PROGRESS IN
NEUROLOGY AND
PSYCHIATRY

Edited by
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Emeritus Professor and Head of the Department of Experimental Neurology, Temple University School of Medicine, Philadelphia.
IT MAY BE considered a healthy sign that among the over 5200 papers re­viewed in this volume nearly one third (about 1600) deal with basic sciences; also that the number of papers devoted to organic neurology and allied disciplines (over 1800) somewhat exceeds the productivity in the field of psychiatry (nearly 1500 papers). The neurosurgeons apparently prefer deeds to words, so that their literary output is relatively small (about 360 papers). Of the biennially reported subjects the present volume contains General Neurophysiology (Biochemical Aspects), Neuro-Ophthalmology, and a chapter dealing with neurosurgical aspects of Pain and Motor Disorders. Due to circumstances beyond the editor’s control, the chapters on the Autonomic Nervous System and on Neuroendocrine Relationships could not be included in this volume; these subjects will have to be reviewed for a 2-year period in the next volume.

Again it is the pleasant duty of the undersigned to express his deep ap­preciation to all contributors for their painstaking endeavors and unfailing co­operation and to Dr. P. Gildenberg for his help in proofreading.

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I. BASIC SCIENCES

CHAPTER 1

Neuroanatomy

By ELIZABETH C. CROSBY, Ph.D.
AND EDWARD W. LAUER, Ph.D.

THE CAREER of Dr. Oliver Wendell Holmes as a scientist and an anatomist throws a new light on the personality and abilities of that well-known literary figure.

A very understanding and appreciative account of the life and scientific achievements of the internationally known anatomist, Dr. Davenport Hooker, has been written by his colleague and research associate, Dr. Tryphena Humphrey.

TECHNIQUE

Westrum and Lund concluded that poor results following the use of formalin-perfused tissue, for both light and electron microscopy, are due to the subsequent technique and not to the initial perfusion. A continuation study of aldehyde perfusion for electron microscopy deals with the effects of delayed perfusion. Ha has published a modified Golgi-Cox technique which can be used with cresyl violet counterstain. The optimal time for the demonstration of degenerating fibers by the Nauta method following section of the vagus nerve is 3–7 days. Also, the Nauta-Gygax technique with the pretreatment stages omitted gives better results for neurofibrils than either the Glees or the regular Nauta-Gygax methods. Eager and Barnett have made a careful analysis of the Nauta method to determine the necessity for each step and ways to improve them. Beresford has discussed critically the various histological techniques used for the nervous system.

A new method for the measurement of the volume and the surface area of neurons has been presented by Mannen. Various lesions produced by freezing caused essentially a hemorrhagic necrosis in the canine cortex; lesions produced by heat caused a coagulation necrosis, usually with preservation of the vessels.

HISTOLOGY

The differences between oligodendroglia and microglia in the rabbit's cortex as revealed by a modified Hortega method have been reported. Characteristics
of the macroglia of the cat's optic nerve have been studied with the electron microscope. An in vitro study of satellite cells from the rat's superior cervical ganglion showed 2 types of cells. Sympathetic cells do not survive if isolated from the satellite cells. An excellent article dealing with the perineural epithelial layer, which lies between the pia-arachnoid layers centrally, and with the capsules or covering layer of both sensory and motor endings peripherally, and acts as a diffusion barrier for peripheral nerves.

Muscle spindles containing 2–8 intrafusal fibers are present in the extraocular muscles of the macaque. From an area in the dorsolateral part of the sheep's semilunar ganglion, potentials could be recorded upon stretching the extraocular muscles. Two interesting articles on Meissner's corpuscles stated that there is a decrease in number with age and in persons affected by certain hereditary disorders. The progressive complexity of joint receptors has been traced in a series of mammals, and their structure and variability described in man. Using the electron microscope, Andres found from 10 to 12 types of sensory cells in the olfactory epithelium of rats, cats and dogs. Two papers on the retina have described the synapses of the horizontal cells in cats and rabbits, as shown by the Golgi-Kopsch technique, and the dendritic fields of the ganglion cells as revealed by in vitro methylene blue methods.

Experiments involving implantation of nerves into the muscles of rats indicated that "the deciding factor" in the formation of new motor endplates is the availability of denervated muscle. The outgrowth from the distal stump of severed nerves 6–7 days after section was described by Thomas. Blank has reported that, in hens, on the 8th day after sectioning the sciatic nerve 5 cm. from its spinal exit, the motoneurons showed their maximum change. An excellent, well-documented review of normal and degenerating synapses, as revealed by both the light and electron microscopes, and an account of the structure of the postsynaptic membrane in the myoneural junction have appeared. Alksn et al. stressed the importance of the electron microscope for the study of degeneration.

The early post mortem changes which occur in the rat's cerebellum following interruption of its blood supply have been described by Van Nimwegen and Sheldon. Very rapid freeze-drying (30 sec.) of the cerebellum of the mouse revealed extracellular space between axons of the granular layer. This space could not be demonstrated if as much as 8 minutes elapsed between decapitation and freeze-drying. Another paper reported that the extra-cellular space is greater between unmyelinated than between myelinated fibers of the cerebellum.

Blood Supply

Various papers, which need to be consulted for details, cover the blood supply of the rabbit's brain as revealed by corrosion technique or injection of a fluorescent material, the origin of the hypophysial arteries in the cat, and the blood supply of the rat's brain and brain stem. The changes occurring in the
developing choroid plexus of the chick were described by Smith. The distribution of the anterior choroidal artery in the dog was studied by the injection of red lead or a mixture of red lead and gum arabic and in man following an injection of a gelatin-india ink mixture.

The blood supply of the human spinal cord and of the human cervical cord only were studied by perfusion with barium sulfate and examination by microradiological technique. Variations in the location of radicular arteries and in the size and the distribution of the central arteries are given. A similar study of the lumbar area in dog, monkey and man was made using fluorescent material.

Aneurysms of the anterior communicating artery and anomalies of the circle of Willis were reported following an examination of 1,000 brains. A study of the arterial supply of the temporal lobe in 26 hemispheres showed 2 groups of arteries—an anterior group coursing towards the inferior horn of the ventricle and a posterior group inclining toward the “collateral trigone” of the lateral ventricle.

Injection of the fluorescent material acriflavine neutral into several mammals revealed no transport of the substance from the optic nerve to the vitreous body or vice versa. Experiments in rabbits showed that injection of endotoxin alters the blood-brain barrier and permits colloidal iron oxide to enter the capillary epithelium and the neighboring astrocytes.

**Development and Growth**

The length of the various stages of the cell cycle and the nuclear migration during neural tube closure were studied in the chick embryo by means of thymidine-H3 and by the injection of vincristine which arrests mitosis in the metaphase. Gamble used the electron microscope to investigate the development of peripheral nerves in human fetuses of 3.8 to 20 cm. CR length. Relationships between Schwann cells and nonmyelinated fibers were observed at 3.8 cm. CR and myelination was well advanced by 14 cm. CR. A perineural sheath was present except in the youngest embryos. Humphrey, studying the development of the cutaneous fibers of the trigeminal nerve in human embryos, determined that the oral mucosa is innervated before the perioral area, and that the maxillo-mandibular fibers reach the perioral region earlier than the ophthalmic to the upper eyelid. These facts were correlated with Hooker’s observations of the time of appearance of early fetal reflexes. Bodian reported on the fine development of the spinal cord in monkey fetuses at about the time of earliest fetal activity. An autoradiographic study was made of the histogenesis of certain tegmental regions.

Using thymidine-H3, Fujita et al. demonstrated the production of neuroblasts in the external granular layer of the mouse’s cerebellum and their migration into the internal granular layer; 80–92 per cent of this migration occurred later than 7 days after birth. Altman and Das, using the same means to trace neonatal growth in various parts of the rat’s brain, found that only short-axonal neurons develop postnatally. Mitotic figures are said to increase in the mouse’s
cerebellum up to 7 days after birth and then to show a steady decrease to 15 days. The normal differentiation (although not necessarily the inherent pattern) of the human dentate gyrus is believed to depend on the development of the olfactory bulbs. A correlative development between the lateral geniculate and the layers of the occipital cortex in human embryos has been reported. The genesis and development of the Edinger-Westphal nucleus in mice, rats and man has been considered by Hogg.

Vitamin A in large doses caused defects in the nervous system of pregnant rats (and mice) because of failure of the neural tube to close. X-irradiation of embryos on the 19th day resulted in widespread destruction of cortical cells, clearly evident by 12 hours after irradiation.

Comparative

Only brief mention can be made of the many papers dealing with submammals. Among these are papers on the ventral spinal roots in Amphioxus, and the cutaneous sense-organs, the tectal commissure, the olfactory tubercle (of the lungfish) and the retinal architecture of fish. Reports on toads and frogs consider the development of the spinal cord after metamorphosis, the mitosis of neurons in the brain following injury, the structure of muscle spindles and of Schmidt-Lanterman incisures, the changes in some neurons following starvation, and the forebrain of Bufo marinus and of Hyla cinerea. The blood supply of the nervous system of Xenopus, the structure of the choroid plexus in Necturus, and the innervation of the pineal gland of the lizard, Lacerta viridis, were also reported. Articles on the nervous system of birds deal with sensory cells of the pineal organ, the afferent connections of the nucleus rotundus, the projection of the retina on the tectum, and the termination of centrifugal fibers in the retina.

Received too late for discussion in this review is a publication of the papers given at the Comparative Neurology Conference held under the auspices of the Max Planck Institute at Frankfurt in August, 1965. This book contains a wealth of material on the ontogenetic and the phylogenetic development of the vertebrate telencephalon.

Spinal Cord

The fine structure of the dorsal horn neurons of the rat's spinal cord and the synapses of dorsal root fibers upon them were described. A comparative study was made of the types of synapses in the spinal cords of vertebrates. Synapses with clefts were found in all forms; tight junctions were not present in mammals nor axo-dendritic types in fish. Bodian described 2 major types of synaptic bulbs in the ventral horns of macaques.

Mikeladze studied the termination of afferent fibers in the lumbosacral area of the cat's cord. Following destruction of the dorsal roots, degeneration was observed in all parts of the gray matter, with the greatest rostrocaudal extension in the intermediate zone. Removal of the ventral roots or of the first
2 lumbar chain ganglia produced a small amount of degeneration in the ventral and, more markedly, in the lateral horns. Young\textsuperscript{216} reported the changes occurring in the ventral horn cells of the L\textsubscript{7} segment of the cat's cord following deafferentation accompanied by section of the cord both above and below the segment. In the cat's cord, Prestige\textsuperscript{164} found little evidence for initial collaterals from motor axons in Golgi preparations. The accessory nucleus of the horse has been studied by Flieger.\textsuperscript{59}

Hand,\textsuperscript{80} using the Nauta method, studied the pattern of termination in nucleus gracilis after cutting various lumbosacral dorsal roots in the cat. Marchi or Nauta preparations, following lesions at various levels of the cord in cats and rabbits, indicated that spino-olivary fibers arise from ventral and intermediate areas, particularly in lumbosacral levels. They ascend bilaterally to end in the medial and the dorsal accessory olivary nuclei of both sides.\textsuperscript{136} Ha and Liu\textsuperscript{78} stated that the lateral cervical nucleus in the cat receives collaterals from the dorsal and the ventral spinocerebellar tracts and that these fibers apparently arise from Clarke's nucleus and the large neurons of the dorsal horn.

