Arch. Neurol. & Psychiat. **25:** 356, 1931.

HORRAX, G., AND BAILEY, P.: Tumors of the pineal body. Arch. Neurol. & Psychiat. **13:** 423, 1925.

Neurinomas

CUSHING, H.: Tumors of the nervous acusticus. Philadelphia and London, 1917.

DOERING, G.: Histologische Veränderungen des Hirnstammes bei Kleinhirnbrückenwinkeltumoren. Ztschr. f. d. ges. Neurol. u. Psychiat. **165:** 256, 1939.

GESCHICHTER, F.: Tumors of the peripheral nerves. Am. J. Cancer **25:** 377, 1935.

PENFIELD, W.: Tumors of the sheaths of the nervous system. In Penfield, W. (ed.): Cytology and cellular pathology of the nervous system, 1932, vol. 3, p. 953.

SCHERER, H. J.: Untersuchungen über den geweblichen Aufbau der Geschwülste des peripheren Nervensystems. Virchows Arch. f. path. Anat. **292:** 479, 1934.

Recklinghausen's Disease

GAMPER, E.: Zur Kenntnis der zentralen Veränderungen bei Morbus von Recklinghausen. J. f. Psychol. u. Neurol. **39:** 38, 1929.

Tumors of the Spinal Cord

ELSBERG, C. A.: Tumors of the spinal cord. New York, 1925.

KERNOHAN, J. W., WOLTMAN, A. W., AND ADSON, A. W.: Intramedullary tumors of the spinal cord. Arch. Neurol. & Psychiat. **25:** 678, 1931.

Syringomyelia

JONESCO-SISESTI, N.: Tumeurs médullaires associés à un processus syringomyélique. Paris, 1929.

RILEY, H. A.: Syringomyelia or myelodysplasia. J. Nerv. & Ment. Dis. **72:** 1, 1930.

Metastatic Tumors

HARE, C. C., AND SCHWARZ, G. A.: Intracerebral carcinomatous metastases. Arch. Int. Med. **64:** 542, 1939.

HOFFMAN, J. L.: Intracranial neoplasms; their incidence and mental manifestations. Psychiatric Quart. **11:** 561, 1937.

ACK, C. T., AND LEFEVRE, R. G.: The age and sex distribution and incidence of neoplastic disease at the Memorial Hospital, New York City. J. Cancer Research **14:** 167, 1930.

PUTSCHAR, W.: Zur Pathologie und Symptomatologie der Carcinommetastasen des Zentralnervensystems. Ztschr. f. d. ges. Neurol. u. Psychiat. **126:** 129, 1930.

SOTO-ROMAY, R.: Cerebral metastatic tumors. Arch. argent. de neurol. **20:** 89, 1939; Arch. Neurol. & Psychiat. **42:** 939, 1939.

13. CONGENITAL MALFORMATIONS

DANDY, W. E.: Congenital cerebral cyst of the cavum septi pellucidi. Arch. Neurol. & Psychiat. **25:** 44, 1931.

——— AND BLACKFAN, K.: Internal hydrocephalus. Am. J. Dis. Child. **8:** 406, 1914.

DEPPE, B.: Das Axenskelett in der Anencephalie und Craniorachischisis. Virchows Arch. f. path. Anat. **293:** 153, 1934.

FERRARO, A., AND DOOLITTLE, G. J.: Tuberous sclerosis. Psychiatric Quart. **10:** 365, 1936.

FREEDOM, L.: Cerebral birth palsies. Arch. Neurol. & Psychiat. **26:** 524, 1931.

GLOBUS, J. H., AND SELINSKY, H.: Tuberous sclerosis in infant. Am. J. Dis. Child. **50:** 954, 1935.

HASSIN, G. B.: Hydrocephalus. Arch. Neurol. & Psychiat. **24:** 1164, 1930.

JACOB, H.: Entwicklungsgestörte Gehirne. Zentralbl. f. d. ges. Neurol. u. Psychiat. **88:** 550, 1938.

KING, L. S., AND MEEHAN, M. C.: Primary degeneration of the corpus callosum. Arch. Neurol. & Psychiat. **36:** 547, 1936.

LEWANDOWSKY, M.: Die Missbildungen des Rückenmarks. Handb. d. Neurol. **2:** 446, 1911.

LIECHTENSTEIN, B. W.: Distant neuroanatomic complications of spina bifida. Arch. Neurol. & Psychiat. **40:** 195, 1942.

LLOYD, J. S.: Agenesis of the corpus callosum. J. Ment. Sc. **84:** 995, 1938.

REHBOCK, D. J.: Neuro-epithelial cyst of the third ventricle. Arch. Path. **21:** 524, 1936.

SCHOB, F.: Pathologische Anatomie der Idiotie. Handb. d. Geisteskr. **9**[7]: 818, 1930.

WEIL, A.: Megalencephaly with diffuse glioblastomatosis of the brain stem and the cerebellum. Arch. Neurol. & Psychiat. **30:** 795, 1933.

WINDLE, W. F., BECKER, R. F., AND WEIL, A.: Alterations in brain structure after asphyxiation at birth. J. Neuropath & Exper. Neurol. **3:** 224, 1944.

CUSHING, H., AND BAILEY, P.: Tumors arising from the bloodvessels of the brain. Springfield and Baltimore, 1929.

SPATZ, H.: Über multizentrisch wachsende Gliome. Zentralbl. f. d. ges. Neurol. u. Psychiat. **87:** 683, 1938.

Tumors of the Hypophysis

BAILEY, P.: Tumors of the hypophysis. In Penfield, W. (ed.): Cytology and cellular pathology of the nervous system **3:** 1131, 1932.

