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Animal Models of Hydrocephalus: Recent Developments (41977)

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The presence of a watery fluid that could also be found in large amounts within the brain has been known for many centuries. The idea that this fluid circulated was inspired largely by investigations of the 19th century anatomists. According to Cushing (1) the modern era in research on cerebrospinal fluid (CSF) circulation began with Magendie who was probably the first to fully appreciate the physiological importance of the fluid. Magendie and Luschka described in the roof of the fourth ventricle of the brain, the foramina which bear their names and through which CSF can flow into the subarachnoid space. The existence of these openings may not be present in all animal species. In one investigation in the mid-19th century, they were not found in human pathological studies by Hilton (2); in this particular case, there was an abnormal accumulation of fluid in the interior of the brain.

The source of the CSF had been relegated to the choroid plexus, a view favored by Faivre and by Luschka but not by some who regarded the pia as the source. Though proof was lacking, less doubt remained after Cushing (1) observed the fluid exuding from the surface of the choroid plexus at the bottom of a porencephalic cavity. In the same decade, Weed (3) made extensive studies on the embryological development of the CSF spaces. He correlated the appearances of the villous tufts of the choroid plexus with the extraventricular spread of CSF, the separation of the meninges into its layers and the formation of the cisterns. Further evidence to show that CSF is formed by the choroid plexus was provided by Schaltenbrand and Putnam (4) who observed the formation of greenish fluid on the surface of the choroid plexus after an intravenous injection of fluorescein. More definitive proof of the secretory activity of the choroid plexus was provided in 1963 by Welch (5) who determined the CSF formation rate in rabbits from measurements of choroidal blood flow and of increases in the hematocrit of choroid plexus blood.

Information concerning the sites and mechanisms of CSF absorption is less complete. The early evidence obtained from dye injection experiments by Key and Retzius (6) pointed to the Pacchionian bodies as the site of CSF absorption. The results of studies by Dandy and Blackfan (7) and of those by Weed (8) were in agreement insofar as the absorption of CSF in the subarachnoid space was concerned. The former authors were of the opinion that absorption of fluid took place diffusely through the veins of the subarachnoid space, while the latter author attributed the absorption of CSF specifically to the arachnoid villi. Dandy (9) estimated from the distribution of arachnoid villi that as much as 20–25% of the CSF is absorbed by these structures in the spinal subarachnoid space. Weed (8) demonstrated an accessory passage of CSF accompanying the cranial nerves by noting the appearance of intrathecally injected Prussian blue dye in the cervical lymphatics. It was thought, however, that only a small amount of fluid flowed through this pathway. Some investigators favored the view of the choroid plexus as an absorbing rather than a secreting apparatus. Evidence supporting this minority view is scant.

From early observations on the fate of dye injected intraventricularly into lampblack-induced hydrocephalic cats (10, 11) and into normal cats (10), it was concluded that CSF absorption occurred through the ependymal lining of the ventricles and into the perivascular spaces. Similar conclusions were reported by Bering and Sato (12) in later studies using ventricular perfusion. Whether or not transventricular absorption of CSF occurs has been the subject of numerous investigations for many years. Proponents of this view of CSF absorption base their conclusions on observations made under conditions in which the movement of diffusible dyes contained in the CSF cannot be sepa-

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rated from the bulk flow of fluid. However, the results of more recent studies in experimentally induced feline hydrocephalus support the view that the absorption of CSF formed within the ventricles occurs only in the subarachnoid spaces (96, 99).

Laboratory Models of Hydrocephalus. (A) Dandy concluded in 1919 (13) that "the production of all types of hydrocephalus by precise experimental methods finally lifts the idiopathic veil and reveals hydrocephalus as a disease with a clearly defined etiology and pathology." To initiate a search for an animal model of hydrocephalus, it was necessary to have some preconceived notions of the pathophysiological processes which gave rise to the morphological alterations of the brain in hydrocephalus. The earliest attempts to induce hydrocephalus in animals consisted either of interrupting CSF flow or increasing CSF formation. The development of laboratory models of hydrocephalus became practical when it was realized that hydrocephalus could be induced in animals simply by obstructing the CSF circulation. From observations with human pathological material, it became clear that hydrocephalus can occur readily because narrow portions of the CSF pathway are susceptible to the blockage of CSF flow. The aqueduct of Sylvius and foramen of Monro were therefore preferred sites. Other sites where CSF flow could be impeded included the basilar cisterns and the cisterna magna. Both extraventricular regions were approached surgically or reached with a needle for injection. The effectiveness of most materials injected as a suspension depended on their continued presence and an inflammatory response. Chemically inert irritants are used most frequently and result in the deposition of fibrous material. If an inflammatory response involving the meninges or the ependyma is to be avoided in order to obtain histological data referable to the hydrocephalic process, inert materials such as silicone oils and silastic are infused into the subarachnoid space where they remain and impede CSF flow.