Following lesions in the interstitial nucleus of Cajal in 3 cats, Nyberg-Hansen\textsuperscript{146} showed, by silver impregnation methods, that fibers from this nucleus descend in the ventral funiculus to terminate in laminae VII and VIII as far as sacral levels of the cord. Barone\textsuperscript{11} found the rubrospinal tract to be very large in the horse and to extend throughout the cord. With Golgi technique, the Scheible\textsuperscript{178} demonstrated that terminals of the lateral corticospinal tract in kittens, rabbits and mice turn at right angles to end in laminae IV through VII. The more dorsal neurons of these laminae have some dendrites directed towards the corticospinal fibers and others toward the substantia gelatinosa. The more ventral neurons receive pyramidal fibers laterally. Verhaart\textsuperscript{205} found a very small pyramidal tract in the dorsal funiculus of Tupaia. Following cortical lesions in the slow loris, Boyd and his associates,\textsuperscript{27} with Nauta-Gygax preparations, followed crossed fibers into the lateral funiculus. These fibers distribute to intermediate and ventral horn areas as far as lumbar levels. Using the Marchi method, Kuru and Iwanaga\textsuperscript{109} traced fibers in the cat from the vesico-relaxer area of the pons to both ventral horns of the lumbosacral cord by way of the medial reticulospinal tract.

**Medulla and Pons**

Ramón-Moliner and Nauta\textsuperscript{170} classified the cells of the brain stem on the basis of their morphological specialization and stated that the central reticular core is composed largely of generalized (isodendritic) neurons, the dendrites of which form continuous overlapping fields. Petrovicky\textsuperscript{155} studied the reticular formation of the guinea pig and prepared comparative tables of the reticular nuclei in 9 orders of mammals. Another study\textsuperscript{146} stated that the magnocellular lateral reticular nucleus receives numerous terminals from tracts of the lateral funiculus. The synapses of the reticular formation were studied by Bogolepov\textsuperscript{24} in the rat.

Walberg\textsuperscript{207} described the fine structure of the normal feline cuneate nucleus.
and the degenerating boutons after destruction of the fasciculus cuneatus or the sensori-motor cortex. Following lesions in the vestibular nuclei, fibers were traced from all of them to one or more of the eye muscle nuclei. The paper should be consulted for details. The organization of the rat’s posterior ventral cochlear nucleus has been described. Two papers have traced the connections of the anterior ventral cochlear nucleus in the rat and cat. In a study of a series of mammals, Harrison and Irvin found that the medial superior olivary nucleus was best developed in those forms which have well-developed eyes and was absent in those which depended on auditory stimuli. The reverse was true for the lateral superior olivary nucleus.

The localization pattern within the facial nucleus of the cat has been demonstrated by Courville. Winckler has not only described a localization pattern in this nucleus for man but has also added a complete discussion of the relations of the facial nerve. Silver preparations showed rubrobulbar fibers terminating in the dorsal and the lateral parts of the facial nucleus and in the dorsal portion of the lateral reticular nucleus in the cat. The central distribution of fibers of the trigeminal, facial, vagal and glossopharyngeal nerves was traced in the monkey by the Nauta technique after cutting the peripheral nerves. Quantitative determinations of cell numbers have been made in the facial and the vestibular nuclei of dog, monkey and man and in the inferior olivary complex of man. The structure of and the functional pattern in the rabbit’s nucleus ambiguus have been analyzed by Lawn.

An interesting case of rather rare unilateral internuclear ophthalmoplegia caused by a lesion of the medial longitudinal fasciculus at trochlear levels was reported by Harrington et al. On the basis of lesions at upper medulla levels, Kerr was unable to confirm the presence of ascending fibers in the feline pyramidal tract in Nauta material. The same author has also published an account of the ultrastructure of the spinal tract of the trigeminal in cats.

**Cerebellum and Midbrain**

A paper dealing with degenerative changes in the cat’s cerebellum following intrinsic and extrinsic lesions needs to be consulted for details. Eager has described the pattern and the mode of termination of corticonuclear fibers following small lesions in the macaque’s cerebellar cortex. Flood and Jansen studied the origin of cerebellofugal fibers by retrograde degeneration after small lesions were placed in the cerebellar peduncles and medulla of cats. The distribution of cerebellofugal fibers was reported for the monkey following small lesions in the cerebellar nuclei.

Several papers have dealt with the connections of the red nucleus. In the cat, Courville found a caudorostral pattern in the red nucleus corresponding to a mediolateral pattern in nucleus interpositus anterior of the cerebellum. Courville and Brodal described rubrocerebellar fibers to nucleus interpositus anterior. In the monkey, Poirier and Bouvier found complete cell loss in the magnocellular part of the red nucleus following interruption of the rubrosegmental spinal path and in the parvocellular portion after destruction of the cen-
NEUROANATOMY

tral tegmental tract. The localization patterns of corticorubral projection\textsuperscript{119} and of corticonigral termination\textsuperscript{172} have been reported for the cat.

Detailed accounts have been published of the efferent connections of the monkey's inferior colliculus\textsuperscript{188} and of the thalamic connections of both inferior and superior colliculi of the rabbit.\textsuperscript{200} No defects in eye movements could be observed\textsuperscript{151} following either unilateral or bilateral removal of the superior colliculus in monkeys or in conjunction with striate cortex lesions.

After placing lesions bilaterally in the substantia nigra of monkeys, Stern\textsuperscript{193} observed a hypokinesia, evidenced by poverty and slowness of movement. Lesions placed in the ventromedial tegmental area of cats\textsuperscript{66} failed to produce postural tremor. Bucy et al.\textsuperscript{30} destroyed the pyramidal tracts, either unilaterally or bilaterally, in monkeys and found the animals could still perform useful movements and did not show the so-called pyramidal syndrome.

\textbf{Diencephalon}

The ultrastructure of the dog's pineal organ has been described by Sano and Mashimo.\textsuperscript{174} Classifications of the dorsal thalamic nuclei, based on various criteria such as the positions of the nuclei and their types of connection, have been discussed by Ajmone-Marsan.\textsuperscript{3} Kaelber\textsuperscript{98} described the nuclear configuration of the diencephalon of the lesser anteater and compared this pattern with that in the greater anteater and in the cat. The photomicrographs are very informative. A short review of the major nuclear groups in the human thalamus has been given by Walker.\textsuperscript{208} The finer structural organization of the thalamic nuclei, as revealed in Golgi material of the brains of young mice and rats and the adult cat, has been described and beautifully illustrated by Scheibel and Scheibel.\textsuperscript{177,179} Also the ultramicroscopic features of synaptic and nonsynaptic areas of various nuclei in the feline dorsal thalamus have been considered and illustrated by micrographs.\textsuperscript{150} Yakovlev and his associates\textsuperscript{215} regarded the medial, the dorsal, the ventroanterior thalamic region (projecting to the orbitoinsular sector), most of the anterior nuclear group and the lateral dorsal nucleus as "limbic nuclei". These were illustrated and certain connections of the limbic cortex discussed. From 14 to 54 days after hemidecortication in cats, varying degrees of retrograde degeneration were found in the thalamic nuclei.\textsuperscript{182} The paratenial and the parafascicular nuclei and the centrum medianum showed no degeneration, and none was found in subthalamic or midbrain nuclei or in the ventral nucleus of the lateral geniculate. In the owl monkey, Jones\textsuperscript{97} described a parvocellular pregeniculate nucleus with two laminae and a lateral geniculate nucleus with 4 layers. Layers 1 and 4 receive axons of contralateral, and layers 2 and 3 axons of ipsilateral, retinal ganglion cells. The lateral geniculate nucleus of the squirrel monkey\textsuperscript{51} has a parvocellular part not evidently laminated and a magnocellular part in which, one year after enucleation of the eye, transneuronal degeneration was evident contralaterally in layers 1, 4 and 6 and bilaterally in layers 2, 3 and 5. Peters and Paley\textsuperscript{153} studied the laminae of the dorsal part of the feline lateral geniculate by the Golgi method and with the electron microscope. They described the finer cellular characteristics and
the ultramicroscopic details of the synapses in relation to the neurons of these layers. From Golgi preparations, Guillery\textsuperscript{74} analyzed the morphological characteristics of 4 classes of cells in the lateral geniculate of the cat. Classes 1 and 2 are present in laminae A and A1, with the cells of Class 1 largely between the two laminae. Class 3 is found in all major laminae, and Class 4 in lamina B. Two types of extrinsic axons can also be identified.

Laties and Sprague\textsuperscript{112} studied, by use of the Nauta-Laidlaw technique, the effect of experimental disruption of the optic system in the cat. They localized specific degenerated areas in the lateral geniculate resulting from focal destruction in various regions of the retina. Evidence for the origin of the nasotemporal division of the kitten's retina was provided by Stone\textsuperscript{194} from retrograde degeneration in the retina following section of one optic tract. The terminal degeneration in the lateral geniculate of the monkey, demonstrable 2 to 84 days following enucleation of one eye, was studied\textsuperscript{68} under the electron microscope. This degeneration was indicated by the disappearance of synaptic vesicles and by bulbous enlargements of the synapses. Using luxol blue and Marchi techniques, Singleton and Peele\textsuperscript{186} determined the projection of degenerated optic tract fibers following the enucleation of one eye in a monkey. In addition to distribution to the homolateral or contralateral dorsal part of the lateral geniculate, preterminals were traced from fine collaterals of the optic tract to the dorsal third of the lateral area in the ventral part of the lateral geniculate. An accessory optic tract, preterminal fibers and fibers of passage to the pretectal nucleus and to the olivary nucleus of the superior colliculus and fine fibers to the optic tectum were identified. They could demonstrate no preterminal degeneration in either the pulvinar or the hypothalamus. Hayhow\textsuperscript{87} has described the basal optic tract in the opossum. Another study\textsuperscript{195} has shown that, in the cat, the retina projects upon the lateral geniculate in a somatotopic pattern, with areas high in the retina projecting anteriorly, those low in the retina posteriorly, median areas of one retina projecting medially and temporal and medial areas laterally in both homolateral and contralateral lateral geniculates. The central area of one retina projects to the medial edge of lamina A contralaterally and lamina A1 ipsilaterally. Sprouting of optic tract fibers in the caudal one half of the ventral part of the lateral geniculate nucleus and in the caudal part of the lateral nucleus of the optic tract and adjacent pretectal nucleus has been described in the rat by Goodman and Horel.\textsuperscript{69} Rabbits and cats in which the visual cortex had been ablated unilaterally and the animals permitted to survive for various periods up to 50 weeks showed species differences in the effects on the dorsal nucleus of the lateral geniculate.\textsuperscript{85} In cats, 70 per cent of the neurons in this thalamic nucleus disappeared by the 7th postoperative day and 26 per cent continued to be normal up to 50 weeks. In the rabbit, 80 per cent were not present by the 3rd postoperative day and 95 per cent were lacking at 4 weeks.