CUSHING, H.: The pituitary body and its disorders. Philadelphia and London, 1912.

Tumors of the Craniopharyngeal Duct

FRAZIER, C. H., AND ALPERS, B. J.: Adamantinoma of the cranio-pharyngeal duct. Arch. Neurol. & Psychiat. **26:** 905, 1931.

Tumors of the Pineal Gland

GLOBUS, J. H., AND SILBERT, S.: Pinealomas. Arch. Neurol. & Psychiat. **25:** 356, 1931.

HORRAX, G., AND BAILEY, P.: Tumors of the pineal body. Arch. Neurol. & Psychiat. **13:** 423, 1925.

Neurinomas

CUSHING, H.: Tumors of the nervous acusticus. Philadelphia and London, 1917.

DOERING, G.: Histologische Veränderungen des Hirnstammes bei Kleinhirnbrückenwinkeltumoren. Ztschr. f. d. ges. Neurol. u. Psychiat. **165:** 256, 1939.

GESCHICHTER, F.: Tumors of the peripheral nerves. Am. J. Cancer **25:** 377, 1935.

PENFIELD, W.: Tumors of the sheaths of the nervous system. In Penfield, W. (ed.): Cytology and cellular pathology of the nervous system, 1932, vol. 3, p. 953.

SCHERER, H. J.: Untersuchungen über den geweblichen Aufbau der Geschwülste des peripheren Nervensystems. Virchows Arch. f. path. Anat. **292:** 479, 1934.

Recklinghausen's Disease

GAMPER, E.: Zur Kenntnis der zentralen Veränderungen bei Morbus von Recklinghausen. J. f. Psychol. u. Neurol. **39:** 38, 1929.

Tumors of the Spinal Cord

ELSBERG, C. A.: Tumors of the spinal cord. New York, 1925.

KERNOHAN, J. W., WOLTMAN, A. W., AND ADSON, A. W.: Intramedullary tumors of the spinal cord. Arch. Neurol. & Psychiat. **25:** 678, 1931.

Syringomyelia

JONESCO-SISESTI, N.: Tumeurs médullaires associés à un processus syringomyélique. Paris, 1929.

RILEY, H. A.: Syringomyelia or myelodysplasia. J. Nerv. & Ment. Dis. **72:** 1, 1930.

Metastatic Tumors

HARE, C. C., AND SCHWARZ, G. A.: Intracerebral carcinomatous metastases. Arch. Int. Med. **64:** 542, 1939.

HOFFMAN, J. L.: Intracranial neoplasms; their incidence and mental manifestations. Psychiatric Quart. **11:** 561, 1937.

ACK, C. T., AND LEFEVRE, R. G.: The age and sex distribution and incidence of neoplastic disease at the Memorial Hospital, New York City. J. Cancer Research **14:** 167, 1930.

PUTSCHAR, W.: Zur Pathologie und Symptomatologie der Carcinommetastasen des Zentralnervensystems. Ztschr. f. d. ges. Neurol. u. Psychiat. **126:** 129, 1930.

SOTO-ROMAY, R.: Cerebral metastatic tumors. Arch. argent. de neurol. **20:** 89, 1939; Arch. Neurol. & Psychiat. **42:** 939, 1939.

13. CONGENITAL MALFORMATIONS

DANDY, W. E.: Congenital cerebral cyst of the cavum septi pellucidi. Arch. Neurol. & Psychiat. **25:** 44, 1931.

——— AND BLACKFAN, K.: Internal hydrocephalus. Am. J. Dis. Child. **8:** 406, 1914.

DEPPE, B.: Das Axenskelett in der Anencephalie und Craniorachischisis. Virchows Arch. f. path. Anat. **293:** 153, 1934.

FERRARO, A., AND DOOLITTLE, G. J.: Tuberous sclerosis. Psychiatric Quart. **10:** 365, 1936.

FREEDOM, L.: Cerebral birth palsies. Arch. Neurol. & Psychiat. **26:** 524, 1931.

GLOBUS, J. H., AND SELINSKY, H.: Tuberous sclerosis in infant. Am. J. Dis. Child. **50:** 954, 1935.

HASSIN, G. B.: Hydrocephalus. Arch. Neurol. & Psychiat. **24:** 1164, 1930.

JACOB, H.: Entwicklungsgestörte Gehirne. Zentralbl. f. d. ges. Neurol. u. Psychiat. **88:** 550, 1938.

KING, L. S., AND MEEHAN, M. C.: Primary degeneration of the corpus callosum. Arch. Neurol. & Psychiat. **36:** 547, 1936.

LEWANDOWSKY, M.: Die Missbildungen des Rückenmarks. Handb. d. Neurol. **2:** 446, 1911.

LIECHTENSTEIN, B. W.: Distant neuroanatomic complications of spina bifida. Arch. Neurol. & Psychiat. **40:** 195, 1942.

LLOYD, J. S.: Agenesis of the corpus callosum. J. Ment. Sc. **84:** 995, 1938.

REHBOCK, D. J.: Neuro-epithelial cyst of the third ventricle. Arch. Path. **21:** 524, 1936.

SCHOB, F.: Pathologische Anatomie der Idiotie. Handb. d. Geisteskr. **9**[7]: 818, 1930.

WEIL, A.: Megalencephaly with diffuse glioblastomatosis of the brain stem and the cerebellum. Arch. Neurol. & Psychiat. **30:** 795, 1933.

WINDLE, W. F., BECKER, R. F., AND WEIL, A.: Alterations in brain structure after asphyxiation at birth. J. Neuropath & Exper. Neurol. **3:** 224, 1944.

INDEX

PAGE NOT AVAILABLE

PAGE NOT AVAILABLE