(B) Other methods used to induce hydrocephalus included the interference with the flow of blood through the great vein of Galen. It was postulated that ligating the vein of Galen obstructed the venous drainage of the choroid plexus was followed by an elevated CSF production rate. The results of ligation were generally poor. Bering and Salibi (14) were more successful where they occluded the cephalic venous drainage instead. They concluded from the reversed CSF-to-sinus pressure gradient measured after venous occlusion that CSF absorption probably was impaired and resulted in hydrocephalus.

(C) The formation of primary congenital malformations of the neural tube or neurological anomalies secondary to axial skeletal-dysraphic states can be caused by exogenous insults with teratogens directed at pregnant mammals. There is a high incidence of brain and skull malformation with exencephaly, hydrocephalus and spina bifida.

Hydrocephalus by Obstructing CSF Flow. Virtually all of human hydrocephalus, except for those rare cases of choroid plexus papilloma thought to be associated with an increase in CSF formation, is the result of an obstruction to CSF flow. For descriptive purposes, hydrocephalus was classified as either internal or external, communicating or noncommunicating, etc., depending on whether the block to CSF flow was located in the ventricles or either in the subarachnoid space or in the CSF absorbing system. In some instances, when a block to the flow of fluid was not apparent and the ventricles and aqueduct were enlarged, the disorder was known as "idiopathic" or communicating hydrocephalus (13). This type of hydrocephalus was attributed to the overproduction rather than to a diminished absorption (13), but more likely resulted from the inability of the fluid to flow through the absorbing structures where it is returned to the blood. The classification of hydrocephalus was thought to have some practical application with regard to surgical treatment. In the communicating type, it was necessary to increase the area for absorption of the fluid (15). In the obstructive type, the obstruction must be removed.

The first successful attempt to produce experimental hydrocephalus was made by Dandy and Blackfan in 1913 (7). They were able to induce hydrocephalus by placing a small obstruction (cotton pledget in a capsule) into the aqueduct of Sylvius of a dog. The cerebral ventricles proximal to the occlusion became dilated, while the fourth ventricle

did not enlarge. Shortly thereafter and apparently independently, Thomas (16) produced hydrocephalus in dogs following the injection of aleuronat (insoluble granules made from plant protein). The results showed that the aleuronat caused an acute inflammatory reaction with obstruction of the CSF circulation at the interventricular foramina or the foramen of Magendie. Similar results were obtained by Frazier and Peet (17) in their studies on the factors influencing the origin and circulation of the CSF. Other materials successfully used to produce hydrocephalus, injected either intraventricularly or into the subarachnoid spaces, included bacteria (18), mycobacterium tuberculosis (19), blood (20), lampblack (8, 10, 11), India ink (19, 21), powdered wood in olive oil (22), gelatin and gum acaci (23), thorotrast (24, 25) and kaolin (24, 26–30). In some studies (17), the injection of aleuronat was combined with the placement of a gauze plug against the lower end of the aqueduct of Sylvius. Variations in the use of a cotton pledget to occlude the aqueduct included cotton, gauze and fascia soaked in lampblack or iodine (31, 32). In some larger animals, a small rubber catheter with a rubber balloon was inserted into the aqueduct (33, 34). Ventriculomegaly was usually noted in these animals within 24–48 hrs. These techniques were put into historical perspective by Pudenz *et al.* (35).