The somatic sensory representation in the basolateral thalamic complex of the Virginia opossum was studied\textsuperscript{165} by mechanically stimulating various skin areas and picking up the impulses from the thalamus by microelectrodes. The
representation of head and face was large, was medial and relatively far dorsal and extended throughout the anteroposterior extent of the basolateral complex on the side opposite stimulation. The impulses from trunk and limbs were located laterally in the basolateral complex contralateral to stimulation, with those from the trunk more ventral and those from the apices of the limbs more dorsal.

According to Mitchell and Kaelber, cats trained to escape an electrical stimulation of the tooth pulp lost the characteristic response when at least half of the centrum medianum-parafascicular area was destroyed. In Golgi series, the cell arrangement in the thalamic nucleus reticularis of various subprimates and primates was regarded as indicating that this nucleus is concerned in the projection of thalamocortical and corticothalamic discharges to various specific and nonspecific thalamic nuclei and is a regulator of thalamic activity. It is said not to provide a final common pathway for the projection of nonspecific impulses directly to the cortex.

The feline intralaminar thalamic nuclei—the central medial, the paracentral and the central lateral—show severe degeneration after removal of the neocortex. The central medial and the paracentral nuclei show degeneration only when the limbic cortex is involved. The central lateral nucleus receives fibers from the parieto-occipital region. Bowsher regarded the center median nucleus as a receptive area for ascending multisynaptic impulses from the gigantocellular reticular nucleus of the lower brain stem (cat). Mehler, from neurological material and experimental studies on monkeys, concluded that the major efferent connection of the centromedian nucleus was with the pulvinar, its major afferent from forebrain areas rostral to it. He considered that it played a critical role in certain dyskinesias.

Employing the Gomori technique, Peterson studied the magnocellular neurosecretory centers in the rat hypothalamus. In addition to the supraoptic and paraventricular nuclei, the anterior commissural, anterior and posterior fornical and the circular nuclei were said to show evidences of neurosecretory functions.

A well-illustrated account of certain fiber connections of the hypothalamus and ventral thalamus of the lemur, Perodicticus, is too long and too detailed to permit useful abstracting. The authors concluded that the hypothalamic connections in this lemur resemble those of carnivores and rodents. Following lesions in the lateral hypothalamic area of rats, a study was made of degenerated paths above and below the lesion. The results agreed in general with those of other observers, but no degenerated fibers to the ventromedial hypothalamic nucleus were found. Cheatham and Matzke described diffusely scattered descending fibers to reticular centers of the brainstem following stereotaxic lesions in the posterior hypothalamus of the monkey. At lower medulla levels, such degenerated fascicles tended to concentrate in relatively close association with the dorsal motor nucleus of the vagus.

McAdam and Kaelber found that, after operations in the region of the ventral medial hypothalamic nucleus, the cats in which both the nucleus and the nearlying fornix were destroyed were savage. Those in which the ventral
medial hypothalamic nucleus was destroyed but the fornix spared were unfriendly but not savage. Crandall, Bahn and Clark found that stimulation of the dorsomedial hypothalamic nucleus led to periodic cornification of the vagina in the non-estrous cat and behavior peculiar to the physiology of estrous and cycling. Lesions prevented the appearance of this cycling although they did not interfere with the effects of estrogen injection.

Sheehan and Kovács have divided the human hypothalamus, in the region between the infundibular stalk and the mammillary body, into a dorsomedial hypothalamic nucleus and an often not sharply delimitable subventricular nucleus which, however, is well defined in women over 50 and may hypertrophy in younger or older individuals if post-partum hypopituitarism develops. A transient hypertrophy of the nucleus is said to be present in women at childbirth but the nucleus returns to the usual size in from 2 to 4 weeks.

By use of the Golgi technique, a tuberohypophyseal tract was demonstrated arising from the medial eminence of the guinea pig. It distributes largely to blood vessels of the infundibular region. Retraction balls have been demonstrated above and below the levels of section of hypothalamo-infundibular fibers in man, monkey, goat and sheep. The neurohypophysis is believed to swell from operative procedures and, being in a confined space, exert pressure on the nerve fibers, squeezing out the axoplasm and producing the retraction balls.

**Telencephalon**

Numerous small cells with fairly simple cytoplasmic structure and 2 types of larger, more specifically differentiated neurons have been identified in the corpus striatum of the rat. Axosomatic and axodendritic synapses and 5 types of synaptic vesicles, differentiable on the basis of their size or from the fine granules on their membranes, were reported. Szteyn has described the general topography and structure of the mammalian basal ganglia, basing his account on ungulate (largely sheep) brains. The connections of the lenticular nucleus of the macaque have recently been reviewed and minor differences from other accounts reported. Nauta demonstrated the origin of the ansa lenticularis from the globus pallidus only. There was a lack of any connections with the zona incerta and the suggestion of a connection to the habenula. No pallidotegmental fibers terminated caudal to the midbrain. Pilleri discussed a possible temporal cortex projection to the nucleus ansae lenticularis. The lateral part of the striatum in the monkey was found to send striatopallidal fibers to the external segment of the globus pallidus. Whether similar relations exist between the medial part of the striatum and the internal part of the globus pallidus was not determined. Druga described differences in the cytology of the dorsal and the ventral parts of the claustrum of the cat.

The isocortex of the sloth is generally comparable to that of the mesocortex and the juxtallocortex of other animals. Layer IV is absent; layer II has large cells. Variations in the cerebral cortex of several domestic animals have been studied and a description of some features of the whale brain discussed and
Several cortical areas of Galago have been described from study of Golgi-Cox and Nissl preparations. Krompecher and Lipâk compared the weight of the brain and the spinal cord in different vertebrates and claim that this is a simple and reliable method for determining cephalization and intelligence. The cortex of rats subjected to an enriched environment (compared with that of controls) shows increase in cortical depth and in glial number. Pregnant rats were placed in low pressure chambers (that simulated altitudes of 18,000 feet). The brains of their offspring were studied microscopically to determine the effects of hypoxia. The postnatal development of neurons in the canine cortex, during the first 10 weeks after birth, was studied by the Cox-Golgi method. The dog does not have an essentially mature neocortex until approximately a month after birth. The most marked dendritic development is between 2 and 4 weeks of life. Pakkenberg estimated the number of nerve cells in the human cortex as 17,560 per mm$^3$ and the total number of cells in the brain as $2.6 \times 10^9$. The relative weight of the gray matter of the human brain is said to be 48 per cent of the total brain weight—a percentage reduced in certain diseases. An interesting discussion of the relations between cortical structure and cybernetics has been presented by Bauer.

Regions of the limbic lobe have been studied using several techniques and various approaches. Material prepared by the Nauta-Laidlaw method, following lesions in the olfactory bulb of the rabbit which did not injure the anterior olfactory nucleus, showed olfactory tract fibers ending in this nucleus, in the olfactory tubercle, the anterior continuation of the hippocampus, the nucleus of the lateral olfactory tract, the prepiriform (1, 2, 3), the perieriamygdaloid (1, 2, part of 3 and 5) and the entorhinal (1, 2, 4) areas and in crossing fibers of the lateral olfactory tract and the anterior commissure. Damage to the anterior olfactory nucleus produced evidence of degeneration in the contralateral olfactory bulb and anterior olfactory nucleus and, ipsilaterally, in neocortical areas adjoining the rhinal fissure, the medial septal nucleus, the anterior continuation of the hippocampus, the lateral preoptic area and the prepiriform cortex. In a lesion involving the olfactory bulb and part of the anterior olfactory nucleus in the cat, Mascitti and Ortega found degeneration in the contralateral pars externa of the anterior olfactory nucleus and in the granular layer and inner parts of the internal plexiform layer of the olfactory bulb, as well as in other regions.

From lesions involving the septal area and the fornix in the squirrel monkey, degenerating fibers were traced into the various parts of the hippocampal formation, including the caudal presubiculum and parasubiculum, and also into rhinal areas. The septal areas of three representative insectivores, the prosimian Galago and two higher primates (Colobus and Cercopithecus) were compared. All septal nuclei increased in the ascending phylogenetic scale except nucleus triangularis septi and the bed nucleus of the anterior commissure. The nucleus of the diagonal band of Broca showed the most marked increase. Using the Nauta-Gygax technique, Raisman studied the effects of stereotaxic lesions of
various limbic areas in the rat brain. The medial septal region receives fibers from the anterior part of the hippocampal area CA1, the intermediate septal zone from the posterior part of CA1 and the lateral septal zone, bilaterally, from hippocampal areas CA3 and CA4. Fibers from the piriform cortex, and possibly from the amygdala and the olfactory tubercle, end on the nucleus of the diagonal band. The medial septal nucleus and the nucleus of the diagonal band project to the dentate gyrus and the hippocampal fields CA3 and CA4. Various other septal connections were described. Raisman, Cowan, and Powell described the terminations of fibers from various limbic areas (septum, indusium griseum, entorhinal area and piriform areas) to portions of the hippocampus and the relay of such fiber systems as the diagonal band and the dorsal fornix to this area. They considered commissural and association fibers to the hippocampus from various cortical areas. The paper traces the terminations to the layers of the hippocampus. The same authors analyzed efferent projections from various hippocampal fields (as to field) and both origins and terminations of the dorsal fornix and the fimbria. They found no extrahippocampal projection from the dentate gyrus. Another study using Nauta-Gygax technique dealt with the projection, in the rabbit, of the dorsal part of the nucleus of the diagonal band to the stratum oriens (possibly its pyramidal cells) at the rostral end of the hippocampus. Through this path the septum is believed to affect the role of the hippocampus in the sensory regulation of the theta system. Five patients believed to have bilateral hippocampal lesions were tested against 20 normal individuals for the effects of the lesion on memory. The immediate memory span of the patients appeared to be equal to that of the normal individuals, but long-term memory was considerably impaired.

The weights of a dissectable model of the macaque amygdala and of its constituent nuclei were determined. The nuclear pattern and the cytological characteristics of the amygdala of the opossum have been described. The myelinoarchitectonic structure of the canine amygdala agrees in general with that accepted for various mammals, although the basal and the basal accessory nuclei are considered together as a basal complex and nucleus subputaminalis is regarded as part of the amygdala. For the fiber connections, the original figures and descriptions must be consulted. Some interesting species differences in behavior followed lesions in the amygdala in newborn animals. Aphagia and adipsia were the outstanding effects of removal of the amygdala in rats. In cats, wild lynxes and monkeys, this procedure increased the docility of the animal, reduced the fear reaction and, in wild animals, led to greater tameness. The cats became hyperphagic and obese. The monkeys showed an increase in oral tendencies and hypersexuality. Allikmets and Ditrikh found that, for about 2 weeks after bilateral destruction of the basal part of the amygdala, rats were especially relaxed and less likely than normal rats to fight.