Hydrocephalus following Intracerebral Venous Ligation. In their attempts to demonstrate that hydrocephalus can be caused by techniques other than the direct obstruction of the CSF circulation, Dandy and Blackfan (15) ligated the great vein of Galen or the straight sinus. This method was based on observations made on human pathology in which tumors located on or near these vessels were thought to cause venous stasis, increased CSF formation, elevated intracranial pressure and hydrocephalus. There are only relatively few recorded cases of hydrocephalus in which thrombosis of these vessels occurred, and it occurred often with another lesion. To determine the importance of venous obstruction in the production of hydrocephalus, they occluded the straight sinus or the great vein of Galen. However, only 1 of 10 dogs developed hydrocephalus. It was felt nonetheless that hydrocephalus produced in this way was comparable to the so-called human idiopathic or communicating hydrocephalus. Dandy and Blackfan (15) maintained that this type of hydrocephalus resulted from the continuous increase in CSF production caused by venous stasis. Bedford (36, 37) disputed both their contention and their results, and repeated the experiments in monkeys and dogs. He found that neither species had a Galenic system similar to that of man, and that one of the animals he used developed hydrocephalus. He concluded that the hydrocephalus occasionally found by Dandy and Blackfan in the dogs was not due to occlusion of the vein of Galen but to some other etiology. Moreover, with the high degree of venous anastomosis, an increase in intracranial pressure such as that caused by cerebral tumors pressing on these vessels is nothing more than speculative.

Hydrocephalus following Experimental Intracerebral Viral Infection. In congenital human hydrocephalus, pathological changes including stenosis and forking of the aqueduct, periaqueductal gliosis, and inflammatory or neuroglial septal closing of the foramina of Magendie and Luschka can be found. These lesions obstruct CSF flow and result in ventricular dilatation. The infectious etiology of this disorder was hitherto unknown or thought to be due to embryogenesis defects. The first animal model of hydrocephalus used to study the pathological consequences of intrauterine viral infections for the developing central nervous system consisted of hamsters injected intracerebrally as neonates with nonneuroadapted mumps virus, parainfluenza 2 and influenza A (38–40). The brains of animals dying with hydrocephalus showed aqueductal stenosis related to neither chronic infection nor inflammation, "but developed as a non-inflammatory sequela of a preceding acute, but clinically inapparent ependymal cell infection" (38).

Approximately 20 different viruses of nearly all classes of DNA and RNA viruses have been reported as causing hydrocephalus in laboratory animals such as hamsters, ferrets, rats, mice, cats, and monkeys (41). In one report by Kohn *et al.* (42) mycoplasma pulmonis, a pathogen of the rat respiratory tract, was injected intracerebrally into neo-

natal rodents, and more than 90% of rats and hamsters developed hydrocephalus. Intracerebral route for injection was used most commonly. The pathological findings following the intracerebral injection included ependymitis and meningitis. Kilham and Margolis (43) showed that hydrocephalus could also be induced by extracerebral (subcutaneous or intraperitoneal) inoculation of reovirus type I. This made the laboratory model more analogous to the human disorder because the infectious agent crossed the blood–brain barrier. They were also successful in producing hydrocephalus by intraamniotic inoculation with the common respiratory virus, parainfluenza 2, and in this way bypassed the placenta barrier (44).

Considerable doubt exists concerning the pathogenesis of the hydrocephalus after the experimental viral encephalitis. The results of a study of the murine hydrocephalus model showed that aqueduct stenosis is secondary to hydrocephalus (41). When Sylvian aqueduct stenosis occurred, a severe hydrocephalus already existed. The findings of Masters *et al.* (41) suggested that after intracerebral virus injection there was an acute ependymitis and leptomeningitis, followed by a fibrous arachnoiditis and arachnoid villitis. Detailed findings of the subarachnoid space and arachnoid villi at different intervals after injection are, however, lacking. Hydrocephalus developed in proportion to the degree of inflammatory or fibrotic changes with the CSF pathways. In early hydrocephalus there was some evidence of basal cistern blockage. As the hydrocephalic state progressed, there was axial herniation and compression of the midbrain that resulted in the appearance of aqueduct stenosis. Thus, the stenosis of the aqueduct was a secondary phenomenon, not causally related to the pathogenesis of this model of hydrocephalus. Similar conclusions were reached using other animals and different viruses (45–48). In reovirus type I induced hydrocephalus in 2-day-old hamsters, the deformity produced in the cerebellum resembled that of the Arnold-Chiari malformation but without spina bifida (44). The authors argued that the downward displacement of the hindbrain was the result of hydrocephalus and not the cause of it. Recent studies suggested that similar secondary compression of the aqueduct may occur with hydrocephalus in man (49–52). Masters (51) examined the pathogenesis of hydrocephalus in 37 cases of nonbacterial intrauterine and postnatal hydrocephalus, and concluded that the size, shape, and configuration of the aqueduct were not a constant feature, but when it was narrowed it could be attributed to external compression by the expanding cerebrum. Moreover, infective agents cause hydrocephalus by a common pathogenetic mechanism that probably begins by an inflammatory occlusion of the extraventricular CSF pathway. After secondary occlusion of the aqueduct, communicating hydrocephalus is converted into an internal hydrocephalus.

Spontaneous and Inherited Forms of Hydrocephalus. There are several strains of mutant mice with spontaneous hydrocephalus. The hydrocephalus is transmitted as an autosomal recessive. The inherited forms of murine hydrocephalus are comparable to viral induced models even though the cause of the spontaneous hydrocephalus is unknown. In oh mice (53–56) morphological evidence strongly suggests that the temporal sequence of events is communicating hydrocephalus followed by aqueduct stenosis. The aqueducts of these animals are compressed to a slit-like space by the expanding ventricles of the cerebral hemispheres. A similar sequence is thought to occur in the hydrocephalus found in a new mutation of the Syrian golden hamster (57).

The pathogenesis of the inherited form of communicating hydrocephalus in rodents is poorly understood. The extraventricular CSF pathways leading to and including the CSF absorption sites have not been carefully examined histologically. Little is known of the pathophysiological changes in CSF turnover or intracranial pressure that occur in the evolution of the ventriculomegaly. In an electron microscopic study of the brains of hy-3-mice, McLone *et al.* (55) determined stereologically that the two- to threefold increase in the brain extracellular space after occlusion of the aqueduct and that the subsequent return to normal following spontaneous ventriculostomy were thought to represent the morphological substrate for an alternate CSF pathway in these hydrocephalic brains.

Hydrocephalus and Teratology. Various exogenous insults directed at pregnant mam-

mals result in anomalous offsprings. The developing central nervous system is particularly sensitive to the injection of toxic substances or dietary deficiencies which cause the interference with the normal closure of the neural tube. Experimental dysraphism is reproducible in laboratory animals such as pregnant rats and hamsters injected with trypan blue (58–60) or large amounts of Vitamin A (61–63). Craniospinal dysraphia can also be produced in chick embryos using tissue specific antibodies (64). Rabbit anti-chick brain antiserum was also found to have a highly teratogenic action on the embryonic nervous system during neurulation (65).

A hindbrain deformity with spina bifida and the Arnold-Chiari malformation has been described in the progeny of trypan blue injected rats (66). In many respects, these lesions resemble the human malformation; however, the presence of hydrocephalus in these animals was variable as was the range in severity of the hindbrain defect.

The relatively low incidence of hydrocephalus with hindbrain deformities in guinea pigs (60, 67–69) as opposed to humans with the Chiari type II malformation may be attributed to several factors. The embryos of pregnant rats injected with trypan blue are removed before birth to study the development of the neural dysraphism. They do not survive postnatal life because they are cannibalized. Increasing numbers of older embryos with myeloceles become moribund and are resorbed. The spinal cord central canal of these animals remains patent and allows the escape of CSF from the ventricles. In humans with spina bifida, hydrocephalus usually occurs when CSF flow is iatrogenically obstructed after closing the spinal defect. The malformation of the hindbrain prevents the fluid from flowing into the cranial subarachnoid space. The CSF pressure dilates the central canal which then functions as a conduit for the flow of fluid into the spinal subarachnoid space where it is absorbed. Clinical features suggest that the neonatal period is the time when the hydrocephalus develops. About 90% of these children will develop hydrocephalus when the open spina bifida is surgically repaired (70).