After hemidecortication of 15 monkeys, demyelinization and gliosis could be followed from the posterior part of the corpus callosum to the “upper crown and band” of the cingulate gyrus. The richness of commissural connections and
the amount of thalamic efferents from the cingulate gyrus were in inverse proportion to each other.

An electron microscope study demonstrated the presence of axodendritic, axoaxonic and relatively sparse axosomatic synapses in the motor area of the rat. The axodendritic synapses were the most numerous. Such terminations were found at the ends or along the sides of the dendrites or on the spines. A single axon may have several synapses along the dendrites or a single dendritic spine may be in synaptic relation with one or several axons.

The medially situated cortex of area 6 (part of a supplementary motor area) was ablated in several monkeys. Aside from some tendon jerks and some inconsistent increases in tonus there were no significant persisting effects. A paper dealing with experimental lesions (up to bicortectomies and complete cerebellectomies) in monkeys has been the basis for discussing the anatomical and the functional interplay between extrapyramidal cortex, basal ganglia and cerebellum. Human cases with comparable involvements have also been studied.

The somatotopic pattern was obtained on the primary sensory cortex of the sloth by Meulders et al. The same observers also located motor, auditory, visual and association cortical areas in this animal. The EEG studies showed patterns comparable to those of other macrosmatic mammals. An interesting paper points out that the size of the excitatory receptive fields of neurons of the feline somatosensory cortex may be increased by direct stimulation of the pyramidal tract.

The myeloarchitecture of the occipital cortex of the dog and of various primates has been reported. From lower to higher primates, the number of radiating bundles per unit area of area 17 decreases but the size of a bundle and its fiber content usually increases although, in the baboon, the bundles are wider than in the chimpanzee. Man, in general, has fewer bundles but more fibers than do other primates. In most primates, a greater number of bundles and more radiating fibers were found in the right than in the left hemisphere.

Retrograde degeneration in the parvocellular part of the medial geniculate in the macaque resulted on ablation of the auditory focal zone. The medial geniculate showed almost complete degeneration if the anterior supratemporal cortical area was ablated also. Lesions involving primary auditory cortices produced “severe and permanent” impairment in the recognition of noise. Growing mice kept in complete darkness for 2 months after birth showed smaller nuclei and less internuclear substance in the auditory cortex than did the control animals. However, if the mice were kept in darkness for 4 months after birth, the nuclei became larger and the internuclear substance increased in amount. “Hypotrophy was succeeded by hypertrophy”.

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CHAPTER 2

General Neurophysiology
(Biochemical Aspects)

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INTRODUCTION

MANY FINE REVIEWS have appeared in the field of neurochemistry, psycho-pharmacology and behavioral sciences in the past two years. Peeters has edited an excellent volume dealing chiefly with the metabolism of proteins and related enzymes under normal and pathological conditions. The Progress in Brain Research Series continues to make its contribution, and the recent volume edited by Himwich and Schade deals with the various parameters of psychopharmacology. Investigations of brain chemistry and biochemical advances made in Russia have been edited by Palladin, and Brozek has reviewed Russian contributions to brain and behaviour. A volume, Amine and Schizophrenia, which discusses current research in this field has been edited by Himwich, Kety and Smythies. Biochemical Aspects of Neurological Disorders has been prepared by Cumings and Kremer. Richter has been the editor of two books, Comparative Neurochemistry and Aspects of Learning and Memory.

DEVELOPING BRAIN

The work on the developing brain continues in several fields in various species of animals. This section will deal only with a fraction of the papers with a biochemical orientation. The ability of the cerebral microsome cell sap system of the rat brain to incorporate C valine suggests that microsomes from young animals have a greater capacity for amino acid incorporation that those from adult. Brain homogenates from young mice incorporated labelled arginine, lysine, phenylalanine, and valine rapidly into acid-insoluble proteins in vitro. With maturation the ability of brain cells to incorporate these labelled amino acids into proteins decreased.

P incorporation into the phospholipid and phosphoprotein of the nerve endings of newborn and adult brain was inhibited when the homogenate was fortified with acetylcholine in vitro. Moreover, the nerve endings incorporated P at a slower rate than the other subcellular fractions. The author suggests that acetylcholine may also exert a similar influence in vivo.

Thyroidectomy in hypothermic rats at 5 days of age caused a reduction in body weight from 20 days of life onwards; at 60 days of age the body weight of these animals was half that of normal controls. Oxygen consumption of cortex
and sub-cortical structures was lowered. In contrast, hypothermia alone stimulated body growth and enhanced oxygen consumption of the brain at 14 and 25 days. Hormones may play a significant role in thermoregulation and other oxidative and metabolic processes which in turn effect the physiological and biochemical maturation of the CNS.\textsuperscript{216}

In positive radial acceleration of rats the favorable influence of hypothermia was absolute and relatively maximal until the 12th day of life. In the adult animal the maximum elevation of resistance is reached under a relatively mild hypothermia.\textsuperscript{215} Dravid and Jilek\textsuperscript{58} found that ligation of the carotid arteries in rats at 25 days of age caused convulsions, with decreased glutamic acid, GABA and aspartic acid in the prosencephalon. The increase of the specific activity of aspartate aminotransferase in rat brain after the 17th day and the shift in the ratio between the pyridoxal and pyridoxamine form of the enzyme may play a part in the concomitant decrease in resistance to anoxia in the maturing rat.\textsuperscript{12}

Timiras and Woolley\textsuperscript{212} reported that brain maturation of rats born and reared at high altitudes was delayed compared to sea level controls. Marked differences were observed in rats reared for 2 generations at high altitudes. GABA, protein, and acetylcholinesterase were lower in high altitude animals; electroconvulsive responses were delayed for 1 to 3 days, possibly due to the increase in carbonic anhydrase activity. The data suggest that faster cellular loss of CO\textsubscript{2} and increased sodium permeability may be related to alterations in the development of neuronal excitability. Acetylcholinesterase studies have also been done by Burdick and Strittmatter\textsuperscript{38} and Krnjevic and Silver.\textsuperscript{121}

Analysis of the free amino acid pool of the developing rat and rabbit brain revealed that only members of the glutamic acid family increased during development, whereas most of the amino acids either decreased or remained constant, the most striking changes being the gradual reduction in the concentrations of taurine and ethanolamine phosphate with a simultaneous increase in glutamic acid. Concentrations of taurine and ethanolamine reached their maximum at 3 days, while the greatest change in the composition of the free amino acid pool occurred at 14 days of age in the rat and 21–30 days in the rabbit. The data exhibited no true species difference with regards to amino acid composition.\textsuperscript{6,7} Numerous papers on changes in free amino acids, protein, RNA, DNA nitrogenous compounds, free nucleotide and inositide content of rat, rabbit and dog brain have also appeared.\textsuperscript{56,57,67,102,142,161,224,230}

The metabolism \textit{in vivo} of C\textsuperscript{14}-L-glutamic acid topically applied was studied in cerebral cortex of kitten and adult cat. The ratios of specific activities of glutamine to that of glutamic acid rose to values significantly greater than 1 after the 3rd postnatal week. The data suggest that the compartmentation of glutamic acid in the cerebral cortex follows a developmental pattern. Two categories of compartmentation can be envisioned, cellular and intracellular. The compartments may consist simply of 2 or more cell types, one of which contains only a low level of glutamate but converts the amino acid readily into glutamine. The other cell type or parts of cells could contain substantial amounts of glutamate and relatively less glutamine with little capacity to make it and
would dilute the isotopic glutamic acid to a great extent. Compartmentation continues to increase during the period of active proliferation of glial cells and beyond the period of neuronal development. In the mature cortex the greatest evidence for compartmentation is obtained from the layers of cortex most dense in neuronal cells. Berl and van Kempen et al. have extended these studies to glutamine synthetase and the enzymes involved in GABA metabolism.

When radioactive glucose was given to 1-day-old mice and the protein-bound amino acids studied, essential and non-essential amino acids were found labelled to the same extent. The incorporation of carbon from uniformly labelled glucose into the essential amino acids in 1-day-old mouse brains is clearly not a reproducible phenomenon for in a recent study 1-day-old minces studied in vitro failed to show any radioactivity in the essential amino acids. The oxidative and glycolytic metabolism of newborn mouse brain was the same as that of adult brain and was very similar to the adult and the 7-day-old mouse brain previously studied by Rafelson et al. In contrast, previous studies with 1-day-old mouse brain showed slower longer-lasting oxygen consumption, glucose utilization and lactate production. Oxygen and glucose consumption and lactate production ceased after periods of 12 to 15 hours in vitro, perhaps due to the differences in amino acid metabolism. It is most likely that this difference in carbohydrate metabolism is the basis of the differences in amino acid metabolism observed between the present and previous work. Oxidation of neutral amino acids fortified in rabbit brain tissue slices have also been carried out by Swaiman and Milstein.

The concentration of polyamines in mouse brain was shown to be higher in prenatal and neonatal life than in the adult, a trend which was even more apparent when the results were calculated on a dry weight basis. A high concentration of spermidine and spermine during the proliferation stage was followed by a drop. Most substances and enzyme activities increased during development, in contrast to the polyamines and to the DNA. Serotonin and 5 HTP decarboxylase activity in newborn guinea pig were 50 and 60 per cent of the adult values respectively, with serotonin attaining a mature level by 9 weeks and decarboxylase by 3 weeks. No sex differences in brain serotonin were recorded in contrast to Kato's work on rats. Similar studies on the rat brain during development have been reported by Bennett and Giarman and Agrawal et al.

A few studies have been made using autoradiography to characterize the incorporation of radioactive lipid precursors into various anatomical parts during maturation. Torvik and Sidman, using various labelled metabolites in the young mouse brain, found that acetate was incorporated into the lipids and serine into proteins and nucleic acids. The most rapid incorporation in lipids took place in nerve cell bodies and the slowest in white matter. Metabolically stable lipids were not detected in nerve cell bodies but were present in white matter and in areas largely free of myelinated fibers, such as the molecular layer of the cerebellum and the striatum of the hippocampus.