The close association of spina bifida with hydrocephalus and the Arnold-Chiari malformation has been a subject of interest for more than 100 years. The complex appears neurologically as a spectrum of a condition with varying degrees of spinal cord involvement and brain stem malformation (71, 72). There is also evidence of a widespread teratogenic influence in many of these patients with skeletal, renal, and other mesodermal abnormalities present (73). The Arnold-Chiari malformation in patients with spina bifida has been described in detail (74, 75). The essential feature pertinent to the development of hydrocephalus consists of a prolongation of the cerebellum which is bound to the elongated medulla. Both structures enclose the elongated fourth ventricle and occlude the foramen magnum to varying degrees. A communicating hydrocephalus may arise from the displacement of the fourth ventricle into the spinal canal, preventing CSF from flowing to the cranial subarachnoid space. The malformation does not impede the communication between the ventricles and the spinal cord central canal as evidenced radiologically, and by the initiation of the hydrocephalus after removal of the sac covering the spinal cord defect.

The mechanisms responsible for the cause and relationship of the various deformities have been the subject of many communications. Teratologically, the pathological process was thought to begin at the site of the neural tube closure by a teratogen acting on a genetically susceptible embryo (70). Hydrocephalus occurs when the brain stem malformation is sufficient to impede CSF flow. An alternate explanation has also been offered (76). The basic defect of the teratogen was thought to be the underdevelopment of the occipital bone resulting in a posterior cerebral fossa inadequate to contain that region of the central nervous system. Consequently, the developing cerebellum is displaced downward into the foramen magnum and compresses the medulla. All of the neurological anomalies which are characteristic of the Arnold-Chiari malformation are considered to be secondary to the axial skeletal defect rather than a primary abnormality of the nervous system.

Recent Developments Using Animal Models of Hydrocephalus. In the 50 years since the first animal model of hydrocephalus was successfully produced, information on sites of formation and absorption and on circu-

lation of CSF has become available, including the structure of the choroid plexus and the arachnoid villi. Although the mechanism of CSF absorption by the arachnoid villi is still unresolved, it has become clear that hydrocephalus occurred when the flow of CSF between its sites of formation and absorption is obstructed. Hydrocephalus became a disorder rather than a disease because in most cases some form of obstruction of the CSF circulation can be demonstrated. The number of different techniques used to induce hydrocephalus in laboratory animals has diminished since the 1930s, but have not disappeared. When newly synthesized materials such as silicone oils (77) and silastic (78) became available some 30–40 years later, they were also tried. These substances were of particular interest since they did not cause tissue reactivity and would not mask the histological changes caused by the hydrocephalic process. Hydrocephalus, however, is readily produced when fibrous tissue forms in reaction to foreign material injected.

A predictable and reproducible animal model of hydrocephalus has evolved to study the changes in CSF dynamics when the normal CSF pathway was interrupted. Kaolin is used to induce hydrocephalus since it is effective, readily available, chemically inert, and easily administered intracisternally. The morphological changes in the brain and spinal cord of dogs and cats have been well documented (24, 26, 79, 80). Kaolin causes an inflammatory response of the meninges with obliteration of the outlets of the fourth ventricle. The intense inflammatory response encircles the brain stem but is usually limited to the meninges. The model of kaolin-induced hydrocephalus was used by Bering and Sato (12) to measure changes in turnover of CSF by perfusing the ventricular system. The technique of ventricular perfusion was critically evaluated in normal animals by Pappenheimer *et al.* (81, 82). The method was adopted for use in kaolin-induced hydrocephalic animals by perfusing the ventricular system from one lateral ventricle to the other (12, 79).

From the results of their studies on CSF turnover, as measured by ventricular perfusion, Bering and Sato (12) concluded that kaolin-induced chronic hydrocephalic dogs could not be distinguished from normal dogs. They found a reduction in CSF formation rate, and attributed it to the exclusion by kaolin of the CSF formed in the subarachnoid space rather than to the hydrocephalic process. In both normal and hydrocephalic dogs, CSF was absorbed from the ventricles; the resistance to absorption, however, was greater in the normal than in the chronic hydrocephalic dog. These conclusions are disputed (91).