The data on young rats injected with acetate 1-C suggest that the palmitate
of the gangliosides and glycerophosphatides is made from acetate, but that the stearate present in these lipids is made by elongation of palmitate. The palmitate used for elongation is not the freshly synthesized acid but rather the acid recently liberated by the breakdown of the complex lipids. Lignocerate also appears to be made by elongation, but it is possible that the stearate of cerebroside is made de novo. The data presented confirm the theory that the precursors of the lipids are incorporated most efficiently during the early stages of myelination, i.e., at about 13 days of age in the rat. The authors suggest, however, that: 1) the brain lipids may be turning over more rapidly at this age, so that the synthetic rate is really higher even though the accumulation rate is unchanged; 2) the body pool of acetate, serine, etc., may be smaller at this age so that the specific activity of the precursor available to the brain is higher; and/or 3) the small molecules may penetrate the blood-brain barrier more readily at this age, thus allowing the brain to get a larger share of building blocks.114

Lipid studies of rat brains from 7 days before birth to 275 days of age showed that ganglioside stearate accumulated steadily during the first 20 days of life, more slowly for the next 32 days, and finally began to decrease. Ganglioside arachidate, on the other hand, accumulated steadily throughout the period. The acids present in glycerophosphatide showed several inversions in ratios, the trend being toward increasing unsaturation and chain length. But galactolipids and cholesterol were deposited at similar rates after 15 days of postnatal life.115

Recent work on the fatty acid components of the brain, especially the gangliosides and the sphingolipids, showed that the conditions used for release of the fatty acids are very important. Variations in the arbitrary conditions may lead to completely different results. Ceramide, which is composed of C18 sphingosines and C18 fatty acids, is a structural feature of the three sphingolipids. In the mature animal, however, the C18 fatty acids diminished to a negligible level in the cerebrosides, and there was at the same time a concomitant decrease in the C18 fatty acid content of the gangliosides and the sphingomyelin.185

Intracranially administered radioactive phosphorus in animals at varying ages is incorporated into the phospholipids and phosphoproteins of the various cellular fractions as determined by density gradient centrifugation. The highest specific activity of the phospholipids and phosphoproteins was between 12 to 15 days post partum. At the age of maximal lipid synthesis the radioactive specific activity of a given phospholipid was similar regardless of the cytoplasmic fraction from which it was derived. The sequence of degradation of the phospholipids during myelinization was phosphatidyl inositide, phosphatidic acid, phosphatidyl serine, phosphatidyl ethanolamine, phosphatidyl choline.2

As in the rat,114 esterified cholesterol in the chicken brain decreases during development, whereas the concentration of free and total cholesterol is almost doubled.83 Cholesterol biosynthesis in the brain of the neonatal rat has been studied by injecting acetate 1-C14 into the peritoneum. The time course of the distribution of C14 activity among the fractions indicated that the zymosterol fraction is a precursor of the desmosterol which in turn is a precursor of cholesterol.97
Bennett et al.\(^\text{23}\) found that light deprivation and blinding caused 5 per cent and 8 per cent loss in the weight of visual cortex and mid-brain, respectively. Kling et al.\(^\text{118}\) have published similar data showing in rats that handling during the first week of life resulted in an increase in acetylcholinesterase activity in neocortex and a decrease in caudate nucleus, whereas light stimulation had a similar effect on enzyme activity in caudate nucleus. These observations suggest that physiological stimulation is required for the development of normal patterns of behavior and for biochemical maturation of CNS.

The consequences of maternal deprivation on the development of rats in their second week of life are increasingly attracting the interest of physiologists and psychologists. Nováková\(^\text{155,157}\) has shown that weaning rats at 15 days of age impairs the normal development of the CNS as far as learning, conditioned reflex and memory are concerned, suggesting that the mediating role the mother plays between the newborn and their environment has significant effects in the modulation of adult behaviour patterns. Such weaning, however, does result in thirst and starvation, since rats weaned the 15th day began to take food and drink only on the 18th day.\(^\text{156}\) It is impossible in such studies to distinguish between the effects of maternal care, starvation, and thirst. The lack of food and water in this period markedly affects the higher nervous activity in adult life, although during the second half of the suckling period there is little histological change in rat brain except myelinization, changes in the size of cell body and nucleus, and development of brain dendrites and synapses.\(^\text{156}\) The effects of undernutrition of rats from the time of weaning to 11 weeks of age can, however, be completely repaired biochemically by unlimited feeding from 11 to 19 weeks of age.\(^\text{56}\)

In vitamin-deficient rats with a chronic lesion in the brain stem, remyelination does occur despite the continuance of the deficiency state. The cell involved has been described but not identified. The process of myelinization, however, was somewhat different from that occurring normally. Apparently remyelination is not restricted to a single pattern and can be accomplished in a number of ways, being dependent upon the geometric features of the lesion as well as other factors.\(^\text{45,167}\)

DNA synthesis in rat cortex ceases when the animal is about 18 days of age. Nuclear and transfer RNA follow a similar pattern. Between 2 and 7 days the total DNA in mouse forebrain increases by 17 per cent. The microsomal and ribosomal RNA increases until the animal reaches 25 grams of body weight and then declines, in association with a change in RNA base composition. The incorporation of C\(_{14}\) orotic acid into the nuclear RNA proceeds at a similar rate in 4-day-old and adult animals. However, there is a lag of about 60 minutes in the young animal during which incorporation into the ribosome fraction proceeds slowly. In adult animals such a lag is not seen.\(^\text{4}\) Corticosterone, given to mice between 2 and 7 days of age, may interfere with some aspects of brain maturation; 1) it reduces brain and body growth proportionally, and 2) the ratios of RNA/DNA and cholesterol/DNA are also reduced.\(^\text{98}\)

The work in irradiation in young animals\(^\text{52,88}\) continues to show that the im-
important factor may be the time of irradiation rather than the dosage, although more severe effects are observed with single than with fractionated exposure.\textsuperscript{108} Animals irradiated 17 days postconception showed a marked deficit in negotiating bridge and parallel rod tasks in adult life. In this group it is not surprising to find many neuromorphological disorganizations. Gross cerebellar changes were not seen and the animals exposed at 1 day had a smaller cerebellum than normal but had normal locomotor capacity.\textsuperscript{133}

In newborn and adult rats subjected to irradiation with x-rays (300 to 500 r) to the head, brain LDH (lactic acid dehydrogenase) showed an accelerated maturation of the LDH isoenzymic composite in the developing brain, but no change occurred in the adult. X-ray treatment of newborn rats caused a decrease in the affinity of LDH for pyruvate and a late shift in the acidity of the pH optimum for pyruvate reduction. The same decrease in the affinity for pyruvate, which was followed by a slow return to the normal values, was shown in the brains of adult animals.\textsuperscript{31}

At 11 days post-irradiation of 3-day-old rats with 2,000 r of soft x-ray, there was a lack of myelinization in brain and spinal cord and a decreased number of neuroglia in the irradiated area. At 17 days there was a slight but detectable increase in the amount of myelin and neuroglia, and a rapid return to normal began about 23 days after irradiation, so that by 27 days some of the spinal cords appeared to be normal. By 33 days all of the spinal cords became normal in appearance. The recovery depended upon at least two different but related factors: 1) the ability of the neuroglia to divide and make up for the radiation-induced deficit, and 2) the integrity of the vascular system so as to create the proper tissue environment within which division of neuroglia and subsequent myelinogenesis could take place.\textsuperscript{78}

In early stages of development it is impossible to differentiate by electron-microscopy neuroblasts from glioblasts.\textsuperscript{146} In late prenatal stages glioblasts become recognizable because of their ultrastructure and the over-all structure of the nucleus. These observations indicate that migrating cells have the same characteristics as embryonic ones and it is only when they reach a permanent topographical position that cytological differentiation commences. However, they do not support the view that glioblast formation begins only when neuroblast production is ended.\textsuperscript{69,78,71} Using the same technique, Berry and Rogers\textsuperscript{27} and Fujita\textsuperscript{70} found that, in contrast to the observations of Tilney,\textsuperscript{211} the superficial cells are the last to be populated by the migratory neuroblasts formed in the ependymal layer. These data confirm the results of Angevine and Sidman\textsuperscript{14} on the mouse. Further investigation of histological preparations of fresh material showed that the ependymal cells retained connections with both the ventricular and the pial surfaces of the cortex throughout fetal life. The long processes of these cells were directed towards the pial surface and appeared to provide a channel along the cortex along which newly formed neuroblasts migrated. Not until the neuroblasts reached the pial surface did they separate from the ependymal processes and begin to differentiate.

In rats injected with thymidine-H\textsuperscript{3} at 13 days and killed at times varying
from 6 hours to 60 days after injection, the labelled precursor was studied autoradiographically. From the data obtained Altman concluded that many of the cells in the fibrous regions of the brain are migratory ones, and as the new cells arrived the older ones departed. In the gray matter of the cortex, regional cell proliferation was low at 13 days, but there was a steady gain in the proportion of labelled cells with the increase in survival time. It is concluded that the cells which are destined to reach the cortex form around the lateral ventricle and utilize white matter and corpus callosum as a migratory pathway.

**Brain Composition and Metabolism**

The high concentration of N-acetylaspartic acid (NAA) in CNS, the presence of a converting enzyme in the soluble portion, plus the metabolic inertness of this compound lend further support for an anion role of NAA originally proposed by Tallan. Kakimoto and his coworkers have also characterized and isolated a number of dipeptides chiefly of glutamic acid origin from bovine brain. The physiological or metabolic significance of these peptides in CNS remains unknown.

Marks and Lajtha have successfully separated and partially purified acidic and neutral brain proteinases from rat brain. Brain proteinase activity is lower than kidney, spleen and liver, but higher than muscle. Among the various subcellular fractions studied, the highest activity was recorded in mitochondria. Acidic proteinase concentration is especially high in lysosome rich fractions, while neutral proteinase activity chiefly resides in mitochondrial sub-fractions and nerve-ending particles. In addition, acid proteinases are more stable than neutral proteinases. The authors suggested a possible role for proteinases in the modification of existing proteins in the brain.

Striking regional differences in the amino acid pool of the rat brain have been reported. GABA appears to dominate the pool in subcortical areas and glutamic acid in cortical areas. GABA has been detected in human kidney suggesting that it may not be solely confined to nervous tissue in human beings as it appears to be in animals.

Van Gelder has devised an ingenious histochemical method to localize the pathways by which GABA is known to be utilized in nervous tissue. The method, which is specific and pH dependent, requires the presence of all the three components, GABA, NAD, and α-oxoglutarate, to give positive formazan reaction with β-alanine, aspartate, glutamate and glycine. The reaction is also inhibited by hydroxylamine, aminooxyacetic acid and semicarbazide, which are also known to inhibit the enzyme GABA-transaminase in vivo. Van Gelder also made a comparative study of GABA metabolism in mouse and rabbit brain. The results obtained suggest that the formazan reaction was more pronounced in mouse tissue than in rabbit except in cerebellar tissue, in which the rate is equal. In addition, the cerebellum exhibited the fastest reaction rate in both species of all the anatomical areas studied. The author feels that lower transaminase dehydrogenase activity in rabbit appears to be mainly due to a dilution of positively reacting cells with neurons and fibers which do not metabolize...
GABA. The possible increase in myelinated fibers per unit area in rabbit CNS, relative to mouse, might account for the differences. The author has also been able to show by this method that not only cell bodies of the neurons but also their axons metabolize GABA.

Roberts and his colleagues\textsuperscript{122} studied the time course changes in GABA after administration of aminooxyacetic acid (AOAA) and found that increase in GABA as a function of time was biphasic in the mouse brain. No change in ATP was noted. Susceptibility to electroshock seizures was normal at the time when GABA concentration was highest. During 1–5 hours after AOAA administration, a correlation between decrease in susceptibility and increase in GABA content was found. The authors suggested that increase in GABA and changes in seizure susceptibility are unrelated phenomena after administration of this drug. On the other hand glutamic acid, from which GABA is formed in CNS, and which is known to be an excitatory factor in the brain, did not increase after AOAA.

De Robertis and his coworkers\textsuperscript{186} have extended their study of subcellular distribution of 8 enzyme systems chiefly involved in the metabolism of glutamic acid, glutamine, GABA, aspartic acid and alanine. GDH was found to be strictly mitochondrial and localized within the matrix, both aspartate aminotransferase and alanine aminotransferase in both soluble and mitochondrial fractions. GAD is a soluble enzyme chiefly concentrated in those nerve endings which are poor in ACh synaptic endings, whereas the distribution of GABA-AT and SSADH is similar to GDH. Under isotonic conditions GABA, glutamine, $\beta$-alanine and $\alpha$-oxoglutarate penetrate the cell freely, whereas entry of glutamic and aspartic acid is selectively restricted by the nerve endings and mitochondrial membranes. The most interesting finding is the presence of subcompartments within the nerve endings and perikaryan. The nerve ending contains the following compartments: axoplasm, mitochondrial and synaptic vesicles, whereas perikaryan contains neuroplasm, mitochondrial and endoplasmic reticulum.

Whittaker\textsuperscript{144} has extended his study of subcellular distribution of possible synaptic transmitter substances in neural tissue to glutamic acid and GABA in order to evaluate and obtain information regarding the distribution of these substances within morphologically defined subcellular compartments. The amino acid distribution of the members of the glutamic acid family in the subcellular fractions was similar to that of the soluble cytoplasmic markers such as lactate dehydrogenase and potassium, and no specific localization of amino acids occurred in the fraction rich in isolated presynaptic nerve terminals (see also review by Whittaker\textsuperscript{229}).

Effects of protein deficiency\textsuperscript{131,148,174} on behavioral and biochemical changes in the rat have been investigated by putting rats of 1, 6 and 12 months of age on high and low protein diets for 4 months. Significant changes were found in the protein-deficient animals both in behavior and biochemical constituents. These changes were apparent in all 3 groups, but were more pronounced in the younger age group performing in the discrimination learning test. Low levels of free alanine, aspartic acid and GABA, as well as the enzymes involved in the synthesis and metabolism of glutamic acid, were recorded. The changes
were only partially reversed by replenishing the protein in the diet for a period of 2 months.\textsuperscript{174}

Protein synthesis in CNS is extremely sensitive to changes in the internal environment. If the level of amino acids in plasma or brain was altered, either by variation in diet or by the injection of large doses of amino acids, changes in cerebral protein turnover occurred. The rate of incorporation of amino acid into cerebral ribonucleoprotein particles can be markedly affected by ionic concentration, amino acids, "pH-enzymes" and energy-yielding substances. Moreover, cerebral ribosome possessed unusual physico-chemical characteristics which may be related to their unique biological properties (see review by Datta\textsuperscript{54}). The sensitivity of the brain protein synthesizing systems to alterations in the intracellular environment may represent an adaptive response to the operation of the brain barrier system and may contribute to specialized function in the brain. These observations also suggest that the brain protein synthesizing system has unique structural characteristics.\textsuperscript{181,182}

Lowry and coworkers\textsuperscript{76} found a significant decrease in glycogen content of cerebral cortex, cerebellar cortex, medulla and Ammon's horn of the mouse brain due to anaesthesia. Deeper anaesthesia caused an increase and decrease in glucose and lactate respectively, accompanied by diminished utilization of ATP and P-creatine. Changes in the metabolites with ischemia suggest that metabolic rates are equal in cells from cerebral cortex, cerebellum and medulla but are substantially lower in Ammon's horn cells. Histochemical determination of the inorganic phosphate in all the 3 layers of cerebellum suggest that the rate of metabolism for cerebellar white matter is comparable to that of the cell bodies and dendrites.

Suggestive evidence has been available that brain may synthesize serotonin from tryptophan from studies both in vitro and in vivo.\textsuperscript{72} Consolo et al.\textsuperscript{90} have provided conclusive evidence that tryptophan injected intracerebrally is hydroxylated in the rat brain and, therefore, the brain does not depend on other tissues for synthesis of 5-HT. The authors feel that the hydroxylation in the brain is a local phenomenon and does not occur in other tissue, since relatively high doses of TP given intraperitoneally to rats are unable to change the level of brain 5-HT. It should be noted, however, that a MAOI did not accompany the intraperitoneal injections and so 5-HT that was formed may have been destroyed.

Klee and Sokoloff\textsuperscript{117} have furnished evidence that thyroxin has a selective action in stimulating protein synthesis in the brains of young animals, suggesting that thyroxin stimulates protein synthesis by increasing the rate of uptake of RNA-bound amino acids by ribosomes. However, the validity of this interpretation has been questioned by Tata and Widnell,\textsuperscript{207} who found that the thyroid hormone stimulates the activity of DNA-dependent RNA polymerase. Since this effect of thyroxin preceded the increased incorporation of amino acids into protein, they concluded that this hormone promotes the formation of messenger RNA.

During convulsions produced by several techniques, pyridoxal phosphate
content of the brain was reduced to between 40 to 50 per cent of the normal control value with a concomitant increase in the content of pyruvic acid and little change in pyridoxal. These data suggest that hydrazides exert their effect on brain by inactivating pyridoxal through a carbonyl-trapping reaction, thus limiting the formation of pyridoxal phosphate. Such studies also lend support to the observations of earlier workers who suggested that disturbances in the metabolism of amino acids with hydrazide administration may be due to the reduction in the level of pyridoxal phosphate, which directly affects the enzyme systems in which it serves as a prosthetic group. Amphetamine and iproniazid also caused a diminution of the cerebral pyridoxal phosphate level. The rapid effects of convulsive drugs and the reversible action of amphetamine show unexpectedly high rates of renewal of pyridoxal phosphate in the brain. These observations also are in keeping with very active pyridoxal phosphokinase with a relatively low pyridoxal phosphate content in brain.

Lesions produced in the cortex increase the AChE activity in the medial geniculate body by 17 per cent as compared to lesions of the brachium of the inferior colliculus combined with cortical lesions. The AChE activity decreased 27 per cent from the control value, while BChE was higher in experimental groups in both cases with an average increase of 48 per cent. The data obtained suggest that the greatest concentration of AChE is in the pre-synaptic axon tips. Also the fact that the combined lesions did not cause complete depletion of enzyme activity indicates that there is AChE either in internuncial or other neurons unaffected by the lesions, or in the glial or vascular tissue. The increase in BChE in the medial geniculate body following either lesions of post-synaptic neurons (cortex) alone or combined with presynaptic lesions (brachium) indicates that this enzyme must be mainly in the glial cell-capillary wall portion of tissue, or else in neural tissue not damaged by the lesions.

**Human Brain**

The lipids of brain are so many and so varied that they form an apparently inexhaustable field of research. The sphingomyelins have been studied extensively by the Swedish workers Stållberg-Stenhagen and Svennerholm. In the frontal lobe from the normal brain the proportion of stearic acid in simple myelin (18:0) decreases with increasing age from about 80 per cent in the newborn to about 40 per cent in the adult, whereas the C_{22}-C_{26} acids increase from 10 to 50 per cent. In demyelinating disease or malformation of the nervous system the content of the C_{22}-C_{26} acids is smaller than in the normal brain. In healthy brains the 18:0 fatty acids constitute at least two thirds of the sphingomyelin fatty acids at all stages of development, whereas in mature brain the C_{22}-C_{26} acids represent two thirds of the acids present. The sphingomyelin in cytoplasm as compared to that of the myelin sheath shows striking differences in the chain-lengths of the fatty acids. In patients dying with demyelination the deviation from the normal pattern was more pronounced in cerebral white matter than in the total brain.

The sphingomyelins of the spinal medulla have a fatty acid pattern similar
to that of the adult brain but contain higher amounts of 18:0 and 24:1. The pattern in the peripheral nerves is distinctly different with less 18:0 than in cerebral white matter. The sphingomyelins from gray matter are also quite different from those in the white. This statement is the basis for the conclusion that there is a difference between the sphingomyelin of cytoplasm and that of the myelin sheath. These authors conclude, in contrast to O'Brien, that there is no evidence for a primary failure in the elongation of fatty acids in leukodystrophy. The changes in quotient observed between fatty acids with 14 to 20 carbons and those with 22 to 26 carbons can be completely explained by the changed ratio in these fatty acids between axoplasmic tissue and myelin.

Suzuki has studied the regional distribution of ganglioside in the human brain in both young and adults. Symmetrically lateral patterns which are consistent from one brain to another are shown. One of the disialogangliosides (G₃) shows distinct developmental changes in both man and rats. The pattern suggests that ganglioside metabolism is closely related to the process of myelination. The G₃ predominance in the young human brain, but not in the fetal brain, led Svennerholm to suggest that this was the result of anoxia. Suzuki, on the other hand, has found G₃ predominance in the brain of a child delivered by caesarian section. However, it is possible this brain was also affected by anoxia. The intralaminar distribution of cerebrosides in the human isocortex as determined by microchemistry support the use of these lipids as a referent for quantitative histochemical determination of myelinated fibers.

The principal lipid composition in normal human brain in gray matter, white matter and myelin have been thoroughly studied by O'Brien and Sampson. The infant and adult brain differ not only in the total mass of cerebral white matter but also in the myelin content of the white matter. The difference between the adult and the baby as far as myelin is concerned is in quantity rather than in quality. Since myelin is “chemically mature” at an early age it is tempting to predict that a specific chemical composition must be reached in the cells before myelin can be formed. The extra-myelin portion of white matter had a lipid composition similar to myelin but differing markedly from gray matter. The myelin composition of the human brain is similar to that in other species. If a molecular weight of 28,000 for myelin protein(s) can be calculated, then for each protein molecule in human myelin there are 186 lipid molecules, 111 of which are polar lipids and 75 of which are cholesterol. The molar ratio of protein amino acids to polar lipids in human myelin is 2.38 to 1.

In the human brain the percentages of 20:0 and 21:1 fatty acids increased with age. In the most immature brains the majority of lipid hexose was in the form of glycolipids, which are more polar than cerebrosides and sulfatides and which have tentatively been identified as hematosides and globosides. With maturation, cerebrosides and sulfatides increased progressively, the amounts of the more polar glycolipids remaining constant in relation to the total lipid content of tissue. Two cerebrosides and sulfatides are present in the central nervous system, the first of which is present in the brain before the onset of extensive myelination. It consists principally of 16:0, 18:0 and 18:1 with very long-chain
and hydroxy fatty acids as relatively minor components and is part of the extra-myelin cerebrosides and sulfatides. The second type appears with myelination and consists of the very long-chain and hydroxy fatty acids characteristic of the adult white matter. This type constitutes the overwhelmingly greater portion of cerebrosides and sulfatides. In gray matter, mainly as a consequence of the presence of radially oriented myelinated fibers, it also forms the major portion of the cerebroside-sulfatide fraction. The presence of these 2 types of cerebrosides and sulfatides fits well with the current theories of fatty acids biosynthesis. The formation of very long-chain fatty acids requires two systems: the first to synthesize the "primary" fatty acid (mainly 16:0 or 18:0), the second to lengthen the chain by the addition of acetate units. It is likely that while the first system is active in the immature brain the second does not function until the time that myelin is deposited.