Kaolin-induced hydrocephalus was also studied in other animals and at different intervals after kaolin injection. Factors affecting ventricular size and the role of the dilated spinal cord central canal in the development of an alternate CSF pathway were also evaluated. Spinal cord changes secondary to the adhesive arachnoiditis were described by McLaurin *et al.* (80), Becker *et al.* (26), Brocklehurst *et al.* (70), and Torvik and Murthy (83). They demonstrated, on serial section, myelomalacia and cavitations of the spinal cord resulting in marked dilatation of the central canal (hydromyelia and syringomyelia), and a fistula between the terminal central canal and the spinal subarachnoid space. Hochwald *et al.* (84) showed that these changes were brought about by the caudalwards flow of CSF, and not by the adhesive arachnoiditis of the spinal cord. The laboratory findings of syringomyelia and spina bifida were thought by Gardner (85) to be highly relevant to the clinical situation. The dilatation of the spinal cord central canal was accompanied by an increase in spinal cord water content which was greatest in the dorsal columns (84). It was not clear, however, how the edema was associated with the enlargement of the central canal. The increase in spinal cord water content was greater than that measured in the brains of these cats or in dogs also made hydrocephalic with kaolin (86). Lux *et al.* (87) found the edema greatest in the periventricular white matter, where it extended to a distance of 600 μm from the ependymal surface.

The effects of intracisternal kaolin were apparent within 48 hr of the injection. At this interval the foramina of the fourth ventricle were occluded, and the intraventricular pressure in both rabbits (88) and cats (89) increased as much as 10-fold. The intraventricular pressure returned to preinjection levels within days in rabbits, while approximately

2–3 weeks were needed for cats. As the intraventricular pressure increased during the first few days after kaolin (acute hydrocephalus), the ventricular volume expands—from a normal of about 1.0 ml (90, 91) to approximately 2.6 ml (91). Granholm (92) showed with rabbits that the diversion of CSF by means of a ventriculo-subcutaneous shunt at this interval after kaolin was followed by a significant decrease of the enlarged ventricles. The blood flow in the cerebrum, cerebellum, and brain stem of these cats was reduced by approximately 20% (84). The mechanism responsible for the changes in CSF dynamics was derived from the results of perfusion experiments. The mean opening ventricular pressure of acute hydrocephalic cats perfused 7 days after kaolin was 5 times greater than that of normal cats (89). The CSF formation rate measured during ventricular perfusion at an elevated perfusion pressure was greater than the rate of CSF absorption determined in the same animals. Hochwald *et al.* (89) concluded from these studies that in acute hydrocephalus, the increase in intraventricular pressure was the result of the increased resistance to CSF absorption.

Approximately 2–3 weeks after kaolin, when the intraventricular pressure of cats (89) returned to within normal range (chronic hydrocephalus), the cerebral ventricular volume expanded to more than twice that measured in the acute hydrocephalic cat with a fivefold higher CSF pressure. In these chronic hydrocephalic cats, brain blood flow was greater than in acute hydrocephalus, but it did not completely return to control values (84). The return of intraventricular pressure to normal range was associated with an increase in CSF absorption capacity (89). CSF formation rates in both groups of cats were similar. The resistance to CSF absorption in the chronic cats decreased. The transition of acute to chronic hydrocephalus in the feline model of kaolin-induced hydrocephalus can, therefore, be characterized by an increase in CSF absorption capacity. The resistance to CSF absorption remained greater in the chronic hydrocephalic than in the normal cats (93).

It was held for many years that transventricular flow is the means by which CSF is absorbed by the hydrocephalic brain. This mechanism was first proposed by Wislocki and Putnam in 1921 (11) and then by Nanagas (10) in the same year. It was also thought to be active in normal animals (8) in removing ventricular CSF. The existence of such a mechanism was questioned by Rall *et al.* (94) when they were unable to distinguish between bulk flow and diffusion in their studies. Sahar *et al.* (93) and Ogata *et al.* (95) also failed to show a difference in the distribution in the brain of either radiolabeled cat serum albumin or horseradish peroxidase after perfusing the ventricles of normal and hydrocephalic cats with these substances. Eisenberg *et al.* (96, 97) showed that the dilatation of the spinal cord central canal is the compensatory mechanism in cats responsible for the decreased resistance to CSF absorption. Through this canal, communication between the ventricles and the subarachnoid space was reestablished and CSF formed within the ventricles was absorbed in the spinal subarachnoid space. Communication between the cranial and spinal subarachnoid spaces was interrupted by the kaolin; CSF was then absorbed in the latter space. Similar results in the intact hydrocephalic cat were seen with isotope ventriculography (97, 98) and by positive contrast ventriculography (99). That flow through the dilated central canal of the spinal cord is essential was shown by the absence of CSF absorption after ligation of the lumbar spinal cord during perfusion (96).