In man the sphingosine portion of brain gangliosides changes from almost exclusively \( C_{18} \) at birth to nearly equal quantities of \( C_{18} \) and \( C_{20} \). In the sphingosine of the cerebrosides and sphingomyelin the \( C_{18} \) variety remains at all stages of brain growth. The gangliosides of the Tay-Sachs brain have a high \( C_{18} \) fatty acid and \( C_{18} \) sphingosine content typical of those of the fetal brain. This chemical difference may yield a clue to the pathogenesis of Tay-Sachs disease.

Unlike the free amino acid pool of the brain, a preponderance of glutamic acid and aspartic acid was not observed in protein hydrolysate of cerebral gray and white matter of human brain. Auditore and his colleagues have detected and characterized 2 peptides of glutamic acid origin of unknown physiological function.

The enzymatic content of senile plaques in cases of senile dementia or arteriosclerotic dementia and, in one case, of Alzheimer's disease have been investigated with histochemistry. Except for the central deposition of granular material there was an increase in dehydrogenases, in cytochrome oxidase and in NAD-diaphorase but no increase for monoamine oxidase or for glucose-6-phosphatase dehydrogenase activity. Acid phosphatase activity was also increased and was extremely strong in the microglia invading the plaques. The acid phosphatase activity increased in the central deposition of granular material, in contrast to the oxidative enzymes. Alkaline phosphatase and the cholinesterases are increased in senile plaques, but are dependent on the normal pre-existing pattern of enzyme distributions—in other words, regions which normally lack enzymes do not show their presence in the plaque.

Homovanillic acid (HVA) in the human brain is found in the highest concentration in the neostriatum. This is not surprising, since this area is rich in dopamine (DA) and it is known that HVA is the end product of dopamine metabolism. HVA is also present in the substantia nigra. The presence of HVA in the globus pallidus, which does not contain dopamine, may be due to the presence of neurons with an intimate connection to the dopaminergic nerves of the neostriatum. In other parts of the brain lacking DA, HVA may be formed as a by-product of noradrenaline (NA) metabolism. One way to explain HVA content of parts low in DA and NA would be to assume the occurrence of an
unknown substance which also has HVA as an end metabolite. In Parkinsonism all the samples showed low values and no HVA could be detected in the mesencephalon. Patients with advanced dementia senilis and with disturbances of motor functions appeared to have low HVA values in the neostriatum. Furthermore, it seemed that the HVA values correlated better with the intensity of the symptoms and reduction of motor function than with the age of the patients.\textsuperscript{82}

**MENTAL DEFICIENCY**

Much biochemical and electron microscopy data have accumulated on the various mental deficiency states in the past 2 years, but space does not permit a detailed discussion of the work. The current work on lipidosis is represented by work on gargoylism,\textsuperscript{10,80,129} Tay Sachs,\textsuperscript{3,80,129,187} juvenile lipidosis,\textsuperscript{10,80} Alzheimer's disease,\textsuperscript{44,199} Jakob-Creutzfeldt disease,\textsuperscript{119} systemic infantile lipidosis,\textsuperscript{80,129} multiple sclerosis,\textsuperscript{44,202,209} the amaurotic idiocies,\textsuperscript{120,202} Gaucher's disease,\textsuperscript{120,202} Niemann-Pick's disease,\textsuperscript{82,33,120} Schilders disease,\textsuperscript{154} and Pelizaeus-Merzbacher disease.\textsuperscript{77}

The demonstration of the genetic defect in mongolism has sparked a number of metabolic studies.\textsuperscript{21,62,113,152,225} The metabolic types of mental deficiency have been reviewed by Garrod\textsuperscript{74} and Hsia.\textsuperscript{99} Maple sugar disease is one that is beginning to excite interest\textsuperscript{54} as is also homocystinuria.\textsuperscript{59,76,93,112,127,128,164,165,194,228}

Phenylketonuria continues to escape an explanation of the reason for the accompanying mental deficiency. Investigations in children with PKU range from studies of motor conduction velocities\textsuperscript{73} to studies of cerebral lipids\textsuperscript{148} and the myelin sheath,\textsuperscript{141} of bone growth and development,\textsuperscript{47,65} of EEG recordings\textsuperscript{46,135} and of tryptophan transport.\textsuperscript{232} Animal studies have also been undertaken in rats,\textsuperscript{84,40,79,91,166,168,210,233} guinea pigs,\textsuperscript{105} monkeys,\textsuperscript{226} dogs,\textsuperscript{41,95} and in tissue culture\textsuperscript{184} in the hope of clarifying the problem. The whole subject of the value of animal studies has been reviewed by Karrer and Cahilly.\textsuperscript{110}

**Edema**

The production of edema in the brain has proved a useful tool not only for the classification of cerebral edema in patients but also for studies of the blood-brain barrier. Many means of producing edema are available; however, the changes are very similar irrespective of the method used.

In experimental cerebral edema produced in rats by local extradural freezing with solid carbon dioxide, the changes in ultrastructure were limited to the frozen hemisphere.\textsuperscript{130} Abnormalities, including swelling of the astrocytes and their processes, enlargement of extracellular space in white matter and a numerical increase of pinocytotic vesicles in the blood capillaries adjacent to the lesion, could be observed within 6 hours after the injury and reached their peak in 24 to 48 hours. Ferritin administered intravenously was found in the vesicles. The uptake of ferritin was greatest near the lesion and decreased in linear proportion with the distance from the injury. These findings demonstrate an increase in the permeability of the blood-brain barrier in the area of the lesion.
In cerebral edema induced in rabbits by means of triethyl tin sulfate (TET), clinical improvement followed the simultaneous administration of steroids with the TET. Biochemical changes, however, occurred both in the animals receiving corticosteroids and those receiving TET alone. The water content in the group receiving therapy fell 36.7 per cent as compared to 15.6 per cent in those not receiving therapy. If the ultrastructure of the white matter edema of the TET animals receiving corticosteroids is compared with that of animals receiving only TET the difference is probably a quantitative rather than a qualitative one.

Apparently there is a marked dichotomy in edema in gray and white matter. In edema associated with a metastatic intracerebral tumor in the rabbit, the edema within the gray matter was primarily intracellular. The glial processes were distended with rupture of glial membranes in some areas. The water content, however, was not significantly increased as compared to gray matter at some distance from the tumor or to gray matter from control animals. The molar NA/K ratio and S\(^{35}\)O\(_4\) were increased slightly. Edema of the gray matter irrespective of its cause showed little change in the extracellular space until a late stage. In white matter the edema was much more pronounced. In the deep compact white matter adjacent to the tumor the edema was clearly extracellular. The water content and molar NA/K ratio were also increased as well as the S\(^{35}\)O\(_4\). These changes correlated with the electron microscopic picture. In white matter there is a simple relation between the morphologic and biochemical findings almost irrespective of the type of edema produced. These include an increase in water and electrolytes even in white matter distant from the tumor, indicating that there is probably a spread of the edema through the densely myelinated tracts prior to the ultrastructural changes. The demonstration by Gonatas and his colleagues and by Klatzo and his colleagues, suggesting that there is a greater width of extracellular space in white matter than in gray, could explain some of these findings.

In the shark brain when edema is produced by electric coagulation the gray matter reacts with swelling of the glial cells. Extracellular fluid accumulates in areas where myelin fibers are crowded. The electron microscopical studies indicate that changes in the capillary and pericapillary structures following this injury result in a reduction of the blood-brain barrier. This paper is of special interest because it discusses the relation between the molecular structure of the brain of the shark as compared to mammals.

Van Harreveld has shown that after intravenous infusion of distilled water (up to 20 per cent of body weight) the water content of the rabbit brain was increased by about 10 per cent, with a loss of sodium and of chloride but not of potassium. A decrease in water content (about 18 per cent) was found after the injection of 50 per cent glucose (5 per cent of body weight) in mice. It has been shown in both hydrated and dehydrated brains that sodium and chloride appeared to be lost from the extracellular space but potassium was little affected. Electron micrographs did not show any increase in extracellular space in
the hydrated animals as compared to the normal. Asphyxia caused a reduction of extracellular space.

The degree of generalized cerebral edema may be estimated by measuring wet/dry brain weight ratios. Since the increasing edema is accompanied by increasing cerebral impedance, the latter can be used as an indicator of the moment-to-moment development of the edema. In the deeply anaesthetized monkey the 2 components of the normal EEG, i.e., the "barbiturate bursts" and the paroxysmal delta activity, can be separated by the use of edema produced by infusions of distilled water. Increasing cerebral edema initially increases burst activity, but subsequently reduces it to below normal levels and may abolish it completely. The delta activity shows a gradual reduction in amplitude and incidence, and there is an increase of the "flat" silent periods of the record. Control infusions of the isotonic glucose solutions, which cause equivalent electrolyte dilutions, fail to produce either edema or comparable EEG or impedance changes.

In rabbits with cerebral edema produced by the extradural or subdural placement of psyllium seed and treated with glucosteroids, there was an actual reduction of the amount of structural abnormalities. The authors suggest that the transport system for water and electrolytes across the capillary-glial interface may be disturbed by the edema and that glucosteroids prevent this derangement.

Blood-Brain Barrier

Van Harreveld, who on the basis of much experience in many experimental situations has maintained that the extracellular space of the brain is larger than is shown by conventional electron microscopy studies (1962) has succeeded in a series of elegant experiments in showing that asphyxia of even 8 minutes duration reduces the extracellular space appreciably. If by an ingenious method of freeze-substitution, tissue was frozen within 30 seconds of circulatory arrest, appreciable extracellular space showed between the axons of the granular layer cells. This experiment, although it requires confirmation by other workers, reopens the problem of the extracellular space in the brain.

The problem of the blood-brain barrier has been further explored by Van Gelder and his data suggest that for GABA this barrier may be the high transaminase-dehydrogenase activity in the ependymal cells lining the cerebrospinal fluid spaces and the muscular layer in the walls of blood vessels. If transaminase-dehydrogenase activity is diminished, GABA does penetrate into the nervous system of rabbits and mice.