The dilated spinal cord central canal communicates with the ventricular system and contains remnants of the lining ependyma. The hydrosyringomyelia can develop within days after intracisternal kaolin, and is accompanied by intramedullary extravasation of CSF into the dorsal columns (99). The animal model of kaolin-induced hydrocephalus shows spinal cord changes that have similarities with syrinxes in humans. The development of hydrosyringomyelia is thought to illustrate Gardner's hydrodynamic theory of human dysraphism and syringomyelia (85). According to the theory, obstruction of the roof of the fourth ventricle distends the central canal with either prenatal myelocele or a postnatal cavitation hydrosyringomyelia of the spinal cord.

Hydrocephalus with Severe Ventriculomegaly and Its Reversibility. In yet another animal model described by Hochwald *et al.*

(100), severe hydrocephalus in cats can be produced with a ventricular volume that is sufficiently large to reduce cerebral cortical mantle to less than 1 mm. This model provides a means to study the effect of hydrocephalus on the cortical mantle thickness with particular reference to the reversibility of the changes. In a series of studies, Rubin *et al.* (101–104) examined the histological and ultrastructural changes in the cerebral cortical mantle of cats with severe hydrocephalus. They also measured the changes in cell number, size, and myelin content as well as the effects of ventricular fluid shunting on the reconstitution of the cerebral cortical mantle. This model was produced by the intracisternal injection of kaolin into cats whose supratentorial calvarium and underlying dura (except for the sagittal sinus) were removed. Similar results were obtained when kaolin was injected prior to the craniectomy. (In noncraniectomy, kaolin-injected cats (91) the ventricular volume was only about 2.5 ml.) Maximal ventricular volume was reached in about 10 days. Ventricular volumes as large as 30 ml were measured. The ventriculomegaly caused a disruption of the ependyma with periventricular edema, axonal destruction, secondary myelin disintegration, and reactive astrocytosis. Despite the marked thinning of the cortical mantle, there was little loss of total dry weight of the brain. When the number of cells in the brain and their size were calculated from the total brain DNA, RNA, and protein, there was only a slight increase in these values which presumably reflected the increase in small inflammatory cells. There did not seem to be a significant diminution in the number of cortical cells. Hydrocephalus resulted in a loss of white matter with remarkable sparing of the gray. Galactolipids, a measure of myelin content, were decreased due to the myelin loss.

Forty-eight hours after ventricular shunting of cats with massive ventriculomegaly, the ventricular system resumed its slit-like configuration because of the reconstitution of the cortical mantle. No new elements were acquired by the thickened mantle since none of the old ones had disappeared. The mantle thickened because the decrease in CSF pressure allowed the preexisting elements to be rearranged. The mantle after shunting consisted of less edema, reactive astrocytosis, and a paucity of myelinated fibers. The reparative process of the brain is limited because cell renewal by mitosis is uncommon and remyelination is limited. There was a significant loss of axons, however, that may eventually restrict communication between neurons, or with time, result in retrograde neuronal loss. The extent to which these changes may affect function in humans is not clear. This is difficult to evaluate because of, for example, a poor correlation between cortical mantle thickness and intelligence (16, 105). In the clinical setting, the return of function after shunting may not result from the reacquisition of lost elements of the brain but to the improved function of the remaining elements. It can be inferred from these studies that prompt reversal of hydrocephalus would seem to preserve the anatomical and functional integrity of the brain. In man, however, little information is available in prenatal hydrocephalus to indicate the extent to which motor and mental deficits can be attributed to the hydrocephalic process or to an underlying cerebral dysfunction. It may be possible by combining these with behavioral studies involving the measurement of functions such as learning and memory in laboratory animals to provide a more rational understanding of the pathophysiology of hydrocephalus and a framework on which to evaluate therapy.

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