In order to evaluate the use of the dye test for post mortem studies in man, the blood-brain barrier in rabbits was studied in vivo, post mortem, and after barrier injury with mercurial ions or other substances administered via the internal carotid artery. The staining of the brain tissue and of the choroid plexus showed essentially a similar pattern in all series. The most conspicuous difference was noticed in the damaged vessel walls, which stained markedly on post mortem but not on intravital dye injection. When the barrier had been
damaged in vivo small droplets stained with trypan blue or hyalin formations were seen perivascularly or within the walls of the damaged vessels. The droplets appeared to contain polysaccharides.36

Air embolisms in pial and brain vessels were studied in rabbits also as a means of following the effects of post mortem conditions on the blood-brain barrier. Air embolism for 6 minutes or more produced blood-brain barrier damage, with trypan blue staining the arterial wall and also the brain tissue. If the air embolism was less than a half minute in duration the staining was regularly restricted to the vessel walls.85

The blood-brain barrier may be altered by various means, some physiological and other pathological. The relation of thyroid function to brain permeability to various labelled substances in rats demonstrated that the hyperthyroid brain was more permeable to sucrose and to sulphate, with a decrease in water content. In both hyperthyroidism and myxedema, brain sodium content and space were increased, while the rates of entry of sodium varied directly with the thyroid activity. In the hyperthyroid animal, in addition, the entry of potassium was decreased. The deranged sodium and potassium exchange of the hyperthyroid brain suggest some inhibition of the sodium-potassium pump.176

The simultaneous injection of intravital dyes and EEG recording were applied in rabbits with cold-induced cerebral lesions. A structure deranging lesion produced a concomitant blood-brain barrier alteration. Spikes in the EEG tracing seemed to accompany an increase in the penetration of the dye. The blood-brain barrier damage lasted for 3 to 4 days, with a tendency after that time to restitution of barrier function.64

Evidence accumulated by Pollay169 indicates that the active transport of thiocyanate out of the cerebrospinal fluid into the blood170 is responsible for maintaining the observed concentration gradient between brain and cerebrospinal fluid which does not allow thiocyanate in plasma and brain water to reach an equilibrium. If the effectiveness of this transport process is altered by various means, such as saturation, competitive inhibition or inhibiting cellular respiration, there is no net flux between blood-brain and cerebrospinal fluid compartment. As a consequence a more accurate estimation of thiocyanate space is possible. In other words, when the concentration of thiocyanate in the blood is high, there is no transport between the compartment and an equilibrium is reached between blood and brain and an accurate determination of thiocyanate distribution volume in brain can be accurately determined.

The transfer of penicillin between blood and cerebrospinal fluid suggests a transport system close to the CSF, presumably in the choroid plexus, which actively transports organic acids from the CSF and is analogous in function to the proximal renal tubule. It differs, however, from the latter in that it is not augmented by the intracisternal injection of sodium acetate nor could a probenecide effect on the transport of uric acid be demonstrated. Probenecide prohibits protein binding in sera, and thus achieves higher CSF levels by raising the blood level. It also inhibits the active transport of penicillin from
CSF and increases the diffusible penicillin in plasma by competing for binding to serum protein.\textsuperscript{63}

L-DOPA and dopamine penetrate into the capillary walls of the mouse brain, as demonstrated both by biochemical determinations and histochemical localization of the monoamines and their precursors. The walls contain dopa decarboxylase and MAOI which impede the further passage of L-DOPA into the brain. None of the compounds pass into the endothelial lining of noncapillary intracerebral vessels although passage occurs in peripheral tissues as well as in those brain areas known to be outside the blood-brain barrier.\textsuperscript{28}

Filtration and reflection coefficients of the rabbit blood-brain barrier have been studied by making the plasma hypertonic with various substances, with an osmotic loss of water from the central nervous system to the plasma. The reflection coefficients so obtained for formamide, urea, glucose, sucrose and raffinose were used to estimate an effective pore radius of 7 to 9Å for the blood-brain barrier.\textsuperscript{61}

The blood-brain barrier in the optic nerve has been studied \textit{in vitro} by following the penetration of diaminoacridines administered in non-toxic doses and detected by fluorescence. Although diaminoacridine concentration of 10^{-6}M or higher in blood failed to penetrate the brain, fluorescence was found in the dura mater of optic nerve, all orbital and dural vessel walls, the choroid, the sclera and Kuhnt's tissue, but not the optic nerve. Similar concentrations in cerebrospinal fluid produced fluorescence in optic nerve vessels and tissues including the endothelium and mesothelium, but not in the retina or vitreous humor. In the vitreous humor diaminoacridines showed fluorescence in the retina and optic nerve tissues but no further in the optic nerve. From these data the author concluded that there is a blood-optic nerve barrier located in the mesothelium lining, the inner dural surface, in pial and optic nerve vessels, endothelium and Kuhnt's tissue. There is a one-way permeability into the endothelium and mesothelium and a vitreous-optic nerve barrier which works both ways.\textsuperscript{184}

Angel et al.\textsuperscript{13} measured the interaction of the effects of trypan red and electroconvulsive shock, as reflected by alterations in the permeability of the blood-brain barrier to cocaine and the retention of a previously learned behavioral response. If a rat is subjected to one electroconvulsive shock per day for 12 days, an increase in blood-brain permeability to cocaine occurs 6 hours after the last shock. But within 24 hours this permeability is lost. If the animal receives 12 electroshocks at 12-hour intervals, a sustained increase is evident after the last electroshock for at least 144 hours. If, however, animals are pretreated with trypan red, this pretreatment prevents the effects of electroshock on the blood-brain barrier. These data extend the original observation of Aird\textsuperscript{9} on the protective effect of trypan red on the blood-brain barrier. In this study the effect of trypan red is accompanied by a parallel protective effect on a learned mechanism.

The blood-brain barrier has been investigated in goldfish using the injection
of various dyes. Apparently the barrier is quite similar to that in the mammal in being destroyed by alcohol or stab wounds. However, the thiocyanate space was significantly larger than the chloride space, leading the authors to suggest that there are significant differences between the blood-brain barrier mechanism of bony fishes and of mammals. The distribution of thiocyanate in the brain, however, may also be dependent upon other physiological mechanisms and not be entirely a function of the blood-brain barrier.

An experimental model has been developed using bilirubin labelled with radioactive carbon in newborn jaundice (Gunn) rats. Significant radioactivity was found only in the brain tissue of the jaundiced animals. Their brains contained more isotope than those of the jaundiced nonkernicteric animals. This model is useful for the exploration of the pathogenesis of kernicterus and the problems of transport of the blood-brain barrier as well as the cytotoxicity of bilirubin.

Research on the neuronal effects of kernicterus and anoxia has been followed in rabbits in order to cast light on kernicterus occurring in newborn infants. In human kernicterus the most characteristic microscopic feature is the icteric ganglion cells. Electron microscopic analysis demonstrates both anoxic and toxic effects of bilirubin on the neuron, with some vacuolation and swelling of mitochondria and an increase in the extracellular space. These changes are all reversible 2 to 3 hours after the animals have been removed from the nitrogen chamber. Icteric ganglion cells undergo irreversible necrosis marked by cytolysis, caused by the cytotoxic effect of bilirubin on the neuron. The mechanism of bilirubin access to the intracellular compartment is assumed to be dependent upon the effects of acute anoxia, which produces an increase in permeability in cerebral capillaries and simultaneously breaks down cell barriers.

Cerebral Metabolism and Blood Flow

A great deal of additional information has been accumulated using either the Lassen technique for regional blood flows with Krypton 85, or the Scheinberg modification of the Kety and Schmidt technique with nitrous oxide. Studies made on regional blood flow in the last few years have been well summarized in the series of papers delivered at the Conference on Regional Blood Flow held in Lund in March, 1965, and published as a supplement to Acta Neurologica. This collection of papers contains the latest work from the laboratories of Lassen and Ingvar, among others. Extensive reviews of current methods have also been published by Lassen and by McHenry.

McHenry, in studies of total cerebral metabolism and blood flow in patients with middle cerebral artery occlusion and/or internal carotid occlusion, obtained data on the effects of occlusion of these arteries which agree rather well with the predictions of Clark et al. made from studies of a hemodynamic model of the circle of Willis. Waltz et al. were able to demonstrate in both monkey and cat the expected decrease in clearance of Kr 85 from the cortex after the occlusion of the middle cerebral artery.
Häggendal and his colleagues have shown the relation of carbon dioxide tension in the arteries and oxygen saturation, as well as the influence of various drugs on regional blood flow in the cortex of the dog. Together with Ingvar and Lassen, Häggendal has also considered the pre- and postoperative measurements of regional cerebral blood flow in patients known to have intracranial arteriovenous aneurysms, and was able to obtain some quantitation of flow through the aneurysms. The regional blood flow technique may form a valuable adjunct to angiographic analysis, since it is relatively simple to use and involves little risk for the patient.

In bilateral determinations of cerebral blood flow and oxygen consumption, Beteta et al. determined in patients that if the arterial occlusion was complete and the collateral circulation was meager, cerebral blood flow and oxygen consumption were greatly reduced on the side of the infarction. In the absence of occlusive arterial disease the blood flow was not greatly reduced on the affected side. The reduction of cerebral oxygen consumption correlated best on the side of the infarction. The extra- and intracranial cerebral circulation was visualized by angiography for comparison with the blood flow data.

At high altitudes cerebral blood flow increases 24 per cent in the first 12 hours, 13 per cent at 3 to 5 days, and then tends to return to normal. On the basis of the data obtained, Severinghaus and his colleagues theorize on the relation of CSF, pH and arterial CO₂ to blood flow regulation.

Meyer and his coworkers have continued their important contributions to the studies of cerebral blood flow. Using electromagnetic flow meters on the carotid and vertebral arteries in the neck, they have studied intracranial hypertension and regional pharmacological responses of the vertebral and internal carotid arteries in the monkey and of the vertebral and common carotid (with the external carotid tied) in the cat. The authors realize that these sites do not give accurate measures of the blood flow in the brain, but they do give indications, and at the present state of instrumentation these sites are all that can be studied. Their results using Kr 79 in man suggest that the ionic homeostasis of the brain, as well as its electrical activity, are dependent upon normal glucose oxygenation. During the Valsalva maneuver the brain becomes hypoxic; the data suggest that if continued long enough EEG slowing and unconsciousness could occur.

The Japanese worker, Miyazaki, has started to investigate cerebral blood flow in man using the Doppler technique. The crystals were placed upon the internal carotid artery in the neck and upon the vertebral artery near the mastoid process. His results showed that, independent of blood pressure or cerebral vascular disease in the aged individual, the blood flow pattern in the vertebral artery is more discontinuous than that in the internal carotid. In the aged the cerebral vascular resistance is increased more in the area irrigated by the vertebral artery than in the area receiving blood from the internal carotid. He feels that arteriosclerosis in the area is probably the most important factor in increasing cerebral vascular resistance. Vasodilation to drugs is less effective in the patient with cerebrovascular disease than in the normal individual. This
difference may arise because the cerebral vessels are already near the point of maximum dilation.

In man intra-arterial bridges are found in the brain attaching themselves to the inside of the cerebral arterial wall and crossing the lumen. Frequently they are of a size which can be demonstrated by conventional x-ray techniques. The bridges probably cause some circulatory disturbance with turbulence and might produce clinical signs. Moreover, in the presence of an intra-arterial bridge catheterization of the large cerebral arteries is dangerous. These bridges are largely composed of calcium hydroxyapatite.

Shalit has measured the effects of drugs upon the blood flow in the brain cortex by recording the impedance of the area being perfused. If a solution of sodium chloride is injected into the area, a sudden increase in electrical conductivity results and the amplitude of the wave is proportional to the amount of the injected solution.

Ayala and Himwich have published further work on the cerebral hemodynamics of the dog recording simultaneously the middle cerebral and lingual artery pressures and the effects of occlusion of the main afferents to the circle of Willis. The work demonstrates that in the dog the basilar-vertebral pathway is very important, perhaps more so than in the man.

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